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Positioning filgotinib in the therapeutic landscape of rheumatoid arthritis - alternative or complementary?

Filgotinibin romatoid artrit tedavisindeki konumu - alternatif mi, tamamlayıcı mı?

Rukiye Menemencioğlu[1], Burcu Şahinbaş[2], Ahmet Altun[2]

[1]*Sivas State Hospital, Clinic of Pharmacy, Sivas, Türkiye*
[2]*Sivas Cumhuriyet University Faculty of Medicine, Department of Pharmacology, Sivas, Türkiye*

Abstract

Rheumatoid arthritis is a chronic inflammatory disease characterized by persistent immune activation and progressive joint damage. Although conventional and biological disease-modifying antirheumatic drugs have substantially improved disease control, treatment resistance and failure to achieve sustained remission remain important clinical challenges. This narrative review evaluates filgotinib, a preferential Janus kinase 1 inhibitor, focusing on its clinical efficacy, safety profile, and therapeutic potential for rheumatoid arthritis. Clinical studies have demonstrated that filgotinib provides rapid and sustained clinical benefits in patients with moderate-to-severe rheumatoid arthritis, particularly in those with an inadequate response to, or intolerance of, methotrexate or biologic therapies. The most commonly reported adverse events include mild infections and nasopharyngitis, while overall tolerability remains favorable. Overall, filgotinib represents a well-tolerated targeted therapeutic option for patients with difficult-to-treat rheumatoid arthritis. Nevertheless, further long-term studies and real-world evidence are required to better define its safety profile and clarify its optimal positioning within contemporary treatment strategies.

Keywords: Adverse effects, DMARDs resistance, filgotinib, JAK1 inhibitor

Özet

Romatoid artrit, bağışıklık sisteminin süreğen aktivasyonu ve ilerleyici eklem hasarı ile karakterize kronik bir enflamatuvar hastalıktır. Geleneksel ve biyolojik hastalık modifiye edici antiromatizmal ilaçlar hastalık kontrolünü önemli ölçüde iyileştirmiş olsa da, tedaviye direnç ve sürekli remisyon elde edilememesi önemli klinik zorluklar olmaya devam etmektedir. Bu derleme makalesi, romatoid artritte klinik etkinliği, güvenlik profili ve terapötik potansiyeline odaklanarak, seçici bir Janus kinaz 1 inhibitörü olan filgotinibi değerlendirmektedir. Klinik çalışmalar, filgotinibin orta ila şiddetli romatoid artritli hastalarda, özellikle metotreksat veya biyolojik tedavilere yetersiz yanıt veren veya intoleransı olanlarda hızlı ve sürekli klinik faydalar sağladığını göstermiştir. En sık bildirilen yan etkiler arasında hafif enfeksiyonlar ve nazofarenjit yer alırken, genel tolere edilebilirlik olumlu kalmaktadır. Genel olarak, filgotinib, tedavisi zor romatoid artritli hastalar için iyi tolere edilen hedefe yönelik bir tedavi seçeneğidir. Bununla birlikte, güvenlik profilini daha iyi tanımlamak ve güncel tedavi stratejileri içindeki en uygun konumunu netleştirmek için daha uzun vadeli çalışmalara ve gerçek dünya verilerine ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Advers etkiler, DMARD direnç, filgotinib, JAK1 inhibitörü

Introduction

Rheumatoid arthritis (RA) is a chronic, immune-mediated inflammatory disease characterized by persistent synovitis, progressive joint damage, and systemic manifestations that significantly impair quality of life.[1] The primary goal of RA treatment is to achieve sustained remission; when this is not attainable, therapeutic strategies aim to control symptoms, minimize pain, preserve functional capacity, improve quality of life, and slow structural joint damage. RA is managed through symptomatic treatment, including non-steroidal anti-inflammatory drugs and glucocorticoids, in conjunction with disease-modifying antirheumatic drugs (DMARDs), which are the cornerstone of first-line therapy. Failure of or intolerance to first-line therapy necessitates escalation to alternative DMARDs.[2,3] In cases of inadequate response, biological therapies such as anti-tumor necrosis factor alpha (TNF-α) agents or interleukin-6 (IL-6) receptor blockers are used.[4]

Correspondence / İletişim: Rukiye Menemencioğlu PhD,
Sivas State Hospital, Clinic of Pharmacy, Sivas, Türkiye
E-mail: rukiyegozell@gmail.com **ORCID ID:** orcid.org/0000-0002-7053-8143
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Over the past two decades, the introduction of DMARDs, particularly biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), has markedly improved disease outcomes. Nevertheless, a substantial proportion of patients do not achieve sustained remission or low disease activity despite sequential treatment with conventional synthetic DMARDs (csDMARDs) and biologic agents, prompting recognition of difficult-to-treat RA.[5]

Difficult-to-treat or refractory RA is defined by persistent disease activity that remains inadequately controlled despite the use of conventional therapeutic strategies. A considerable percentage of RA patients develop resistance to two or more (≥2) bDMARDs during the course of their treatment, according to certain studies. In particular, anti-TNF biologics are frequently associated with primary or secondary non-responsiveness.[5]

Janus kinase (JAK) inhibitors have emerged as an important class of therapeutics within this evolving treatment paradigm, allowing oral administration and broad inhibition of cytokine signaling. Filgotinib, a preferential JAK1 inhibitor, is one of the newer agents in this class. While its clinical efficacy and safety have been demonstrated in multiple randomized controlled trials, its precise positioning within the RA therapeutic landscape remains a subject of clinical debate.

Specifically, whether filgotinib should be regarded primarily as an alternative to existing advanced therapies or as a complementary option within sequential treatment algorithms requires a careful narrative synthesis rather than a purely descriptive enumeration of clinical trial data.[6]

Accordingly, this narrative review focuses exclusively on RA and aims to contextualize filgotinib within contemporary RA management. Rather than adopting a systematic review framework, this article integrates evidence from key clinical trials, comparative analyses, and safety evaluations to provide an interpretative assessment of filgotinib's therapeutic role. Through this approach, we aim to address unmet clinical needs and clarify whether filgotinib should be viewed as an alternative or complementary agent in the management of RA.

The Therapeutic Landscape of Rheumatoid Arthritis and Unmet Needs

Current RA management follows a stepwise, treat-to-target strategy, with methotrexate (MTX) remaining the cornerstone of initial therapy. In patients with an inadequate response to or intolerance of csDMARDs, bDMARDs targeting TNF, IL-6, or immune cell co-stimulation are recommended. Despite this structured approach, real-world data indicate that a substantial subset of patients experience primary non-response, secondary loss of efficacy, or unacceptable toxicity across multiple therapeutic classes.[2]

Within this therapeutic landscape, tsDMARDs—particularly JAK inhibitors—have expanded therapeutic options by offering oral administration and modulating intracellular cytokine signaling. Tofacitinib, baricitinib, upadacitinib, and filgotinib are the principal JAK inhibitors evaluated for RA. Current international guidelines do not preferentially recommend one JAK inhibitor over another, reflecting comparable efficacy across the class and the absence of definitive head-to-head superiority data.[7]

The emergence of difficult-to-treat RA has underscored the need for greater therapeutic flexibility. These patients often require multiple treatment switches, and the availability of mechanistically distinct yet clinically effective agents remains essential. Filgotinib's development and approval in several regions occurred within this context, positioning it as a potential solution for patients with refractory disease.[3]

Filgotinib: Mechanism of Action and Pharmacological Profile

JAK inhibitors are considered an effective therapeutic strategy for managing autoimmune diseases, as they enable targeted modulation of inflammatory signaling pathways. Key advantages of JAK inhibitors include oral administration and demonstrated efficacy with acceptable safety profiles.[3,8] Among these agents, filgotinib was one of the most recently introduced JAK inhibitors to the global market for the treatment of RA as of 2020.[9] Filgotinib is a preferential JAK1 inhibitor that selectively suppresses signaling pathways mediated by pro-inflammatory cytokines implicated in RA pathogenesis, thereby inhibiting signaling by IL-6, interferon-γ, interferon-α/β, and γc-chain cytokines through suppression of signal transducer and activator of transcription (STAT) phosphorylation and activation within the JAK-STAT pathway, ultimately leading to reduced innate immune responses, inflammation, and lymphocyte proliferation (Figure 1).[10,11] Compared with earlier JAK inhibitors, which exhibit broader inhibition profiles (e.g., tofacitinib targeting JAK1/3 and baricitinib targeting JAK1/2), filgotinib's selectivity was designed to maintain therapeutic efficacy while potentially limiting adverse effects associated with JAK2 inhibition, such as hematopoietic suppression.[10]

In patients with an inadequate response to conventional therapies, filgotinib represents a clinically viable therapeutic option.[12] Filgotinib has demonstrated a favorable tolerability profile and clinical efficacy comparable to those of biologic agents.[13,14]

Pharmacokinetically, filgotinib is administered orally once daily and primarily metabolized by carboxylesterase 2 (CES2) and, to a lesser extent, by CES1, leading to formation of its major active metabolite, GS-829845, which contributes substantially to sustained JAK1 inhibition. After oral administration, only

a limited percentage of the parent compound is recovered unchanged, with 9.4% excreted in urine and 4.5% in feces. The majority of the administered dose (~87%) is eliminated as metabolites, with approximately 54% and 8.9% excreted in urine and feces, respectively, as GS-829845.[15]

Dose adjustment of filgotinib is not required in individuals with mild renal impairment, defined as those with a calculated glomerular filtration rate (eGFR) of 60-90 mL/min/1.73 m².[16] For patients aged ≥75 years and those with moderate to severe renal impairment, the starting dose is recommended at 100 mg/day. Following recent label revisions, initiation of filgotinib at 100 mg once daily, with up-titration to 200 mg once daily if tolerated, is recommended for this patient population.[8] Filgotinib is not recommended for use in patients with end-stage renal failure (eGFR <15 mL/min/1.73 m²), as it has not been tested in this population.[16]

Filgotinib administration does not require dose adjustment in cases of mild-to-moderate hepatic dysfunction. Filgotinib is not recommended for use in patients with severe hepatic impairment, as this population has not been evaluated in clinical studies.[16,17]

Overall, dose adjustment is generally unnecessary in patients with mild to moderate hepatic or renal impairment; howeveruse is not recommended in individuals with severe organ dysfunction. Filgotinib is contraindicated during pregnancy and breastfeeding; effective contraception is recommended throughout the treatment period.[18]

While these pharmacological characteristics differentiate filgotinib mechanistically, their clinical relevance ultimately depends on whether selective JAK1 inhibition translates into meaningful differences in efficacy or safety compared with other JAK inhibitors.

Clinical Efficacy of Filgotinib in Rheumatoid Arthritis

Clinical development programs have consistently demonstrated the efficacy of filgotinib across diverse RA populations. Phase II DARWIN trials established proof of concept, showing significant improvements in disease activity with both monotherapy and combination therapy with MTX in patients with inadequate response to csDMARDs.[19]

Phase III interim analyses from the filgotinib clinical trials in RA (FINCH) long-term extension program further clarified filgotinib's therapeutic role. In FINCH-1, filgotinib combined with

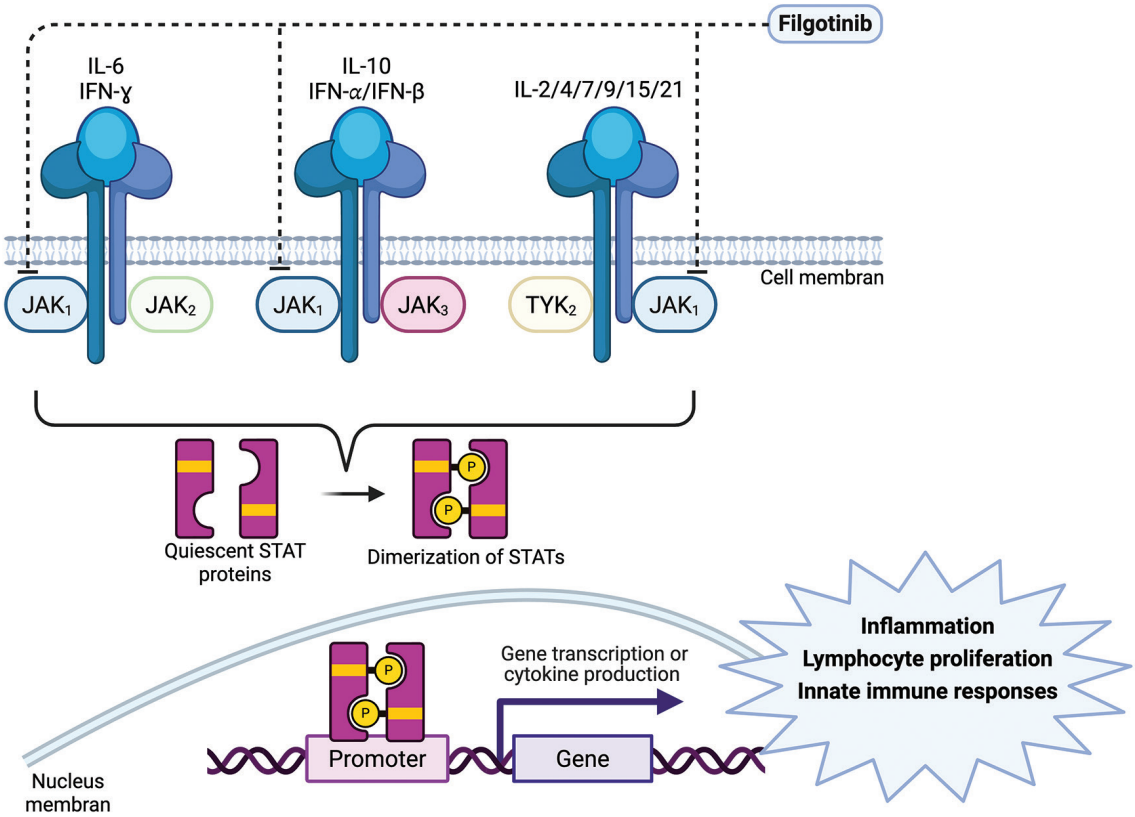

Figure 1. Filgotinib selectively inhibits signal transduction by JAK-1
Filgotinib exhibits strong selectivity for JAK1, thereby inhibiting signaling mediated by IL-6, IFN-γ, IFN-α/β, and γc-chain cytokines. As a result, innate immune responses, inflammation, and lymphocyte proliferation are reduced[10,11]
IFN: Interferon, IL: Interleukin, JAK: Janus kinase, STAT: Signal transducer and activator of transcription, TYK2: Tyrosine kinase 2 (License: https:/BioRender.com/oa72sov)

MTX demonstrated non-inferiority to adalimumab in patients with MTX-refractory RA, supporting its use as an alternative to established biologic therapies.[20] FINCH-2 specifically addressed biologic-refractory disease, revealing robust efficacy in patients who had failed one or more bDMARDs, a population representative of difficult-to-treat RA.[21] FINCH-3 extended these findings to patients without prior MTX exposure, suggesting potential utility earlier in the disease course, particularly in combination with MTX.[22]

Across trials, filgotinib demonstrated a rapid onset of action, meaningful improvements in patient-reported outcomes, and sustained disease control. Importantly, efficacy was consistently maintained across patient subgroups, reinforcing the view that filgotinib is broadly effective rather than confined to a narrow clinical niche.

Safety Profile of Filgotinib and Class-related Considerations

Safety evaluation remains central to the positioning of any JAK inhibitor. In pooled analyses from phase III trials and long-term extension studies, filgotinib exhibited a safety profile largely comparable to that of other agents within the class. Rates of serious infections, malignancies, venous thromboembolism, and major adverse cardiovascular events were low and comparable to those observed in control groups, given the limitations of trial duration and population size.[23] Evidence from randomized trials, long-term follow-up, and pharmacovigilance sources supports a generally consistent safety profile for filgotinib, with no new or unexpected safety signals reported to date.[23-26]

Class-wide safety concerns emerged following post-marketing data with tofacitinib, leading to regulatory warnings applicable across the JAK inhibitor class. Although filgotinib trials did not demonstrate an increased risk of these events, caution remains warranted, particularly in older patients and in those with cardiovascular or malignancy risk factors.[27]

Infections

According to systematic reviews and meta-analyses, tofacitinib, baricitinib, upadacitinib, and filgotinib are effective in the treatment of RA, although differences in efficacy and tolerability have been observed across these agents.[13,15,28,29] The overall risk of infection appears broadly comparable among these agents; however, herpes zoster infections have been reported less frequently with filgotinib.[13,15]

Across clinical trials, the most commonly reported infections associated with filgotinib were nasopharyngitis and upper respiratory tract infections, which were predominantly mild to moderate in severity. Serious infections were infrequent, with pneumonia reported in less than 1% of treated patients.[30] In patients with inadequate response to MTX, filgotinib monotherapy (100 mg and 200 mg) demonstrated rapid clinical improvement and was generally well tolerated, with no reported cases of tuberculosis or opportunistic infections.[19]

In the referenced study, the combinations of tofacitinib 10 mg plus MTX and filgotinib 200 mg plus MTX were associated with improved efficacy in RA patients refractory to bDMARDs.[28] FINCH 4 further demonstrated that the incidence of serious infections remained low and did not differ significantly between the filgotinib treatment groups and placebo.[31] Serious infections were reported more frequently among older patients and those receiving concomitant immunosuppressive therapy. The observation of lymphopenia in a subset of patients underscores the importance of appropriate infection risk mitigation strategies, including screening for tuberculosis, hepatitis B, and hepatitis C prior to treatment initiation, as well as updating recommended vaccinations.[32]

Adverse event reports in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database for filgotinib are consistent with findings from clinical trials. The FAERS analysis included reports submitted between 2017 and 2025, with data retrieved up to the date indicated in reference.[33] In the system organ class distribution based on FAERS data, infections and infestations constituted the most frequently reported adverse event group, accounting for 108 (42.5%) of 254 reports (Figure 2). These findings indicate that infections constitute commonly reported adverse events associated with filgotinib and are generally mild and clinically manageable.

Overall, available clinical trial and real-world evidence suggests that filgotinib is associated with an infection risk comparable to that of other JAK inhibitors, without a disproportionate increase in serious or opportunistic infections. Its relatively low incidence of herpes zoster and a predominantly mild infection profile support its use in appropriately selected patients, provided that standard infection screening and preventive measures are applied.

Laboratory Findings and Metabolic Effects

Across phase II and III clinical studies involving patients with RA, filgotinib treatment was associated with limited, clinically manageable laboratory abnormalities. Platelet counts showed a mild early decline followed by stabilization; neutrophil levels remained largely unaffected, and no cases of clinically relevant neutropenia were reported.[15,34] Notably, filgotinib demonstrated minimal impact on hemoglobin levels and other hematologic parameters, a finding attributed to its preferential JAK1 inhibition. This observation suggests a potentially favorable laboratory profile, although its clinical significance relative to other JAK inhibitors remains uncertain.[34,35]

Transient, asymptomatic elevations in creatine kinase were observed, consistent with class-related effects reported for other

JAK inhibitors, but these changes did not necessitate clinical intervention.[21]

With respect to metabolic parameters, available data suggest that filgotinib treatment is associated with early, dose-dependent increases in total cholesterol, triglycerides, and high-density lipoprotein levels; low-density lipoprotein-to-high-density lipoprotein ratios generally remain stable, and lipid levels tend to stabilize over time.[15]

Cardiovascular Effects

Available data suggest that the incidence of major adverse cardiovascular events with filgotinib is low and comparable to rates reported for other JAK inhibitors. No clear dose-dependent increase has been observed. Although a modest numerical increase has been noted in older patients (≥65 years), a definitive association with filgotinib dose has not been established.[24,36]

Safety studies indicate an increased risk of venous thromboembolism and pulmonary embolism with tofacitinib in the ORAL surveillance study, whereas no comparable safety signal has been identified for filgotinib. Consistent with this, real-world data from the Scottish cohort reported by Gros et al.[24] did not identify such events, even among patients with established cardiovascular risk factors.[27]

Available evidence from thorough QT studies suggests that short-term, once-daily administration of filgotinib at therapeutic and supratherapeutic doses is not associated with QT interval prolongation.[37]

Malignancies

Compared with the general population, patients with RA have an increased risk of developing malignancies, particularly lymphoma, melanoma, and lung cancer. Although filgotinib is associated with a low overall incidence of malignancies, including non-melanoma skin cancer, a numerically higher incidence of malignancies has been observed in patients aged >65 years receiving the 200-mg dose.[15,36] This observation has been hypothesized to reflect potential suppression of immune surveillance at higher doses. Deaths from pneumonia and lymphoma were infrequently recorded during treatment in the DARWIN 3 study, and the low frequency of these events supports the overall safety profile of filgotinib.[23]

Common Adverse Events

Evidence from clinical studies suggests that treatment discontinuation with filgotinib is most commonly driven by lack of efficacy, whereas adverse events and non-adherence occur less frequently. Patients who discontinued treatment due to inefficacy predominantly had prior exposure to advanced-line DMARDs and JAK inhibitors. Adverse events resulting in discontinuation were generally uncommon and most frequently included gastrointestinal symptoms, dizziness or vertigo, and infections.[8]

Comparative Perspective: Filgotinib and Other JAK Inhibitors

In patients with RA who had a poor response to bDMARDs, a randomized clinical trial comparing JAK inhibitors, including tofacitinib, baricitinib, filgotinib, and upadacitinib, found that

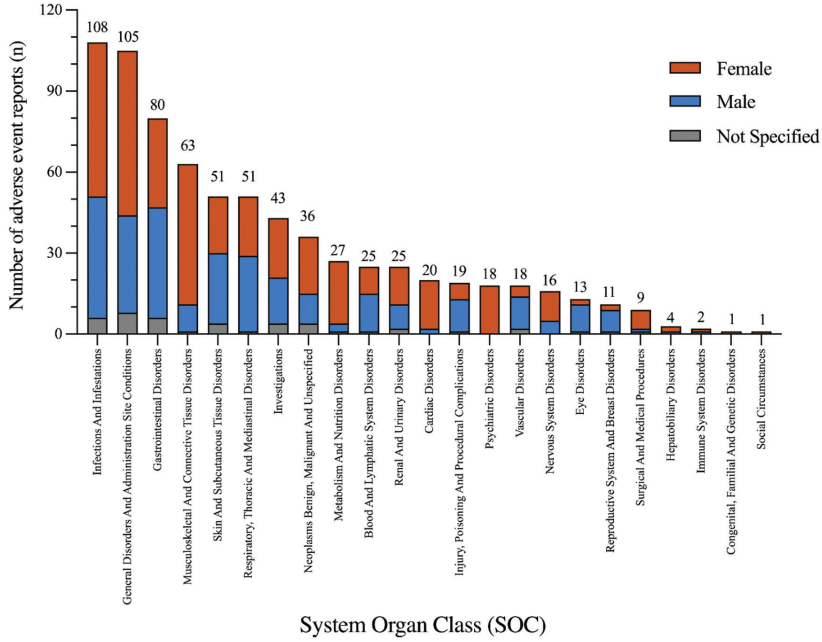

Figure 2. Systematic distribution of adverse event reports associated with filgotinib
Distribution of adverse events associated with filgotinib by system organ class according to the FAERS database (2017-2025)[33]
FAERS: U.S. Food and Drug Administration Adverse Event Reporting Systems

baricitinib and filgotinib were therapeutically comparable to upadacitinib. Nevertheless, further evidence is required because some discrepancies have been reported between the findings for tofacitinib and upadacitinib.[38]

Clinical pharmacology studies indicate that filgotinib can be safely co-administered with therapies commonly used in RA. Phase II and III trials demonstrated that filgotinib does not significantly alter MTX pharmacokinetics and can be be coadministered with MTX without dose adjustment, resulting in improvements in physical function and disease activity.[22,39] In patients without prior MTX exposure, combination therapy demonstrated superior outcomes compared with MTX monotherapy; however, filgotinib monotherapy was inferior to MTX monotherapy in this population.[22] Consistent with these findings, filgotinib 200 mg plus MTX demonstrated disease activity outcomes comparable to those observed with adalimumab plus MTX in MTX-inadequate responders.[20]

Drug-drug interaction studies further support filgotinib's favorable pharmacokinetic profile. No clinically relevant interactions were observed with statins, hormonal contraceptives, P-glycoprotein modulators, or cytochrome P450 3A4 (CYP3A4) substrates, and no dose modification was required when filgotinib was co-administered with these agents.[32,39-42] These findings suggest that filgotinib is compatible with the polypharmacy commonly encountered in RA management.

Indirect comparisons and network meta-analyses indicate broadly comparable efficacy among approved JAK inhibitors in RA. While subtle differences in ranking have been reported, these variations are unlikely to translate into major clinical distinctions at the individual patient level.[38]

From a safety standpoint, all JAK inhibitors share class-wide warnings, and no agent has conclusively demonstrated superior long-term safety. Filgotinib's selectivity may offer theoretical advantages; however, current evidence supports its classification as therapeutically equivalent to, rather than categorically distinct from, other agents within the class.

Positioning Filgotinib: Alternative or Complementary?

Integration of efficacy, safety, and clinical context suggests that filgotinib primarily serves as an alternative advanced therapy in RA management. Its demonstrated efficacy in MTX-refractory and biologic-refractory populations supports its use as a substitute for biologic agents or other JAK inhibitors when prior therapies have failed or are contraindicated.

Filgotinib also complements existing treatment strategies by expanding the therapeutic armamentarium. Its oral administration, consistent efficacy, and acceptable safety profile provide clinicians with greater flexibility in tailoring treatment sequences, particularly in patients with difficult-to-treat RA.

Conclusion and Future Perspectives

Filgotinib represents a meaningful addition to the RA therapeutic landscape. While it does not fundamentally redefine treatment paradigms, it offers an effective alternative among advanced therapeutic options and complements existing strategies by addressing unmet clinical needs. Ongoing real-world data and long-term safety surveillance are expected to further clarify its optimal positioning and inform individualized treatment decisions.

As a result, filgotinib emerges as a well-tolerated targeted therapeutic option, particularly for patients who are intolerant of or do not respond adequately to conventional treatment regimens. Nevertheless, its broad clinical application remains limited in certain regions because regulatory approval has not yet been granted in several countries. Consequently, further evidence is needed to better characterize its long-term safety profile, rare adverse events, and potential drug-drug interactions. Comparative studies supported by pharmacovigilance databases and real-world evidence will be essential to further elucidate its role within therapeutic algorithms.

Footnotes

Author Contributions

Concept: R.M., Design: R.M., B.Ş., A.A., Data Collection or Processing: R.M., B.Ş., Analysis or Interpretation: A.A., Literature Search: R.M., B.Ş., Writing: R.M., B.Ş.

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Thrombotic microangiopathy in patients with systemic vasculitis: A systematic literature review

Sistemik vaskülit hastalarında trombotik mikroanjiopati: Bir sistematik literatür taraması

Ege Sinan Torun[1], Selin Çelen[2]

[1]Demiroğlu Science University, İstanbul Florence Nightingale Hospital, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye
[2]Dörtyol State Hospital, Clinic of Internal Medicine, Hatay, Türkiye

Abstract

Features of thrombotic microangiopathy (TMA) rarely arise in patients with systemic vasculitis. We identified cases in which patients with systemic vasculitis developed clinical, laboratory, and/or histopathological features of TMA. A comprehensive, systematic literature review was conducted. It identified patients diagnosed with systemic vasculitis who showed clinical, laboratory, and/or histopathological features of TMA at or after vasculitis diagnosis. A total of 61 cases of TMA accompanied by systemic vasculitis were included. Antineutrophil cytoplasmic antibody-associated vasculitis was most commonly associated with TMA, accounting for 31 cases. Biopsy-proven renal TMA was present in 30 of the 61 patients. Systemic vasculitis was active in 46 cases and inactive in 11 (the remaining 4 cases could not be assessed for vasculitic activity). TMA attributed to secondary causes included drug- and vaccine-induced TMA (9 cases), thrombotic thrombocytopenic purpura (8 cases), hypertension including preeclampsia (8 cases), atypical hemolytic uremic syndrome (5 cases), and cytomegalovirus infection (2 patients). For TMA treatment, glucocorticoids were administered to 52 patients, plasma exchange to 35, cyclophosphamide to 26, and eculizumab to 6. TMA due to secondary causes can also occur in patients with systemic vasculitis. TMA features may develop with new-onset vasculitis or during relapses, and vasculitic activity may trigger TMA. Recognizing the underlying mechanisms is essential for targeted therapy. In cases associated with active systemic vasculitis, plasma exchange is often performed alongside immunosuppressives, and complement inhibition with eculizumab may offer benefits. These findings highlight the importance of timely diagnosis and individualized management to improve patient outcomes.

Keywords: Systematic literature review, thrombotic microangiopathy, vasculitis

Özet

Trombotik mikroanjiyopati (TMA) bulguları, sistemik vaskülitli hastalarda nadiren gelişebilmektedir. Bu çalışmada, TMA'nın klinik, laboratuvar ve/veya histopatolojik özelliklerinin geliştiği sistemik vaskülit olgularını derlemeyi amaçladık. Sistemik vaskülit tanısı konulmuş ve vaskülit tanısı anında veya sonrasında TMA'nın klinik, laboratuvar ve/veya histopatolojik özellikleri gelişen hastaların belirlenmesini sağlayacak kapsamlı bir sistematik literatür taraması yapılmıştır. Sistemik vaskülite eşlik eden TMA'lı 61 olgu çalışmaya dahil edilmiştir. Toplam 31 olgu ile TMA ile en sık ilişkili olan sistemik vaskülit grubu antinötrofil sitoplazmik antikor ilişkili vaskülitlerdi. Altmış bir hastanın otuzunda biyopsi ile kanıtlanmış renal TMA mevcuttu. Kırk altı olguda sistemik vaskülit aktifti, 11 hastada vaskülit inaktifti (kalan 4 olguda vasküliti aktivitesi değerlendirilememiştir). Bu olguların içinde ilaçlar ve aşılar (9 olgu), trombotik trombositopenik purpura (8 olgu), preeklampsi dahil olmak üzere hipertansiyon (8 olgu), atipik hemolitik üremik sendrom (5 olgu) ve sitomegalovirüs (2 hasta) gibi TMA'nın sekonder nedenleri de mevcuttu. TMA tedavisi için 52 hastaya glukokortikoidler, 35 hastaya plazma değişimi, 26 hastaya siklofosfamid ve 6 hastaya ekulizumab uygulanmıştır. Sistemik vaskülitli hastalarda sekonder nedenlere bağlı TMA da görülebilir. TMA özellikleri yeni başlayan vaskülit bulgularıyla beraber veya vaskülit nüksü sırasında gelişiyorsa, vaskülit aktivitesi TMA için potansiyel bir tetikleyici olabilir. Aktif vaskülitle ilişkili TMA olgularında immünsüpresiflere ek olarak, sıklıkla plazma değişimi yapılır ve bazı durumlarda ekulizumab ile kompleman inhibisyonu da faydalı olabilir. Bu bulgular, sistemik vaskülitle ilişkili TMA olgularında zamanında teşhisin ve bireyselleştirilmiş tedavinin daha iyi sonuçlar almak için ne kadar önemli olduğunu vurgulamaktadır.

Anahtar Kelimeler: Sistematik literatür taraması, trombotik mikroanjiyopati, vaskülit

Correspondence / İletişim: Ege Sinan Torun MD,
Demiroğlu Science University, İstanbul Florence Nightingale Hospital, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye
E-mail: egesinantorun@hotmail.com **ORCID ID:** orcid.org/0000-0002-4842-0683
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Introduction

Thrombotic microangiopathy (TMA) is defined clinically by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and ischemic organ injury.[1] The kidney is the most frequently injured organ. Other systems may also be affected, including the central nervous system, cardiovascular, respiratory, and gastrointestinal systems.[2] The definitive histological lesions and clinical findings of TMA result from several diseases. Therefore, the clinical term TMA refers to a group of conditions with these shared features.[3] TMA may develop in cases of reduced a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity, such as in thrombotic thrombocytopenic purpura (TTP). It may also occur in complement-mediated TMA (CM-TMA) due to dysregulation of the alternative pathway. This form is called atypical or CM-hemolytic uremic syndrome (aHUS). TMA can also occur secondary to infections, drugs, pregnancy-related disorders, such as preeclampsia, transplantation, malignancy, hypertension, and autoimmune disorders. These include systemic lupus erythematosus, antiphospholipid syndrome, scleroderma renal crisis, and vasculitides.[2]

Over the last decade, we observed TMA in two patients with systemic vasculitis. One patient had Takayasu arteritis. The other had granulomatosis with polyangiitis (GPA). Each case involved a different mechanism, which increased our interest in the topic.[4,5] In the case of Takayasu arteritis, malignant hypertension secondary to renal artery stenosis triggered TMA. Intensive antihypertensive treatment and renal artery stenting resolved the TMA. Immunosuppression was continued.[4] In the GPA case, disease activity caused TMA, which responded to rituximab.[5] Therefore, we inferred that TMA may develop in patients with vasculitis, either as a consequence of active disease or of secondary causes. Different causes require different treatment strategies, depending on the underlying mechanisms. A brief literature review found publications on TMA in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).[6,7] However, TMA in other vasculitides is not well-studied. Most reports are limited to case descriptions.[8-10] No comprehensive review has analyzed TMA features in different systemic vasculitides.

This systematic literature review aims to assemble all available cases of TMA in patients with systemic vasculitis, explore potential mechanisms of TMA, review therapeutic options, and analyze TMA outcomes, with an emphasis on histopathologically proven renal TMA.

Materials and Methods

We conducted this systematic literature review in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[11] The PRISMA Checklist is provided in the Supplementary Materials section. This review was not prospectively registered in International Prospective Register of Systematic Reviews (PROSPERO). This is acknowledged as a methodological limitation of this study.

Information Sources and Eligibility Criteria

We conducted a systematic literature review using the Cochrane Database, MEDLINE, Ovid, Scopus, and Web of Science. We considered studies published between January 1, 1950, and February 1, 2025, with no language restrictions. We included all patients with systemic vasculitides who showed clinical, laboratory, and/or histopathological features of TMA at or after diagnosis. TMA was diagnosed clinically based on either the classic triad—MAHA, thrombocytopenia, and ischemic organ injury—or histopathological features, as reviewed by Genest et al.[12] We also manually searched the reference lists of the collected literature for relevant articles. We excluded studies and case reports that did not provide details on clinical, laboratory, and histopathological features, treatment, and TMA outcome. Abstracts without full texts were omitted. We also excluded patients who developed features of vasculitis after an initial diagnosis of TMA. Grey literature was not included.

Search Strategy

The search strategy is presented in detail in the Supplementary Materials.

Selection Process, Data Collection Process, Data Items

Initially, two reviewers (Ege Sinan Torun and Selin Çelen) independently reviewed only the abstracts of all results. Following this review, they independently identified studies that met the screening criteria. The full texts of the selected abstracts were independently examined, and duplicates were removed to identify eligible studies. After a final assessment and discussion of studies not selected by both reviewers, the reviewers reached a decision and confirmed the studies to be included. The following data were collected from each selected study and recorded in a table: patient sex and age at the time of TMA diagnosis; type of the systemic vasculitis and its clinical and laboratory features; vasculitis activity at the time of TMA diagnosis (determined from information in each case report); clinical, laboratory, and histopathological features of TMA; TMA treatment; TMA outcome; and general outcome of the patient (if present). The activity status of vasculitis at the time of TMA and the possible etiologies of TMA were determined by interpreting information in each case report. In cases where the two reviewers did not agree on the status of vasculitic activity at the time of TMA and/or its etiology, a consensus was reached after discussion among the authors.

Statistical Method

For continuous variables, mean ± standard deviation, median (25-75%), and quartiles were used. Frequencies and percentages were used to describe categorical variables used. The IBM SPSS 25 statistical package was used.

Quality Assessment

The methodological quality of the included case reports was assessed by Ege Sinan Torun using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case reports. A single-assessor evaluation of this checklist is a methodological limitation of this systematic literature review.

Results

Our systematic literature review yielded 85 relevant manuscripts. Sixty-one cases of TMA in patients with systemic vasculitis were reported in 57 articles.[4,5,8-10,13-64] The flowchart of the systematic literature review is presented in Figure 1. Excluded cases and the reasons for their exclusion are presented in Supplementary Table 1.

Clinical Features of the TMA Cases Associated with Systemic Vasculitis

Descriptive features of TMA cases associated with systemic vasculitis are presented in Table 1. Forty patients were female and 21 were male. The mean age of the patients at the time of TMA diagnosis was 48.6±19.1 years (range, 10-84). Rheumatological diagnoses were as follows: microscopic polyangiitis in 12 patients, GPA in 11 patients, eosinophilic GPA in 7 patients, AAV in 1 patient, renal limited vasculitis in 1 patient, anti-glomerular basement membrane antibody disease in 3 patients, immunoglobulin A-associated vasculitis in 4 patients, cryoglobulinemic vasculitis associated with Sjögren syndrome in 1 patient, small vessel vasculitis in 2 patients, necrotizing vasculitis associated with monoclonal protein in 1 patient, polyarteritis nodosa in 3 patients, adenosine 2 deaminase deficiency in 1 patient, Takayasu arteritis in 1 patient, Behçet's disease in 3 patients, thromboangiitis obliterans in 1 patient, immune checkpoint inhibitor associated vasculitis in 1 patient, vasculitis associated with systemic lupus erythematosus in 5 patients, antiphospholipid syndrome in 1 patient and amyopathic dermatomyositis in 1 patient. Detailed information on the TMA cases associated with systemic vasculitis is presented in Supplementary Table 2.

The rheumatological diseases were active in 46 (75.4%) patients and inactive in 11 (18.0%). Information on disease activity was unavailable for 4 patients (6.6%). MAHA and thrombocytopenia were each present in 50 patients (82%), absent in 10 patients (16.4%), and unavailable in 1 patient (1.6%). Information on serum complement 3 and complement 4 levels was available for 16 and 13 patients, respectively. Serum complement 3 levels were low in 15 patients, and serum C4 levels were low in 9 patients. Thirty patients (49.2%) had biopsy-proven renal TMA. Sixteen patients (26.2%) did not have TMA on kidney biopsy. In 15 patients (24.6%), a kidney biopsy was not performed. Two patients had diffuse TMA observed in multiple organs. Two patients had TMA features on skin biopsy. TMA was observed on liver biopsy in 1 patient. One patient had TMA features in the cholecystectomy specimen. Twelve patients (19.7%) had neurological features associated with TMA. In 1 patient, details of neurological involvement were not specified. Alteration of consciousness was present in 3 patients; generalized tonic-clonic seizures were present in 2 patients; headache was present in 2 patients; mood changes were present in 2 patients; personality disorder, aphasia, and vision loss were each present in 1 patient. In one patient, the deterioration could also be associated with posterior reversible encephalopathy syndrome (PRES), which accompanied TMA. In one patient, grand mal seizure and coma were associated with hypertensive encephalopathy accompanying TMA, and in another patient, speech disturbance and disturbance of movement in the right upper extremity could also be associated with a small cerebral infarct accompanying TMA.

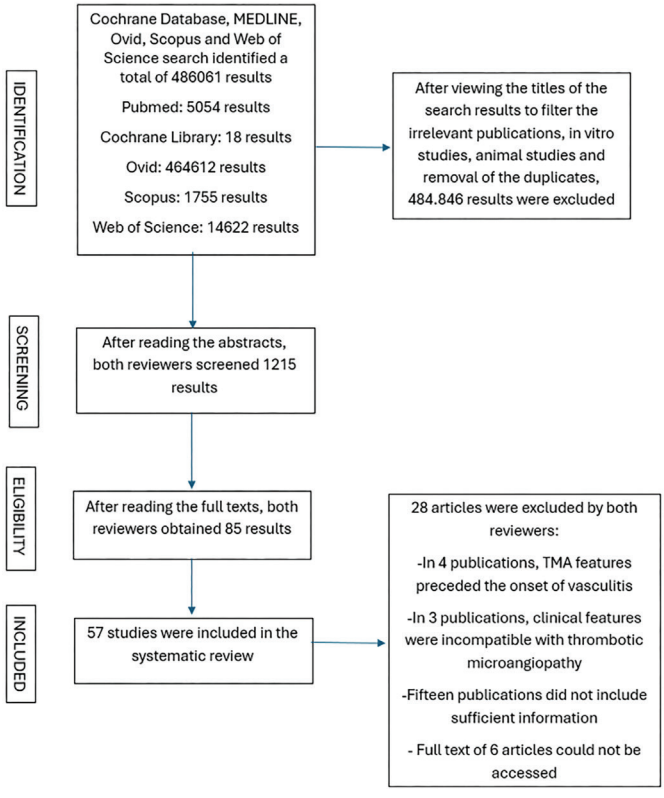

Figure 1. Flowchart
TMA: Thrombotic microangiopathy

Table 1. Descriptive features of cases of thrombotic microangiopathy associated with systemic vasculitis	
Sex	40 female, 21 male
Mean age	48.6±19.1 (minimum 10, maximum 84)
Vasculitis diagnoses of patients	- Microscopic polyangiitis (12 patients, 19.7%)-with accompanying systemic sclerosis in three patients, one of which is triggered by a silicone breast implant, - Granulomatous polyangiitis (11 patients, 18.0%), including one patient with a concurrent coronavirus-19 infection, - Eosinophilic granulomatous polyangiitis (7 patients, 11.5%), including one patient with concurrent systemic lupus erythematosus, - Antineutrophil cytoplasmic antibody-associated vasculitis (1 patient, 1.6%), - Renal-limited vasculitis (1 patient, 1.6%), - Anti-glomerular basement membrane antibody-associated disease (3 patients, 4.9%), including one patient with concomitant anti-proteinase 3 positivity and another with concomitant anti-myeloperoxidase positivity, - Immunoglobulin A-associated vasculitis (4 patients, 6.6%), - Cryoglobulinemic vasculitis associated with Sjögren syndrome (1 patient, 1.6%), - Small vessel vasculitis (2 patients, 3.3%), - Necrotizing vasculitis associated with monoclonal antibody (1 patient, 1.6%), - Polyarteritis nodosa (3 patients, 4.9%), - Adenosine deaminase 2 deficiency (1 patient, 1.6%), - Takayasu arteritis (1 patient, 1.6%), - Behçet's disease (3 patients, 4.9%), - Thromboangiitis obliterans (1 patient, 1.6%), - Immune checkpoint inhibitor-associated vasculitis (1 patient, 1.6%), - Systemic lupus erythematosus-associated vasculitis (5 patients, 8.2%)-with accompanying perinuclear antineutrophil cytoplasmic antibody positivity in one patient, accompanying antiphospholipid antibody positivity in one patient, and accompanying antiphospholipid syndrome in one patient, - Antiphospholipid syndrome (1 patient, 1.6%), - Amyopathic dermatomyositis (1 patient, 1.6%).
Vasculitis activity status	Active vasculitis in 46 patients (75.4%), inactive vasculitis in 11 patients (18.0%), insufficient data to assess disease activity in 4 patients (6.6%)

Table 2. Etiologies of thrombotic microangiopathy cases associated with systemic vasculitis	
Etiology	- Presumed vasculitic activity-31 patients (50.8%), - Thrombotic thrombocytopenic purpura-8 patients (13.1%): • Secondary to microscopic polyangiitis-2 patients, • Secondary to anti-glomerular basement membrane disease-2 patients, • Systemic lupus erythematosus (SLE)-1 patient, • SLE and eosinophilic granulomatous polyangiitis (EGPA)-1 patient, • Small-vessel vasculitis-1 patient, • Infection or clopidogrel-1 patient. - Atypical hemolytic uremic syndrome-5 patients (8.2%): • EGPA-3 patients, • Microscopic polyangiitis-1 patient, • Granulomatous polyangiitis-1 patient. - Presumed vasculitic activity and malignant hypertension-4 patients (6.6%), - Transplantation, tacrolimus use, and presumed vasculitic activity-2 patients (3.3%), - Malignant hypertension-1 patient (1.6%), - Preeclampsia-1 patient (1.6%), - Cyclosporine A and hypertension-1 patient (1.6%), - Vasculopathy (secondary to hypertension and possibly interferon signature)-1 patient (1.6%), - Micafungin use and cytomegalovirus (CMV) infection-1 patient (1.6%), - CMV infection-1 patient (1.6%), - Gemcitabine+carboplatin chemotherapy regimen-1 patient (1.6%), - Immune checkpoint inhibitors (combination of nivolumab and ipilimumab)-1 patient (1.6%), - Cyclosporine use-1 patient (1.6%), - Granulocyte colony-stimulating factor-1 patient (1.6%), - Early summer meningoencephalitis vaccine-1 patient (1.6%).

Among 30 biopsy-proven renal TMA cases, histopathological features were not specified for 10 patients. Thrombi and/or fibrin were detected in the lumen of glomerular capillaries or small arteries/arterioles in 13 patients. Thickening of capillary loops, double contouring of the basement membrane, thickened arterioles, and thickening and proliferation of the tunica intima were present in 8 patients; narrowing of the vessel lumen was noted in 8 patients; and intimal, endothelial, or subendothelial edema (swelling or expansion) was detected in 6 patients.

The etiology of TMA in each case is presented in Table 2. The most common etiologies were presumed vasculitic activity in 31 patients (50.8%), TTP in 8 patients (13.1%), and aHUS in 5 patients (8.2%). Other TMA etiologies included a combination of presumed vasculitic activity and malignant hypertension in 4 patients (6.6%) and a combination of transplantation, tacrolimus use, and presumed vasculitic activity in 2 patients (3.3%).

Treatment modalities for TMA are presented in Table 3. The main treatment modalities included glucocorticoids in 52 cases (85.2%), plasma exchange in 35 cases (57.4%), cyclophosphamide in 26 cases (42.6%), rituximab in 9 cases (14.8%), antihypertensive drugs in 9 cases (14.8%), eculizumab in 6 cases (9.8%), withdrawal of the offending drug in 6 cases (9.8%), and anticoagulation in 5 cases (8.2%).

Treatment modalities for TMA resulted in a complete response in 29 patients (47.5%), a partial response in 19 patients (31.1%), a poor response in 12 patients (19.7%), and in one patient, TMA was detected postmortem; therefore, that patient did not receive any treatment for TMA. Among thirty patients with TMA proven by kidney biopsy, creatinine returned to normal (with residual hematuria and/or proteinuria remaining in some cases) in 8 patients (26.7%), 5 patients (16.7%) had chronic and stable kidney disease; and 17 patients (56.6%) remained dialysis dependent. Eleven patients (18.0%) died ; 1 patient was diagnosed with TMA postmortem. Four patients passed away after deterioration of their general condition, 2 patients died suddenly, 2 patients experienced acute bowel perforation, 1 patient suffered myocardial infarction, and 1 patient died a few months after TMA onset due to urothelial malignancy.

Quality Assessment

Quality assessment of the included articles, according to the JBI Critical Appraisal Checklist for case reports, is presented in the Supplementary Materials section.

Table 3. Treatment modalities for thrombotic microangiopathy cases associated with systemic vasculitis

Treatment modalities	- Glucocorticoids-52 patients (85.2%), - Plasma exchange-35 patients (57.2%), - Cyclophosphamide-26 patients (42.6%), - Rituximab-9 patients (14.8%), - Antihypertensive drugs-9 patients (14.8%), - Eculizumab-6 patients (9.8%), - Withdrawal of the offending drug-6 patients (9.8%), - Anticoagulation-5 patients (8.2%), - Azathioprine-4 patients (6.6%), - Fresh frozen plasma transfusion-4 patients (6.6%), - Transfusion of other blood products-3 patients (4.9%), - Intravenous immunoglobulin-3 patients (4.9%), - Mycophenolate mofetil-3 patients (4.9%), - Acetylsalicylic acid-3 patients (4.9%), - Ganciclovir-2 patients (3.3%), - Delivery (birth)-2 patients (3.3%), - Renal artery stenting-1 patient (1.6%), - Cholecystectomy-1 patient (1.6%), - Infliximab-1 patient (1.6%), - Tocilizumab-1 patient (1.6%), - Dipyridamole-1 patient (1.6%), - Prostacyclin analogue-1 patient (1.6%).

Discussion

To our knowledge, no other systematic review has assembled TMA cases among multiple vasculitis subtypes. The relatively small number of cases indicates that the clinical and histopathological features of TMA are rarely observed in patients with systemic vasculitis. However, clinicians should remain vigilant for these TMA features, as they may also occur in patients with active vasculitis or history of vasculitis, albeit rarely. Currently, there are no specific treatment recommendations for patients with vasculitis and accompanying TMA.

TMA features secondary to TTP, aHUS, infections, medications, malignancy, transplantation, hypertensive emergencies, and pregnancy pathologies can also be observed in any patient, including patients with newly diagnosed active vasculitis or patients with a history of vasculitis. In this regard, the clinical approach and treatment modalities for these secondary TMA etiologies (such as plasma exchange for TTP, complement inhibition for aHUS, treatment of the underlying infection, malignancy, or hypertension, withdrawal of the causative medication, delivery, among others) do not seem to differ from those used in patients without clinical features or a history of vasculitis.[65,66]

The most important message of this review is that, in many of these vasculitis cases, underlying secondary causes of TMA were absent and clinical, laboratory, and histopathological features of TMA occurred in the context of presumed vasculitic activity. Among our 61 cases of vasculitis with associated TMA, the possible mechanism was presumed to be vasculitic activity in 31 cases (50.8%). It should be noted that in several of the cases in which we interpreted the possible mechanism of TMA as "presumed vasculitic activity", a necessary workup for the detection of TTP and aHUS was not performed. Therefore, we may have overestimated the percentage of TMA cases due to "presumed vasculitic activity". However, among 61 cases, 7 of the 8 TTP cases were presumed to be secondary to vasculitis, and all 5 of the aHUS cases were presumed to be associated with vasculitis. Endothelial damage is a core component of TMA.[3] In the clinical course of many vasculitic diseases, endothelial dysfunction and injury are key drivers in disease pathogenesis.[67-71] Therefore, endothelial damage induced by vasculitic activity may lead to features of TMA in genetically predisposed individuals. In cases where TMA was presumed to be due to vasculitic activity, including TTP and aHUS cases secondary to accompanying vasculitis, potent immunosuppressive treatments administered to appropriately control vasculitic activity also helped resolve the underlying TMA in most cases. As our preliminary literature review suggested, TMA was most often observed in AAV cases. Among the 61 cases, 31 (50.8%) had concomitant AAV. In the study by Dellal et al.[72], among 8 vasculitis patients, 4 were diagnosed with AAV. In addition, a series by Chen et al.[6] reported 30 histopathologically confirmed renal TMA cases among 220 AAV patients, and Manenti et al.[7] reported 8 histopathologically confirmed TMA cases among 46 AAV patients. Therefore, we hypothesize that complement activation and endothelial injury, both of which are important for AAV pathogenesis,[73] can also lead to TMA in some genetically predisposed patients. However, TMA can also be observed in other vasculitides, albeit less frequently. Identifying the factors that predispose some vasculitis patients to develop TMA features during active disease episodes will be a promising area for future research, and, given the rarity of TMA in vasculitis patients, global collaboration among multiple vasculitis centers may be necessary.

MAHA, thrombocytopenia, and ischemic organ injury are key features of TMA.[1] Hematological features of TMA are widely recognized by clinicians. However, these features may not accompany histopathological TMA in some cases, and the kidney is the most frequently injured organ in TMA.[2] A case series of AAV demonstrated histopathologically proven renal TMA to be associated with poor renal survival and high risk of progression to end-stage renal disease.[6,7] Among the 61 cases of TMA associated with vasculitis that we have assembled, 30 patients (49.1%) had renal biopsy findings compatible with TMA. Creatinine levels normalized in only 8 cases, and 17 patients became dialysis dependent. As in the case series reported by Chen et al.[6] and Manenti et al.[7], the renal prognosis was poor among these patients. Data from Chen et al.'s[6] study demonstrated that renal TMA was associated with all-cause mortality, whereas the data from Manenti et al.'s[7] study found no association between TMA and hazard of death. The creation of global databases for reporting TMA cases associated with vasculitis, specifically ANCA-associated vasculitis, and the long-term clinical follow-up of these patients may provide further information on this potentially significant subject. However, histopathological TMA is not confined to the kidneys. Among 61 cases, TMA features were observed in multiple organs in 2 patients, on skin biopsy in 2 patients, in liver biopsy in 1 patient, and in cholecystectomy material in 1 patient. Therefore, pathologists should also be vigilant for TMA features in other organs in appropriate settings, including patients with active systemic vasculitis and/or a history of vasculitis. Neurological involvement related to TMA was present in approximately 20% of cases, although it was not histopathologically confirmed. In three patients, concomitant etiologies of the neurological symptoms were identified: PRES, cerebral infarct, and hypertensive encephalopathy. In an observational cohort of 49 patients with a first TMA event between 1995 and 2016, neurological manifestations were observed in 42 patients (85.7%) Most of them were considered severe, including confusion, personality changes, sensorimotor loss, seizures, stupor or coma, and ischemic or hemorrhagic stroke. Authors highlighted that, while the effect of neurological

manifestations on the acute clinical course of TMA appears modest, these manifestations may have an important impact on the development of chronic cognitive impairment.[74] In their retrospective cohort study of adult patients hospitalized at a tertiary center between January 2004 and October 2016 who were diagnosed with TTP, HUS, and aHUS, Weil and Rabinstein[75] analyzed a total of 42 TTP, 16 HUS, and 20 aHUS episodes in 37 TTP, 16 HUS, and 15 aHUS patients. They reported that at least one neurologic symptom was observed in 83% of TTP episodes and 88% of HUS episodes, but in aHUS patients in only 35% of episodes; neurologic symptoms were less likely to be present in aHUS than in TTP ($p<0.001$) or classic HUS ($p=0.002$). The most common neuroimaging finding was PRES (observed in 8 episodes of TTP, 4 episodes of HUS, and in both episodes of aHUS). Most patients had favorable long-term outcomes. Among the TMA features in the vasculitis patients we assembled, the percentage with neurological symptoms was somewhat lower. This may be due to the low percentage of TTP and aHUS cases among the patients with systemic vasculitis we have assembled.

No studies have evaluated the treatment of AAV cases presenting with clinical and/or histopathological features of TMA. However, most AAV cases can cause rapidly progressive glomerulonephritis, and therapeutic plasma exchange is recommended in this scenario.[76] Plasma exchange is the cornerstone of TTP treatment and can be used for many TMA etiologies.[2] Thus, plasmapheresis could be considered in AAV cases with TMA, even if they do not present with clinical features of rapidly progressive glomerulonephritis.

Among the 61 cases of vasculitis with accompanying TMA, 15 patients had low complement 3 levels and 9 patients had low complement 4 levels. Therefore, one can hypothesize that complement activation occurs during the development of TMA in some patients with systemic vasculitis, leading to consumption of serum complement 3 and/or complement 4. It is well established that complement inhibition with eculizumab is the treatment of choice for CM-TMA observed in aHUS. There is also rationale to use this treatment modality in other types of secondary TMA, including TMA secondary to autoimmune diseases.[67] Therefore, complement inhibition with eculizumab may also have a role in the treatment of TMA cases secondary to active vasculitis. Both therapeutic plasma exchange and complement inhibition can also help control vasculitic activity and mitigate TMA features. However, data demonstrating the efficacy and safety of therapeutic plasma exchange and/or eculizumab, when used in addition to immunosuppressive treatment, for TMA cases secondary to presumed vasculitic activity are needed before further recommendations can be made.

Study Limitations

A limitation of this review is our arbitrary determination of possible mechanisms of TMA in some cases. The low number of cases, the lack of assessment of ADAMTS13 activity and complement regulatory factors in many cases, the nature of the included publications (all case reports), and the relatively low prevalence of TMA among patients with systemic vasculitis are additional limitations of this review. Since this review is based exclusively on published case reports, publication bias is an additional limitation: cases with favorable, dramatic, or unusual outcomes are likely overrepresented, while unremarkable or fatal cases may remain unpublished. The absence of registration of this systematic literature review in PROSPERO and the single-assessor evaluation using the JBI Critical Appraisal Checklist are additional methodological limitations.

Conclusion

Physicians should be vigilant for the clinical, laboratory, and histopathological features of TMA in patients with active or prior systemic vasculitis. Once TMA features are detected, careful history-taking and appropriate laboratory tests are necessary to determine the etiology and detect secondary causes, such as TTP, aHUS, drug-induced TMA, infection-associated TMA, hypertensive emergencies, pregnancy-related pathologies, malignancy, and transplantation-associated TMA. If TMA features develop in the context of new-onset systemic vasculitis or during a vasculitis relapse, disease activity may be a trigger and an etiologic factor for TMA, especially in AAV patients. Although there are no guidelines for the management of concomitant TMA during the treatment of systemic vasculitides, plasma exchange is frequently performed in addition to immunosuppressive therapies, and in some cases, complement inhibition may be beneficial. Biopsy-proven renal TMA may be associated with a poor renal outcome and possibly with increased mortality.

Footnotes

Author Contributions

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Recommendations of the Turkish Society for Rheumatology on tuberculosis screening and treatment in patients receiving advanced antirheumatic drug therapy

Gelişmiş antiromatizmal ilaç tedavisi alacak hastalarda tüberküloz taraması ve tedavisi için Türkiye Romatoloji Derneği önerileri

Cemal Bes[1], Rabia Deniz[1], Mustafa Ekici[2], Ufuk İlgen[3], Burak İnce[4], Zehra Özsoy[5], Şerife Çoşkun Sağırkaya[6], Mehmet Soy[7], Veli Yazısız[8], Şükran Erten[9], Timuçin Kaşifoğlu[10], İhsan Ertenli[2]

[1]University of Health Sciences, Başakşehir Çam and Sakura City Hospital, Clinic of Rheumatology, İstanbul, Türkiye
[2]Hacettepe University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
[3]Mersin University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Mersin, Türkiye
[4]İstanbul University, İstanbul Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye
[5]Başkent University Faculty of Medicine, Ankara Hospital, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
[6]Ankara Bilkent City Hospital, Clinic of Rheumatology, Ankara, Türkiye
[7]Altınbaş University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye
[8]Akdeniz University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Antalya, Türkiye
[9]Ankara Yıldırım Beyazıt University, Ankara Bilkent City Hospital, Department of Rheumatology, Ankara, Türkiye
[10]Eskişehir Osmangazi University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Eskişehir, Türkiye

Abstract

Tuberculosis (TB) remains a significant public health concern in endemic countries despite widespread Bacillus Calmette-Guérin vaccination. In rheumatology practice, biologic and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) alter immune responses and increase the risk of reactivation of latent TB infection or development of new TB. Therefore, appropriate screening, treatment, and follow-up strategies before, during, and after initiation of advanced therapies are essential. These recommendations were developed by the Tuberculosis Working Group of the Turkish Society for Rheumatology through a systematic literature review, an evaluation of national and international guidelines, and a Delphi consensus process involving 12 experts. The recommendations address key clinical questions, including the definition of latent TB, the interpretation of the tuberculin skin test and the interferon-gamma release assay, the selection and duration of treatment regimens, management during pregnancy and lactation, the approach to patients with prior TB, and the management of TB occurring during advanced therapies. Isoniazid is

Özet

Tüberküloz (TB), Bacillus Calmette-Guérin aşılamasına rağmen ülkemizde önemini koruyan bir halk sağlığı sorunudur. Romatolojik hastalıkların tedavisinde kullanılan biyolojik ve hedefe yönelik sentetik hastalık modifiye edici antiromatizmal ilaçlar (b/tsDMARD'ler), immün yanıtı baskılamaları nedeniyle latent tüberkülozun reaktivasyonu ve yeni TB gelişimi açısından ek risk oluşturur. Bu nedenle gelişmiş tedavi öncesinde, sırasında ve sonrasında uygun tarama, tedavi ve izlem stratejilerinin belirlenmesi kritik öneme sahiptir. Türkiye Romatoloji Derneği Tüberküloz Çalışma Grubu tarafından hazırlanan bu öneriler, sistematik literatür taraması, ulusal ve uluslararası kılavuzların incelenmesi ve 12 uzmanın katıldığı Delphi konsensus süreci ile oluşturulmuştur. Rehber; latent tüberküloz tanımı, tüberkülin deri testi ve interferon gamma salınım testlerinin kullanımı ve yorumlanması, latent tüberküloz tedavi rejimleri ve süreleri, gebelik ve emzirme döneminde yaklaşım, geçirilmiş TB öyküsü olan hastalarda izlem, gelişmiş tedavi altında TB gelişimi ve yeniden tedavi planlaması gibi başlıkları kapsamaktadır. Latent tüberküloz saptanan hastalarda öncelikli

Correspondence / İletişim: Cemal Bes Prof. MD,
University of Health Sciences, Başakşehir Çam and Sakura City Hospital, Clinic of Rheumatology, İstanbul, Türkiye
E-mail: cemalbes@hotmail.com **ORCID ID:** orcid.org/0000-0002-1730-2991
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Abstract

recommended for nine months as the first-line treatment, with alternative options specified for particular clinical scenarios. The timing of advanced therapy initiation relative to latent TB treatment should be individualized based on disease activity and TB risk assessment. These recommendations aim to provide clinicians with a practical roadmap for latent and active TB screening and management in patients receiving b/tsDMARD treatments, and are consistent with national data.

Keywords: Latent tuberculosis, biologic therapy, bDMARD, tsDMARD, anti-TNF, IGRA, tuberculin skin test, rheumatic diseases, Delphi consensus

Özet

latent tüberküloz tedavi rejimi izoniazid 9 ay olarak önerilmiş, alternatif şemalar tanımlanmıştır. Latent tüberküloz tedavisi ve gelişmiş tedavilerin zamanlamasının hastalık aktivitesine göre planlanması önerilmiştir. Bu rehber ile, b/tsDMARD tedavilerinde latent ve aktif TB tarama ve yönetimi hakkında klinisyenlere pratik ve ulusal verilerle uyumlu bir yol haritası sunulması amaçlanmıştır.

Anahtar Kelimeler: Latent tüberküloz, biyolojik tedavi, bDMARD, tsDMARD, anti-TNF, IGRA, tüberkülin deri testi, romatolojik hastalıklar, Delphi konsensus

Introduction

Tuberculosis (TB) remains an important public health problem in countries where it shows endemic characteristics despite Bacillus Calmette-Guérin (BCG) vaccination.[1] Advanced therapies used in the treatment of rheumatologic diseases, namely biologic and targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs and tsDMARDs), may create an additional risk for the development of TB or reactivation of latent TB infection due to their effects on the immune response.[2] Therefore, it is essential to define appropriate screening, adequate treatment for latent TB, and safe follow-up strategies before, during, and after advanced therapy.

On behalf of the Turkish Society for Rheumatology (TSR), the Tuberculosis Working Group planned to develop practical and applicable recommendations that are consistent with scientific evidence and national real-life data, while taking into account the conditions of Türkiye, to address clinical problems frequently encountered in rheumatology practice related to TB. The aim in developing these recommendations is to provide up-to-date, consistent, and practical information on latent TB screening, definitions, and treatment approaches for patients who will receive b/tsDMARD agents. In addition, it is intended to create a guide to assist clinicians in (a) the follow-up of patients receiving b/tsDMARD therapy with respect to TB risk, and (b) the determination of treatment strategies for patients diagnosed with latent or active TB.

Materials and Methods

Study Group

These recommendations were developed with participation from members of the "Tuberculosis Working Group" established by the TSR. Twelve rheumatology specialists participated in the group. All participants declared potential conflicts of interest. This study is based on a systematic literature review and expert opinion; it does not include patient or public participation.

Development of Clinical Questions

Thirteen research questions were identified concerning TB-related issues that are frequently encountered and difficult to resolve in rheumatology practice. These questions cover focus areas such as latent TB screening, interpretation of the tuberculin skin test (TST) or interferon-gamma release assay (IGRA), duration of latent TB treatment and drug selection, approach during pregnancy and lactation, follow-up of patients with a history of TB, and the interaction between advanced therapies and TB. To structure clinical decision-making, all guideline questions were addressed using the PICO system.

The PICO questions that need to be answered regarding TB in rheumatology practice are listed below:

Question 1: What is the definition of latent TB?

Question 2: What are the screening methods? Which of the TST, IGRA, chest radiography should be used? Which should be chosen: TST or IGRA test? What are the advantages over each other?

Question 3: What should be the TST cut-off value for the definition of latent TB?

Question 4: Latent TB treatment: which drug should be used and for how long?

Question 5: What should be the screening and latent TB treatment approach in pregnant and breastfeeding women?

Question 6: What is the duration of protection in patients receiving treatment for latent TB? Is repeat treatment necessary; after how many years should it be repeated?

Question 7: How should screening be performed in patients receiving immunosuppressive drugs?

Question 8: If b/tsDMARD therapies are to be initiated in patients who have previously had TB, how should TB screening and treatment be performed?

Question 9: In patients receiving b/tsDMARD therapy, how frequently and how should patients be screened in terms of TB frequency and development?

Question 10: In patients who develop TB under b/tsDMARD therapy, how should anti-TB treatment be managed, and if advanced therapy is to be restarted, what should be the timing and drug selection?

Question 11: In patients who have received TB treatment or completed latent TB treatment, what should be the follow-up protocol and screening approach?

Question 12: After initiating latent TB treatment, when can b/tsDMARD therapies be started, and can latent TB treatment and b/tsDMARD therapies be given simultaneously?

Question 13: Is there a difference between drugs in terms of TB development risk in b/tsDMARD therapies?

Literature Search

In line with the defined questions, a systematic search was conducted in PubMed, Scopus, and Web of Science, and national guidelines, international recommendations, and real-life data were reviewed.

Delphi Consensus Process

For each PICO question, draft recommendations were prepared by combining evidence from the literature with experts' experience. All group members expressed their opinions on the draft recommendations, which were then finalized. The recommendations were submitted to Delphi voting within the group and scored using a Likert scale (1: strongly disagree - 5: strongly agree). The level of agreement for each recommendation was provided.

Recommendations

This section presents the recommendations and summaries that the working group developed and agreed upon by combining the systematic literature review conducted within the scope of the research questions with expert opinions.

1. What is the Definition of Latent TB?

Recommendation 1: It is defined as cases without clinical complaints or findings related to TB, having positive IGRA or TST results indicating prior encounter with the TB bacillus, typically having normal chest radiographs, or, in those with abnormal chest radiographs, cases in whom active TB has been excluded by appropriate methods (agreement score: 5.0).[1,2]

2. Recommendations for Latent TB Screening

2.1. How should patients be screened for latent TB before receiving advanced therapy?

Recommendation 2: For latent TB screening, TST or IGRA testing should be performed in addition to chest radiography (agreement score: 5.0).[3-6]

2.2. Which test should be preferred in latent TB screening?

Recommendation 3: TST or IGRA may be preferred in latent TB screening, and there is no drawback in using either of them; however, if available, IGRA should be preferred (agreement score: 5.0).[7-14]

IGRA should be preferred in latent TB screening because it shows high specificity and sensitivity and is less affected by BCG vaccination.[5,6,15-22]

2.3. What should be the approach according to the TST result before advanced therapy?

Recommendation 4: When TST is preferred as the first test in latent TB screening, induration of 5 mm and above is accepted as positive and treatment for latent TB is given (agreement score: 4.83).[23-25]

Recommendation 5: In cases with induration below 5 mm, IGRA or repeat TST (booster) after 1-3 weeks is recommended (agreement score: 4.83).[24-26]

2.4. When should screening tests be repeated in patients with negative TST and/or IGRA before advanced therapy?

Recommendation 6: In high-risk patients receiving bDMARD or tsDMARD therapy whose initial screening TST or IGRA is negative, repeat latent TB screening is recommended after the first year following physician evaluation (agreement score: 4.92).[27-31]

2.5. What should be done in patients found to have a positive follow-up screening test?

Recommendation 7: If positivity is detected in the repeated test, latent TB treatment should be given (agreement score: 4.92).[19,32,33]

Recommendation 8: It is appropriate that screening be performed primarily with IGRA blood tests, and if access is not available, by using TST (agreement score: 5.0).[27-31]

2.6. How should patients with unclear treatment information for latent TB or previous active TB be approached?

Recommendation 9: In patients with positive TB screening tests whose treatment history for latent TB is unclear or who have not received treatment, with no findings of active TB infection at the current visit, a standard latent TB treatment regimen should be planned by approaching them as if latent TB were present (agreement score: 4.83).

3. Drug Options and Duration of use for Latent TB Treatment

3.1. Which drug should be used for latent tb treatment and for how long? What should be the priority of isoniazid (INH), rifampicin (RIF), pyrazinamide (PRZ), and ethambutol (ETB) options in treatment?

Recommendation 10: For latent TB treatment, INH monotherapy should be given as the first option at a dose of 300 mg/day for 9 months (agreement score: 4.92).[3,34-37]

Recommendation 11: Even if the advanced antirheumatic agent is discontinued, if latent TB treatment has been started, it should be completed if possible (agreement score: 5.0).[37]

As long as they are receiving INH, neuropathy prophylaxis with pyridoxine supplementation is recommended for patients (agreement score: 4.83).

3.2. What should be the alternatives, drug combinations, and recommended duration in patients who cannot receive INH?

Recommendation 12: In patients who cannot use INH, the first alternative should be RIF 600 mg/day as a treatment for 4 months treatment (agreement score: 4.92).[3,34,36-39]

Recommendation 13: Alternatively, the combination of RIF 600 mg + INH 300 mg for 3 or 4 months, INH 900 mg once weekly and rifapentine 900 mg once weekly as a 3 months combination, daily combination of RIF and PRZ for 2 months with attention to hepatotoxicity, or the combination of levofloxacin (1000 mg/day) or moxifloxacin (400 mg/day) with ETB (2000 mg/day) or ethionamide (750 mg/day) for 6 months may be given (agreement score: 4.92).[3,27,34,36,37,39-46]

4. How Should Screening be Performed When Advanced Antirheumatic Therapy Will be Initiated in Patients Who Have Had TB?

Recommendation 14: In patients who have previously had TB, tests such as TST and IGRA are not appropriate for screening; screening for active TB should be performed using clinical, laboratory, and imaging methods (agreement score: 5.0).[37]

5. Follow-up Recommendations in Patients Who Have Received Latent TB Treatment

5.1. For how long is this treatment considered protective in patients who have received latent TB treatment?

Recommendation 15: Those who complete INH monotherapy for 6 months are considered protected for 7 years; those who complete 9 months are considered protected for 10 years; and those who complete uninterrupted TB treatment of appropriate duration according to organ involvement are considered protected for 10 years (agreement score: 4.92).[47-53]

Recommendation 16: In patients who have completed latent TB treatment, protection has been shown to continue for more than 10 years, and there are no data regarding the administration of repeat treatment (agreement score: 4.92).[54]

Recommendation 17: Re-treatment is recommended in individuals who are approaching the end of the specified periods and who are in high socioeconomic-risk conditions/high-risk populations for TB contact/activation (high-risk population: if there is an active TB case in the immediate environment such as home or workplace, history of imprisonment, substance use, military barracks living, daily use of public transportation...) (agreement score: 4.83).[37]

Recommendation 18: Advanced therapy may be started directly in patients with a history of completed TB treatment within 10 years (the durations given above) and without findings suggestive of TB infection (agreement score: 4.92).[54,55]

5.2. How should the adequacy and effectiveness of treatment given for latent TB be evaluated?

Recommendation 19: Whether TB treatment has been received appropriately, uninterruptedly, and for a sufficient duration should be verified with TB Dispensary records and patient documents (agreement score: 4.83).[37]

5.3. When can bDMARD or tsDMARD therapy be started after initiating latent TB treatment?

Recommendation 20: In patients in whom latent TB is detected and treatment for it is started, bDMARD or tsDMARD should be started 4 weeks later if rheumatologic disease activity permits (agreement score: 4.92).[32,34,36,37,56]

5.4. Can latent TB treatment and bDMARD or tsDMARD therapy be given simultaneously?

Recommendation 21: If there is severe rheumatologic disease activity, bDMARD or tsDMARD therapy may also be started together with latent TB treatment without waiting 4 weeks; however, close follow-up with clinical, laboratory, and when necessary imaging is recommended in terms of TB development (agreement score: 5.0).[28,34,57]

Recommendation 22: According to real-life data from Türkiye, since no TB flare was observed in patients in whom latent TB treatment and b/tsDMARD were started simultaneously, latent TB treatment and advanced therapies may be started simultaneously in patients with severe rheumatologic activity and in whom active TB infection has been shown to be absent (agreement score: 4.92).

6. Is There a Difference Between bDMARD or tsDMARDs in Terms of the Risk of TB Development?

Recommendation 23: Among biologic drugs, the risk of TB development is higher in the anti-tumour necrosis factor-α (TNF-α) drug group than in non-anti-TNF-α drugs (agreement score: 4.92).[28,29,31,58,59]

Recommendation 24: Within the anti-TNF-α class, the risk of TB development under chimeric (infliximab), monoclonal antibody (adalimumab, golimumab), and pegylated anti-TNF-α

(certolizumab) treatment is higher than with the TNF-α receptor fusion protein (etanercept) (agreement score: 4.92).[28,30,38,60-62]

Recommendation 25: Among drugs outside the anti-TNF-α group, the risk of TB development from highest to lowest is as follows: Janus kinase inhibitors (tsDMARD group drugs: tofacitinib, baricitinib, upadacitinib), interleukin-6 (IL-6) antagonists (tocilizumab, sarilimumab, calakizumab), cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor (abatacept), IL-1 antagonists (anakinra and canakinumab), anti-CD-20 (rituximab), anti-IL-17 (ixekizumab, secukinumab), rituximab, anti-IL-17 (ixekizumab, secukinumab), ustekinumab, and IL-23 inhibitors (guselkumab, risankizumab) (agreement score: 4.75).[2,28,63-83]

7. Active TB Evaluation and Management

7.1. How should patients be approached if there is suspicion of active TB?

Recommendation 26: The presence of active TB clinical findings should be investigated with imaging, clinical, and laboratory examinations (agreement score: 5.0).[3]

Recommendation 27: If there is suspicion of active TB in patients receiving bDMARD or tsDMARD therapies, advanced therapies should be discontinued until the investigations are completed (agreement score: 4.92).[3]

Recommendation 28: If there is active disease, the patient should be evaluated with the relevant specialties in order to restart TB treatment, and advanced therapy should not be given until TB is controlled (agreement score: 4.92).[84]

7.2. In patients who develop TB while receiving bDMARD or tsDMARD drug treatment, how should anti-TB treatment be managed; if bDMARD and tsDMARD therapies are to be restarted, what should be the timing and drug selection?

Recommendation 29: In patients who develop TB under bDMARD or tsDMARD drug treatment, anti-TB treatment is initiated in accordance with the National Tuberculosis Diagnosis and Treatment Guideline (agreement score: 5).[3,34,37]

Recommendation 30: If advanced therapy is to be restarted in patients who develop TB, completion of TB treatment is recommended first. In patients with high disease activity, b/tsDMARD agents may be given at the earliest 2 months after TB treatment has been started (agreement score: 4.92).[27,85]

7.3. How should antirheumatic drug selection be made in patients who develop TB under bDMARD and tsDMARD therapies?

Recommendation 31: Drugs carrying a lower risk in terms of TB reactivation should be preferred in patients. Monoclonal anti-TNF antibodies are associated with a higher risk of TB than receptor fusion proteins. The TB risk associated with tocilizumab (anti-IL-6), abatacept, ustekinumab, secukinumab, apremilast, and rituximab is lower compared with anti-TNF group drugs (agreement score: 5).[2,66,86-92]

8. What Should be the Long-term Follow-up Protocol, Screening, and Re-treatment Approach in Those Who Complete TB Infection or Latent TB Treatment?

Recommendation 32: In those who complete TB infection treatment or latent TB treatment, follow-up with physical examination every 3 months and, if necessary, further evaluation directed to the affected system is recommended. In these patients, TST and IGRA are not recommended because they do not assist in diagnosis. TB activity should be sought according to clinical, laboratory, and imaging methods (agreement score: 4.75).[37,66]

Recommendation 33: If active TB is detected, anti-TB treatment is given. If active disease has not been detected but there is a suspicious situation in terms of previous treatment and re-infection, the patient should be re-evaluated by the relevant specialist in terms of preventive treatment (agreement score: 4.92).[37]

9. Recommendations for Special Groups

9.1. How should latent TB screening be performed in pregnant women?

Recommendation 34: TST and IGRA tests are safe for latent TB screening in pregnant women, and both methods may be used (agreement score: 4.83).[26,93-95]

9.2. How should latent TB treatment be performed in pregnant women?

Recommendation 35: In pregnant women diagnosed with latent TB and planned to receive bDMARD treatment, INH treatment for 9 months is the first choice for treatment. These patients should be followed closely in terms of hepatotoxicity risk, and daily 25-50 mg pyridoxine prophylaxis is recommended due to the risk of peripheral neuropathy (agreement score: 4.92).[96-100]

Recommendation 36: In pregnant women who cannot use INH, RIF treatment may be used as an alternative.[97,99,101] Administration of vitamin K at birth is recommended for newborns exposed to RIF during pregnancy because of the risk of "hemorrhagic disease of the newborn" (agreement score: 4.92).[102-104]

9.3. How should latent TB screening be performed in breastfeeding mothers?

Recommendation 37: In breastfeeding patients, TST or IGRA tests may be used for latent TB screening similarly to the normal population (agreement score: 4.92).

9.4. How should latent TB treatment be performed in breastfeeding mothers?

Recommendation 38: In breastfeeding patients with latent TB detected and planned to receive bDMARD treatment, use of INH for 9 months should be preferred as the first choice for treatment.[105,106] During treatment, use of pyridoxine prophylaxis is recommended for both the mother and the infant (agreement score: 4.92).[107]

Recommendation 39: In breastfeeding patients in whom use of INH is not appropriate, RIF treatment may be preferred as an alternative (agreement score: 4.92).[108,109]

Discussion

This set of recommendations was prepared to guide clinicians in assessing TB-related risks, performing appropriate screening, and determining treatment protocols for patients for whom b/tsDMARD therapy is planned or who have already started these treatments. Türkiye's conditions regarding TB were considered, and recommendations were developed by combining evidence from the literature with approximately twenty-five years of experience in the use of biologic agents. Overall, the mean agreement scores for the recommendations are high. The application of the recommendations to each patient is possible only if the individual and medical characteristics of the patient are taken into account, and the preference of the clinician following the patient should take priority.

In Türkiye, the Ministry of Health's Tuberculosis Diagnosis and Treatment Guideline is updated periodically. The most recent update was made in 2019.[37] The TB guideline for patients using biologic agents was prepared in 2016 to include only anti-TNF drugs.[110] The guideline published in 2016 was prepared with relatively limited clinical experience, based only on anti-TNF drugs, and reflected the opinions and recommendations of chest diseases and TB specialists interested in TB rather than rheumatology specialists. Over the past ten years, the diversity of bDMARDs has increased, tsDMARDs have become widely used, and new scientific evidence regarding TB data in patients using these agents has been published in many sources, including registries. In this set of recommendations, those related to anti-TNF agents (infliximab, adalimumab, golimumab, certolizumab, and etanercept) were updated, and the recommendations were also expanded to include other bDMARDs such as IL-6 antagonists (tocilizumab, sarilimumab, calakizumab), the CTLA-4 inhibitor (abatacept), IL-1 antagonists (anakinra and canakinumab), anti-CD-20 (rituximab), anti-IL-17 (ixekizumab, secukinumab), IL-23 and 12/23 inhibitors (guselkumab, risankizumab, ustekinumab), and Janus kinase inhibitors in the tsDMARD category (tofacitinib, baricitinib, upadacitinib). In the guideline published in 2016, TST and IGRA were considered to have similar effectiveness for latent TB screening, and the preferential use of IGRA was recommended only for patients with psoriasis. In our study, IGRA tests were prioritized, when available, before all b/tsDMARDs because they show high specificity and sensitivity in latent TB screening and are less affected by BCG vaccination. In addition, recommendations were presented regarding TB screening, treatment, and bDMARD use in special situations such as pregnancy and lactation.

European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR), the largest professional organizations in the field of rheumatology, publish guidelines on many issues, including diagnosis, treatment, and associated conditions of rheumatic diseases. These organizations have also provided recommendations on TB at different times. In 2022, EULAR presented recommendations for screening and prophylactic treatment for chronic and opportunistic infections including TB.[3,34] In this set of recommendations, the primary emphasis regarding TB is to follow national guidelines because of differences in BCG vaccination, TB burden, and drug resistance. ACR's approach, on the other hand, has been to implement Centers for Disease Control and Prevention (CDC) and American Thoracic Society (ATS) recommendations. ATS and CDC recommendations were developed based on TB data in the United States of America.[111] Our recommendations were also prepared to guide physicians in Türkiye, based on TB data in Türkiye, BCG vaccination, and clinical experience. National TB data may change over time. Therefore, the National Tuberculosis Guideline, published and revised over the years by the Republic of Türkiye Ministry of Health, Turkish Public Health Institution, should be followed, and updates to the recommendations should be considered when necessary.

The use of drugs that increase the risk of TB and TB activation or reactivation is not solely of interest to rheumatology specialists. However, rheumatology is the specialty that uses b/tsDMARDs most widely, for the longest time, and with the greatest experience. Gastroenterology, dermatology, and ophthalmology, which are involved in the treatment of diseases with inflammation-based pathogenesis, have an undeniable interest in this subject. Although prepared by a working group composed solely of rheumatology specialists, these recommendations will guide the management of latent and active TB in other specialties that use b/tsDMARDs as much as in rheumatology. One of the most important limitations of this set of recommendations is that chest and infectious disease

specialists experienced in TB management and representatives from other scientific fields experienced in the use of b/tsDMARDs were not included in the working group. It is our hope that a national consensus report will be prepared by a working group formed with participation from all parties involved.

Conclusion

In conclusion, this set of recommendations was prepared as a guiding source on TB screening and treatment for clinicians managing patients receiving bDMARD and tsDMARD agents in Türkiye.

Footnotes

Author Contributions

Concept: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E., Design: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E., Data Collection and Processing: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E., Analysis or Interpretation: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E., Literature Search: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E., Writing: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E.

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Türkiye Romatoloji Derneği 2026 erişkin romatoloji hastalarında aşı önerileri

Turkish Society for Rheumatology 2026 vaccine recommendations for adult rheumatology patients

Ahmet İlbay[1], Emine Uslu[2], Serdar Sezer[2], Müçteba Enes Yayla[2], Derya Kaşkari[3], Ahmet Usta[2], Çetin Ergül[4], Melis Dilbil[5], Feyza Şahan Gürpınar[6], Özge Us[7], Hüsna Çevik[8], Elif Nur Özbay Haliloğlu[9], Güle Çınar[10], Nuran Türkçapar[11]

[1]*Kütahya Şehir Hastanesi, Romatoloji Kliniği, Kütahya, Türkiye*
[2]*Ankara Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Ankara, Türkiye*
[3]*Başkent Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İstanbul, Türkiye*
[4]*Ankara Bilkent Şehir Hastanesi, Romatoloji Kliniği, Ankara, Türkiye*
[5]*Sultan 1. Murat Devlet Hastanesi, Romatoloji Kliniği, Edirne, Türkiye*
[6]*Şanlıurfa Mehmet Akif İnan Eğitim ve Araştırma Hastanesi, Romatoloji Kliniği, Şanlıurfa, Türkiye*
[7]*T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü, Aile Hekimliği Eğitim ve İzleme Dairesi, Ankara, Türkiye*
[8]*Ankara Üniversitesi Tıp Fakültesi, Aile Hekimliği Anabilim Dalı, Ankara, Türkiye*
[9]*Sincan Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, Ankara, Türkiye*
[10]*Ankara Üniversitesi Tıp Fakültesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Ankara, Türkiye*
[11]*Ankara Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Emekli Öğretim Üyesi, İstanbul, Türkiye*

Özet

Amaç: Erişkin romatoloji hastalarında, hastaların tıbbi durumu göz önünde bulundurularak aşı ile önlenebilir hastalıklara karşı kanıta dayalı ve uzman görüşlerini içeren bir aşı rehberi oluşturmaktır.

Yöntem: Türkiye Romatoloji Derneği tarafından görevlendirilen ekip tarafından, romatolojik hastalıklar, tedavileri, aşıyla önlenebilir hastalıklar ve aşılara ilişkin klinik sorular popülasyon, müdahale, karşılaştırma ve sonuç (PICO) formatında geliştirildi. Her PICO sorusu için sistematik literatür incelemeleri yapıldı. Kanıt kalitesini değerlendirmek ve önerileri formüle etmek için *Grading of Recommendations Assessment, Development and Evaluation* metodolojisi kullanıldı.

Bulgular: Görevlendirilen ekipçe, 18 yaş ve üzeri romatoloji hastalarının tıbbi durumlarına (hastalık, kullanılan ilaçlar, gebelik, emzirme, seyahat gibi) göre kanıt düzeyi ile aşılama önerileri oluşturuldu. Genel yaklaşım önerileri, her bir aşının kullanımı, canlı ve inaktif aşılar için öneriler, uygulanma zamanları ve immünosüpresif tedavi alan gebe romatoloji hastalarının bebeklerinin aşılanması başlıkları altında öneriler oluşturuldu. Önerilerin

Abstract

Objective: To develop an evidence-based vaccination guideline that incorporates expert opinions on vaccine-preventable diseases for adult rheumatology patients, taking into account their medical conditions.

Methods: The team appointed by the Turkish Society for Rheumatology developed clinical questions related to rheumatic diseases, their treatments, vaccine-preventable diseases, and vaccines in the format of population, intervention, comparison, and outcome (PICO). Systematic literature reviews were conducted for each PICO question. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to assess the quality of evidence and to formulate recommendations.

Results: The appointed team developed vaccination recommendations with evidence levels for rheumatology patients aged 18 years and older based on the medical conditions (disease, medications, pregnancy, breastfeeding, travel, etc.). Recommendations were developed under the headings including the general approach recommendations, usage of each vaccine, recommendations for live and inactivated vaccines, timing of administration,

İletişim / Correspondence: Dr. Ahmet İlbay,
Kütahya Şehir Hastanesi, Romatoloji Kliniği, Kütahya, Türkiye
E-posta: ilbayahmet@gmail.com **ORCID ID:** orcid.org/0000-0002-7645-9462
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Özet

çoğu koşullu olup destekleyici kanıt düzeyi düşüktür. Önerilen aşıların bir kısmının kılavuzun hazırlandığı dönemde T.C. Sağlık Bakanlığı'nın ulusal aşı şemalarında yer almaması veya ülkemizde temin edilememesine rağmen, zamanla güncellenebileceği veya ilgili aşıların temin edilebileceği düşünülerek kılavuzda bu aşılara da yer verilmiştir.

Sonuç: Erişkin romatoloji hastaları, aşıyla önlenebilir hastalıklara karşı bireysel riskler göz önünde bulundurularak aşılanmalıdır. Takip eden hekim ve hasta, aşılama hakkında ortak karar almalıdır. Hastaya aşılanmanın önemi (önerilen aşılar, zamanlaması ve yan etkileri) hakkında bilgi verilerek teşvik edilmeli ve tereddütleri varsa bilimsel veriler eşliğinde giderilmelidir.

Anahtar Kelimeler: Antiromatizmal tedaviler, aşı önerileri, bağışıklama, romatolojik hastalıklar

Abstract

and vaccination of infants born to pregnant rheumatology patients on immunosuppressive therapy. Most of the recommendations are conditional, with low supporting evidence levels. Some of the recommended vaccines were not included in the Turkish Ministry of Health's national vaccination schedules at the time of the guideline's development or were unavailable within our country; however, they are included in the guideline with the understanding that updates may occur over time or that these vaccines may become accessible.

Conclusion: Adult rheumatology patients should be vaccinated for vaccine-preventable diseases based on their individual risks. The attending physician and the patient should make a joint decision regarding vaccination. The patient should be informed about the importance of vaccination (recommended vaccines, timing, and side effects) and encouraged accordingly, with any hesitations addressed through scientific evidence.

Keywords: Antirheumatic treatments, vaccine recommendations, immunization, rheumatic diseases

Giriş

Erişkin romatoloji hastalarına yönelik hazırlanan bu aşılama rehberi, aşıyla önlenebilir hastalıklarda kanıta dayalı bilgi, uzman görüş ve önerilerinden oluşmaktadır. Türkiye Romatoloji Derneği (TRD) tarafından görevlendirilen ekip (GE) tarafından geliştirilen ve onaylanan bu öneriler, belli uygulama kalıpları içinde rehberlik sağlamayı amaçlamaktadır. Asla her hastaya uygulanmasını, dikte etmeyi amaçlamamaktadır. Aşılama planı, hastanın bireysel koşulları göz önünde bulundurularak takip eden klinisyen ve hasta ile oluşturulmalıdır. Bu kılavuz hastayı gelecekte bazı enfeksiyonlardan korumayı amaçlar ancak tam koruyuculuğu garanti etmez. Bu öneriler, tıbbi bilgi, teknoloji ve uygulamalardaki gelişmeler öncülüğünde periyodik olarak yenilenmelidir. TRD aşı önerileri, sosyal güvenlik kurumlarının geri ödeme kararlarından bağımsız bilimsel verilere dayandırılarak hazırlanmıştır. TRD, herhangi bir ticari ürün veya hizmeti desteklemeksizin bağımsız, profesyonel ve bilimsel bir tıbbi topluluktur.

Enfeksiyon hastalıkları, dünya çapında kalp damar hastalıkları ve kanserden sonra üçüncü sırada ölüm nedenidir. Modern sağlık hizmetlerinin ulaşamadığı ülkelerde ise birinci sırayı almaktadır.[1] Günümüzde hala çok sayıda çocuk veya yetişkinin, aşıyla önlenebilir enfeksiyonlardan ölüyor olması şaşırtıcı olduğu kadar üzücü de bir durumdur. Enflamatuvar romatoloji hastaları gerek hastalığa bağlı organ ve sistemlerin tutulumu gerekse tedavide kullandığımız immünosüpresif ilaçların etkisiyle daha fazla enfeksiyonlara bağlı morbidite ve mortalite oranlarına sahiptir. İngiltere ulusal veri tabanından 2000-2007 yılları arasında, 46030 romatoid artrit (RA) hastasının sağlıklı kontrollerle karşılaştırıldığı retrospektif bir çalışmada hem influenza riskinin hem de influenzaya bağlı komplikasyonların RA grubunda 2,75 kat daha fazla olduğu gösterilmiştir.[1] 2007-2010 yılları arasının değerlendirildiği, sistemik lupus eritematozus (SLE), RA, enflamatuvar barsak hastalığı, ankilozan spondilit, psoriatik artrit ve psoriasis hastalarını da içeren yaklaşık 330000 hastanın dahil edildiği retrospektif bir çalışmada özellikle SLE ve RA hastalarında daha erken yaşta ve yaşıtlarına göre 1,5-3 kat daha fazla herpes zoster enfeksiyonu gözlenmiştir.[2] Pnömokok enfeksiyon riskinin ise sağlıklı popülasyona göre RA hastalarında 4,1; SLE hastalarında 4 kat arttığı bilinmektedir.[3] Aynı şekilde RA ve SLE hastalarında insan papilloma virüse (HPV) bağlı serviks kanseri riski 1,5 kat daha fazladır.[4] Bu enfeksiyonların hepsi de aşı ile önlenebilir enfeksiyonlardır.

Erişkin aşıları, bazı seyahat aşıları dışında genellikle inaktif aşılardır; immünosüpresif tedavi alan hastalarda bile aşı ilişkili enfeksiyon endişesi olmadan rahatlıkla uygulanabilmektedir. Ancak aşı önerilerinde bulunurken, hastanın aldığı tedavi, canlı veya inaktif aşıların zamanlaması, aşının etkinliği ve güvenirliği göz önünde bulundurulması gereken konulardır. Yine gebeliği sırasında immünosüpresif tedavi alan annelerin bebeklerine canlı aşıların uygulanması önem arz eden bir durumdur.

TRD, erişkin romatoloji hastalarına yönelik ilk aşı önerilerini 2016 yılında derleme niteliğinde yayınladı. Ardından 2022 yılında Amerikan Romatoloji Koleji *(American College of Rheumatology-ACR)* Romatolojik ve Kas-İskelet Sistemi Hastalıklarında Aşılama Rehberi'ni yayınladı. Ocak 2024'te TRD, erişkin romatoloji hastalarına yönelik aşı rehberini meta-analiz yöntemiyle kanıta dayalı bir kılavuz niteliğinde hazırlanması kararı aldı. GE tarafından hazırlanan ilk taslak öneriler, 2024 Ulusal Romatoloji Kongresi'nde sunuldu. Yeni geliştirilen aşılar ve güncel veriler eşliğinde kılavuzda bazı revizyonlar yapılarak, farklı romatoloji kongrelerinde konuşuldu; nihayet önerilere son hali verildi. Şüphesiz bu kılavuzda yer alan önerilerin, yeni salgınlar, yeni aşılar ve yeni bilimsel veriler eşliğinde güncellenmesi kaçınılmazdır. Kılavuzda yer alan ilaçlar, aşılar ve romatolojik hastalıkların listesi, Tablo 1'de yer almaktadır. Tablo 2'de ise metin içinde kullanılan terimlerin anlamları yer almaktadır.

Tablo 1. Kılavuz kapsamındaki ilaçlar, aşılar ve romatolojik hastalıklar				
Aşılar		**Tedaviler**		
Canlı aşılar	**Canlı olmayan aşılar**	**İmmünosüpresif olmayanlar**		
İntranazal influenza aşısı	Mevsimsel influenza aşısı	Hidroksiklorakin	IVIG	Apremilast
Kızamık-kızamıkçık-kabakulak (KKK) aşısı	Konjuge pnömokok aşısı (PCV 13/15/20/21 valan)	Kolşisin	Sulfasalazin	
Oral tifo aşısı	Polisakkarit pnömokok aşısı (PPSV 23)	**İmmünosüpresifler**		
Oral polio aşısı	Hepatit A aşısı	Glukokortikoidler	Siklofosfamid	Tosilizumab
Suçiçeği aşısı	Hepatit B aşısı	Metotreksat	Adalimumab	Sarilumab
Sarı humma aşısı	Human papillomavirüs aşısı	Leflunomid	Etanersept	Abatasept
Rotavirüs aşısı	Meningokok aşısı	Azatiyoprin	Golimumab	Sekukinumab
Canlı zoster aşısı	Hemofilus influenza tip B aşısı	Mikofenolat mofetil	İnfliksimab	İksekizumab
Japon ensefaliti aşısı	Tetanoz toksoidi/erişkin tip difteri aşısı (Td)	Siklosporin	Sertolizumab	Ustekinumab
	Tetanoz toksoidi/erişkin tip difteri/ aselüler boğmaca aşısı (Tdap)	Takrolimus	Rituksimab	Guselkumab
	Respiratuvar sinsityal virüs aşısı	Voklosporin	Obinituzumab	Risankizumab
	Rekombinant varisella zoster aşısı	Barisitinib	Okrelizumab	Tildrakizumab
	İnaktif polio aşısı	Tofasitinib	Anifrolumab	Anakinra
	SARS-CoV-2 virüs mRNA aşısı	Upadasitinib	Belimumab	Kanakinumab
		Filgotinib	Tabalumab	Rilonasept
		Ruksolitinib		
Romatolojik hastalıklar				
Enflamatuvar artritler	**Bağ doku hastalıkları**	**Diğer enflamatuvar hastalıklar**	**Vaskülitler**	
Romatoid artrit	Sistemik lupus eritematozus	Sarkoidoz	Granulomatoz polianjit	Cogan sendromu
Ankilozan spondilit	Sistemik skleroz	IgG4-ilişkili hastalık	Mikroskopik polianjit	Kriyoglobulinemik vaskülit
Psöriatik artrit	Sjögren sendromu	Otoenflamatuvar hastalıklar	Eozinofilik granulomatoz polianjit	Kutanöz küçük damar vasküliti
Enteropatik artrit	İdiyopatik enflamatuvar miyopatiler	Gut	Poliarteritis nodoza	Ürtikeryal vaskülit
Radyografik olmayan aksiyel spondilit	Miks bağ doku hastalığı	Psödogut	Dev hücreli arterit	Romatoid vaskülit
Undiferansiye spondiloartrit	Antifosfolipid sendromu	Polimiyalji romatika	Takayasu arteriti	IgA vasküliti
	Undiferansiye bağ doku hastalığı	Still hastalığı	Behçet hastalığı	
IVIG: İntravenöz immünoglobülin, mRNA: Haberci ribonükleik asid, SARS-CoV-2: Şiddetli akut solunum sendromu koronavirüsü-2				

Gereç ve Yöntemler

Bu kılavuz, TRD öncülüğünde GE tarafından multidisipliner yaklaşımla hazırlanmıştır. GE, 10 romatoloji uzmanı, 2 enfeksiyon hastalıkları uzmanı, 2 aile hekimliği uzmanı olmak üzere 14 tıp doktoru ve 3 hasta temsilcisinden oluşmaktadır.

GE, kendi içinde çekirdek lider ekip (N.T., E.U., M.E.Y., S.S., G.Ç., E.N.Ö., H.S.Ç., Ö.U., A.İ.) ve literatür inceleme ekibi (D.K., A.U., Ç.E., M.D. ve F.G.) oluşturarak haftalık düzenli toplantılar yaptı (Ek 1). Her iki ekibe de çalışma öncesi TRD öncülüğünde, meta-analiz ve *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) metodolojisi eğitimleri verildi. Çekirdek Lider Ekibi, kılavuzun kapsamı ve klinik popülasyon, müdahale, karşılaştırma ve sonuç (PICO) sorularını hazırladı (Ek 2). Literatür İnceleme Ekibi, PICO soruları için sistematik literatür incelemeleri gerçekleştirerek, GRADE (yüksek, orta, düşük, çok düşük) metodolojisine göre kanıt kalitesini derecelendirdi (Tablo 3) ve kanıt raporunu hazırladı.[5,6]

Sistematik literatür taraması planlanırken 2022 ACR Romatolojik ve Kas-İskelet Sistemi Hastalıklarında Aşılama Rehberi temel alındı.[7] 2022 ACR aşı öneri rehberi MEDLINE, Ovid Embase ve Cochrane Central register of Conrolled Trials veri tabanlarından 31 Ocak 2022'ye kadar belirlenen anahtar

Tablo 2. Terminoloji, tanımlar ve kısaltmalar	
Terminoloji	**Açıklama**
Adjuvan	Bazı aşılarda yer alan ve daha güçlü bir bağışıklık yanıt oluşturmaya yardımcı olan bileşenler
Konjuge	Daha güçlü antijenik yanıt elde etmek için antijenin taşıyıcı bir proteinle kovalent olarak bağlanması
İmmünojenisite	Bir aşının bağışıklık oluşturma yeteneği
Reaktojenite	Aşı uygulamasından sonra günler içinde aşı yerinde veya sistemik olarak gelişen tipik semptomlar (kızarıklık, şişlik, ateş, eklem ve kas ağrıları gibi)
Rekombinant	Patojene ait antijeni kodlayan genetik materyal kullanılarak antijenin sentezlenmesi
Serokonversiyon	Bir aşı veya enfeksiyon yoluyla ortaya çıkan, bir patojene karşı antikorların gelişmesi
Seroproteksiyon	Enfeksiyona veya hastalığa karşı korunma sağlayabilecek antikor seviyesi
Titre	Belirli bir patojene karşı antikor seviyesini gösteren sayısal değer
Kısaltmalar	
BCG	Bacillus Calmette-Guérin
COVID-19	Koronavirüs hastalığı-2019
DMARD	Hastalık modifiye edici antiromatizmal ilaç
HAV	Hepatit A virüs
HBV	Hepatit B virüs
HPV	İnsan papilloma virüs
IVIG	İntravenöz immünoglobülin
JAK	Janus kinaz
KKK	Kızamık-kızamıkçık-kabakulak
KOAH	Kronik obstrüktif akciğer hastalığı
MTX	Metotreksat
PCV	Konjuge pnömokok aşısı
PPSV23	Yirmi üç valanlı pnömokokal polisakkarit aşı
RA	Romatoid artrit
RSV	Respiratuvar sinsityal virüs
RTX	Rituksimab
SARS-CoV-2	Şiddetli akut solunum yolu sendromu koronavirüsü-2
SLE	Sistemik lupus eritematozus
Td	Tetanoz toksoidi/erişkin tip difteri aşısı
Tdap	Tetanoz toksoidi/erişkin tip difteri/aselüler boğmaca aşısı
TNF	Tümör nekrozis faktör
VZV	Varisella zoster virüs

Tablo 3. Kanıtların GRADE sistemine göre kalite değerlendirmesi	
Kanıt düzeyi	**Tanım**
Yüksek	Gerçek ve tahmini etki arasındaki korelasyona dair yüksek güven
Orta	Tahmini etkiye dair orta güven. Gerçek etkinin tahmini etkiden çok farklı olması mümkündür
Düşük	Tahmini etkiye dair sınırlı güven. Gerçek etki tahmini etkiden çok farklı olabilir
Çok düşük	Tahmini etkiye dair çok az güven. Gerçek etki tahmini etkiden çok büyük ihtimalle farklıdır
GRADE: *Grading of Recommendations Assessment, Development and Evaluation*	

kelime ve PICO soruları doğrultusunda ilgili makalelerin taranmasıyla oluşturulmuştu. Mevcut rehberi hazırlarken 2022 ACR Romatolojik ve Kas-İskelet Sistemi Hastalıklarında Aşılama Rehberi'nin bu literatür taraması baz alınarak 31 Ocak 2022'den 15 Aralık 2025 tarihine kadar olan ilgili anahtar kelimeler (Ek 3) dikkate alınarak literatür taraması güncelleştirildi.

Her iki ekip tarafından aynı zamanda ilk öneriler oylandı ve geliştirildi. Hasta ekibi ise aşılar konusundaki bakış açılarını ve endişelerini sundu. İlk oylama ekip içinde yapıldı ve yüzde yüz mutabakat sonrasında TRD üyesi romatoloji doktorlarınca bir ay askıda kalarak oylandı. TRD üyesi romatologların oylaması sonrası %70 ve fazlası katılım oranına ulaşan öneriler nihai

öneriler olarak kabul edildi. Öneriler oluşturulurken 2022 ACR Romatolojik ve Kas-İskelet Sistemi Hastalıklarında Aşılama Rehberi,[7] Kasım-2025 *Center for Disease Control and Prevention* (CDC), *Advisory Committee on Immunization Practices* (ACIP) Kılavuzu,[8] Türkiye enfeksiyon hastalıkları derneklerinden; Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Derneği aşılama rehberi[9] ve Türkiye Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Uzmanlık Derneği 2025 erişkin aşılama kılavuzları[10] da gözden geçirildi. Bu kılavuzun periyodik olarak gözden geçirilmesi ve güncellenmesi planlanmıştır.

Sonuçlar ve Öneriler

Genel öneriler, aşılama önerileri, canlı aşı uygulama önerileri, aşıların immünojenisite ve etkinliği açısından uygulanma zamanlarının planlanması, immünosüpresif tedavi alan gebe romatoloji hastalarında yenidoğan ve bebek aşılama önerileri Tablo 4'te özetlendi.

Tablo 4. Türkiye Romatoloji Derneği 2026, erişkin romatoloji hastalarında aşı önerileri

Öneriler	Kanıt düzeyi	PICO
1. Genel öneriler		
1.1. Romatoloji hastalarına poliklinik değerlendirmelerinde mevcut aşılanma durumları sorgulanmalı ve aşı tipiyle birlikte kaydedilmelidir.		
1.2. Hastalara aşıların önemi ve gerekliliği konusunda bilgi verilmelidir.		
1.3. Aşılama kararı hastayla birlikte alınmalıdır.		
2. Aşı uygulama önerileri		
2.1. İnfluenza aşısı: 18 yaş ve üzeri tüm romatoloji hastalarına yıllık mevsimsel influenza aşısı önerilir.	Orta (yüksek doz için)	9, 10, 11, 12
2.2. Pnömokok aşısı: 18-49 yaş arası immünosüpresif tedavi alan ve ≥50 yaş tüm romatoloji hastalarına pnömokok aşısı önerilir.	Düşük	20
2.3. Rekombinant varisella zoster (VZV) aşısı: 18-50 yaş arası immünosüpresif tedavi alanlara, zona öyküsü olanlara ve ≥50 yaş tüm romatoloji hastalarına rekombinant VZV aşısı önerilir.	Çok düşük (indirekt kanıt)	21
2.4. İnsan papilloma virüs (HPV) aşısı: Daha önce HPV aşılama süreci tamamlanmamış, 18-45 yaş arası romatoloji hastalarına HPV aşısı önerilir.	Çok düşük	19
2.5. Hepatit B virüs (HBV) aşısı: Tüm erişkin romatoloji hastalarına HBsAg, anti-HBs ve anti-HBc'den oluşan tam serolojik değerlendirme yapılmalıdır. Anti-HBs düzeyinin 10 IU/mL'nin altında olması ve aktif enfeksiyon bulunmaması halinde aşılama yapılmalıdır. HBsAg negatif, anti-HBc pozitif, HBV DNA negatif ve anti-HBs <10 IU/mL olan hastalarda hatırlatma dozu (booster) önerilir. Immünosüpresif tedavi almayan hastalarda 0, 1 ve 6. aylarda tek doz aşı yapılması önerilir. Immünosüpresif tedavi alanlarda ise 0, 1, 2 ve 6. aylarda çift doz aşı yapılması önerilir. B hücre deplesyonu tedavisi alan hastalar riskli temas varlığında aşılamayla birlikte hepatit B immünoglobulin uygulaması yönünden değerlendirilmelidir.	Düşük, çok düşük	1, 3, 16
2.6. Hepatit A virüs (HAV) aşısı: Anti-HAV IgG negatif romatoloji hastalarında hepatit A aşısının 0 ve 6. aylarda iki doz olarak yapılması önerilir.	Düşük	3, 22
2.7. Tetanoz-difteri/tetanoz-difteri-asellüler boğmaca (Td/Tdap) aşısı: Çocukluk dönemi tetanoz, difteri ve boğmaca aşılarını tamamlamış romatoloji hastalarında her 10 yılda bir Td veya Tdap ile rapel uygulanması; aşılanma durumu bilinmeyen erişkinlerde önce Tdap verilerek primer aşılama serisinin Td/Tdap ile tamamlanması önerilir. Gebelerde 27-36. haftalar arasında Tdap aşısı yapılması önerilir.	Düşük	3, 22
2.8. Respiratuvar sinsityal virüs (RSV) aşısı: Romatoloji hastalarında 75 yaş ve üzerindekilere RSV aşısı uygulanması önerilir. 60-74 yaş arasında olup ağır RSV hastalığı açısından artmış risk taşıyan (örneğin KOAH, kalp yetmezliği gibi kronik kardiyopulmoner hastalığı bulunan veya immünosüpresif tedavi alan) bireylere RSV aşısı önerilir.	Çok düşük	3
2.9. Kuduz aşısı: Kuduz açısından riskli temas yaşayan romatoloji hastalarında ulusal aşı algoritmasına uyulması; immünosüpresif hastalarda aktif aşının yanı sıra kuduz immünoglobulininin de uygulanması önerilir.	Çok düşük	3
2.10. Seyahat aşıları: Romatoloji hastalarında aşılama gidilecek bölgenin riskine göre planlanmalı; sarı humma, meningokok ve diğer seyahat ile ilişkili aşılar ulusal ve uluslararası önerilere uygun şekilde uygulanmalıdır. Canlı sarı humma aşısı ileri derecede immünosüpresif hastalarda kontrendike olduğundan zorunlu seyahat durumunda tedavi düzenlemesi için değerlendirme yapılmalıdır.	Çok düşük	22, 23
2.11. SARS-CoV-2 (COVID-19) aşısı: İmmünosüprese olmayan romatoloji hastalarında daha önceki aşılanma durumuna bakılmaksızın; 18-64 yaş aralığında bir doz, 65 yaş ve üzerinde altı ay ara ile iki doz güncel sezon aşısının uygulanması önerilir. Orta-ağır derecede immünosüprese kabul edilen 18 yaş ve üzeri romatoloji hastalarında aşılama, önceki aşılanma durumuna göre planlanmalıdır. Daha önce COVID-19 aşısı yapılmamış erişkinlerde üçlü aşılama şeması uygulanmalıdır. Daha önce aşılanmış immünosüprese hastalarda ise güncel sezon aşısı ile iki doz aşı önerilir. Doz sayısı ve aralıklar hastanın önceki aşı öyküsüne ve kullanılan aşıya göre belirlenmelidir.	Çok düşük	1, 2, 3, 7

Tablo 4. Devamı		
Öneriler	**Kanıt düzeyi**	**PICO**
3. Canlı aşı uygulama önerileri		
3.1. Canlı aşılar mümkünse immünosüpresif tedavi başlanmadan en az 4 hafta önce uygulanmalıdır. Immünosüpresif tedavi alan hastalarda canlı aşı genellikle kontrendikedir; mutlak uygulanması gereken durumlarda, kullanılan ilacın yarı ömrüne göre aşı öncesi ve sonrası ilaca ara verme süresi bireysel olarak planlanmalıdır. Canlı aşının inaktif aşı alternatifi varsa tercih edilmelidir. Yüksek doz IVIG (0.4-2 gr/kg) tedavisi sonrasında canlı aşı yapılacaksa, aşının 8-11 ay ertelenmesi önerilir.	Çok düşük, düşük	23, 24
4. Romatoloji hastalarında aşıların immünojenisite ve etkinliği açısından uygulanma zamanlarının planlanması		
4.1. Canlı olmayan aşıların uygulanma zamanlamasında hastalık aktivitesi göz ardı edilebilir.	Çok düşük	13, 18
4.2. Hastalık aktivitesi izin veriyorsa influenza aşısından sonra metotreksat tedavisine 2 hafta ara verilmesi önerilir.	Çok düşük	3, 15, 16
4.3. Immünosüpresif tedavi alan hastalarda, influenza aşısı yapılacak ise metotreksat dışı immünosüpresif tedavilere devam edilebilir.	Çok düşük	3, 15, 16
4.4. Immünosüpresif tedavi alan hastalarda, influenza dışı canlı olmayan aşı yapılacak ise rituksimab dışındaki immünosüpresif tedavilere devam edilebilir.	Çok düşük	3, 16
4.5. Rituksimab tedavisi alan hastalarda, influenza dışı canlı olmayan aşıların uygulanmasının bir sonraki rituksimab tarihine ertelenmesi ve o rituksimab tedavisinin de aşılamadan 2 hafta sonra yapılması önerilir.	Düşük	17
4.6. <20 mg/gün prednizon eşdeğeri glukokortikoid kullananlarda canlı olmayan aşılar istenilen zamanda uygulanabilir.	Pnömokokal aşı için düşük, diğer aşılar için çok düşük	4, 14
4.7. ≥20 mg/gün prednizon eşdeğeri glukokortikoid kullananlarda, influenza aşısı mevsimsel olarak zamanında uygulanabilir.	Çok düşük	14
4.8. ≥20 mg/gün prednizon eşdeğeri glukokortikoid kullananlarda, influenza dışı canlı olmayan aşıların mümkünse glukokortikoid dozunun 20 mg/gün dozunun altına ininceye kadar ertelenmesi önerilir.	Pnömokokal aşı için düşük, diğer aşılar için çok düşük	4
5. Immünosüpresif tedavi alan gebe romatoloji hastalarının bebeklerinin aşılanması		
5.1. Tüm aşılar (inaktif/canlı) intrauterin konvansiyonel sentetik DMARD maruziyeti olan bebeklere uygulanabilir.	Çok düşük	16, 17
5.2. İnaktif aşılar intrauterin biyolojik DMARD maruziyeti olan bebeklere uygulanabilir.	Çok düşük	16
5.3. İkinci ve/veya üçüncü trimesterde intrauterin TNF inhibitörlerine maruz kalan bebeklerde rotavirüs aşılaması ilk 6 ay içinde yapılabilir.	Çok düşük	25
5.4. İkinci ve/veya üçüncü trimesterde intrauterin TNF inhibitöreri dışında biyolojiklere maruz kalan bebeklerde rotavirüs aşısının ilk 6 aydan sonraya ertelenmesi önerilir.	Çok düşük	25
5.5. İkinci ve/veya üçüncü trimesterde intrauterin TNF inhibitörlerine ya da diğer biyolojik DMARD'lere maruz kalan bebeklerde BCG aşılaması 6. aydan sonraya bırakılması önerilir.	Çok düşük	25
5.6. Biyolojik tedavilerin emzirme döneminde kullanılması bebek aşılama programını etkilemez.	Çok düşük	17, 26

BCG: Bacillus Calmette-Guérin, COVID-19: Koronavirüs hastalığı-2019, DMARD: Hastalık modifiye edici antiromatizmal ilaç, IVIG: İntravenöz immünoglobülin, TNF: Tümör nekrozis faktör

1. Genel Öneriler

1.1. Romatoloji hastalarına poliklinik değerlendirmelerinde mevcut aşılanma durumları sorgulanmalı ve aşı tipiyle birlikte kaydedilmelidir.

Poliklinik değerlendirmelerinde hastanın mevcut aşılanma durumu sorgulanarak, hangi aşıların yapıldığı, aşıların tipi (canlı ya da inaktif) ve uygulama zamanları kaydedilmelidir. Böylece eksik aşılar belirlenmeli, planlanan veya devam eden tedavilere göre uygun ve güvenli bir aşılama stratejisi oluşturulmalıdır. Ayrıca bu kayıtlar, olası enfeksiyonların değerlendirilmesi ve önlenmesi açısından klinik karar sürecine katkı sağlayacaktır.

1.2. Hastalara aşıların önemi ve gerekliliği konusunda bilgi verilmelidir.

Hastalara aşıların önlenebilir enfeksiyonlara karşı koruyucu rolü, hastalık alevlenmelerini ve enfeksiyona bağlı komplikasyonları azaltmadaki önemi açık bir şekilde anlatılmalıdır. Ayrıca uygun zamanda ve doğru aşılarla yapılan aşılamanın tedavi sürecini aksatmadan güvenle uygulanabileceği vurgulanarak, aşı tereddüdünün azaltılması ve tedaviye uyumun artırılması hedeflenmelidir.

1.3. Aşılama kararı hastayla birlikte alınmalıdır.

Romatoloji hastalarında aşılama kararı, hastalığın aktivitesi, kullanılan tedaviler ve bireysel riskler göz önünde

bulundurularak hastayla birlikte değerlendirilmeli ve ortak karar verme süreci desteklenmelidir. Bu yaklaşım, hastanın sürece aktif katılımını sağlayarak güven duygusunu artırır ve aşılama uyumunu güçlendirir.

2. Aşı Uygulama Önerileri

2.1 İnfluenza aşısı: 18 yaş ve üzeri tüm romatoloji hastalarına yıllık mevsimsel influenza aşısı önerilir.

Romatoloji hastalarında influenza, hastaneye yatış ve mortalitenin önemli nedenlerinden biridir.[11] İnfluenza aşılarının koruyuculuk süresinin kısa olması ve virüs yapısındaki yapısal değişiklikler nedeniyle her yıl farklı salgınların olması, yıllık mevsimsel aşılanmayı gerektirmektedir. Her yıl Dünya Sağlık Örgütü (DSÖ) tarafından belirlenen suşlara yönelik aşılama sonrası koruyuculuk oranı ortalama %35 civarında olsa da bu oran genel popülasyonda milyonlarca kişide enfeksiyonun önlenmesi ve özellikle immünosüprese hastalarda ciddi komplikasyonların azaltılması açısından büyük önem taşımaktadır. DSÖ, 2025 yılında trivalan influenza aşısı önermiştir.[12] ACR ve ACIP, immünosüpresif tedavi alanlarda adjuvanlı inaktif influenza aşısı (aIIV3) veya standart doz aşının dört katı antijen içeren yüksek doz inaktif influenza aşılarını (HD-IIV3) önermektedir.[7,8] Ancak her iki aşının da temin edilemediği durumlarda standart doz güncel mevsimsel influenza aşısının mevsiminde ertelenmeden yaptırılmasını şiddetle önermektedir. Altmış beş yaş altı RA hastalarında yüksek doz influenza aşılarının standart doza kıyasla daha yüksek serokonversiyon özelliği gösterdiği ve yan etki açısından ek bir uyarı oluşturmadığı bilinmektedir.[13,14] Romatoloji hastalarında 65 yaş altı adjuvanlanmış influenza aşılamasına ilişkin çalışma olmamakla birlikte genel olarak reaktojenite dışında bir güvenlik sorunu bildirilmemiştir.[7] Türkiye'de adjuvanlı ve yüksek doz aşı formları bulunmadığından, tüm romatoloji hastaları, mutlaka mevcut aşı ile vakit kaybetmeden aşılanmalıdır.

2.2. Pnömokok aşısı: 18-49 yaş arası immünosüpresif tedavi alan ve ≥50 yaş tüm romatoloji hastalarına pnömokok aşısı önerilir.

Immünosüpresif ilaç kullanan romatoloji hastalarında pnömokok enfeksiyon riski artmıştır ve pnömokok aşılaması ile romatoloji hastalarında yeterli serokonversiyon sağlanması mümkündür.[3,15-17] Pnömokok aşılarının polisakkarit ve konjuge olmak üzere iki formu vardır. Polisakkarit aşı: 23 valanlı pnömokok polisakkarit aşısı (PPSV 23); 23 serotip içerir, B lenfositlerini uyarır ve %90 koruyuculuk sağlar. Her 5 yılda bir rapel dozu yapılmalıdır. Konjuge pnömokok aşısı (PCV); hem T hem de B lenfosit yanıtını uyarır ve çok uzun süreli neredeyse ömür boyu süren bağışıklık sağlar. Dünyada PCV'nin kullanımda olan 13, 15, 20 ve 21 serotip içeren 4 formu bulunmaktadır. PCV 21, diğer konjuge aşılardan farklı olarak 2019'da ABD'de invaziv pnömokok enfeksiyonlarının %30'unda saptanan 8 farklı serotipi içermektedir ve Haziran 2024'te *Food and Drug Administration* (FDA) onayı alarak ABD'de erişkin aşı programında yer almıştır.[18]

Aşı uygulama önerilerinde bulunurken mevcut şartlara göre temin edilebilecek aşı çeşitleri değişebileceği için alternatifli bir uygulama şeması vermeyi uygun gördük (Tablo 5). Pnömokok aşılaması yapılırken, daha önce hiç aşılanmamışsa, tek doz PCV 20 veya PCV 21 ile aşılamak yeterlidir. Bu aşıya ulaşılamıyorsa, PCV 13/15 (PCV 15 ülkemizde bulunmamaktadır) aşısından ≥8 hafta sonra PPSV 23 önerilir. Daha önce sadece PPSV 23 aşısı olmuş ve üzerinden ≥1 yıl ve daha fazla zaman geçmişse tercihen PCV 20/21 önerilir veya PCV 13/15 önerilir. Yalnızca PCV 13 aşısı olmuş ve üzerinden ≥1 yıl ve daha fazlası geçmişse tercihen PCV 20/21 veya ≥8 hafta ve daha fazla geçmişse PPSV 23 yapılır ve 5 yıl sonra PPSV 23 tekrarlanır. Daha önce PCV 13 ve 1 doz PPSV 23 aşılarını olmuş ve üzerinden ≥5 yıl ve daha fazla geçmişse tercihen PCV 20/21 veya PPSV 23 aşısı önerilir. Daha önce PCV 13 ve 2 doz PPSV 23 aşısı olmuş ve ≥5 yıl ve daha fazla zaman geçmişse PCV 20/21 önerilir. Mevcut bilgilerle ikiden fazla PPSV 23 ile devam etme konusunda yeterli veri bulunmamaktadır. Hasta bazında değerlendirme yapılarak karar alınmalıdır.

2.3. Rekombinant varisella zoster (VZV) aşısı: 18-50 yaş arası immünosüpresif tedavi alanlara, zona öyküsü olanlara ve ≥50 yaş tüm romatoloji hastalarına rekombinant VZV aşısı önerilir.

Romatoloji hastalarında herpes zoster enfeksiyon riskinin arttığı bilinmektedir. Özellikle Janus kinaz (JAK) inhibitörlerinin kullanımı ile bu risk daha fazladır.[2,19] Herpes zoster aşılaması için canlı zayıflatılmış VZV aşısı ve rekombinant VZV aşısı olmak üzere iki alternatif vardır. Herpes zosterin inaktif adjuvanlı aşısının çıkmasıyla birlikte canlı aşı artık neredeyse hiç kullanılmamaktadır. Zona aşısı Türkiye'de henüz yetişkin ulusal aşı takviminde yer almıyor ve geri ödeme listesinde değildir. Ancak eczanelerden ücretli olarak temin edilebilmektedir. Her ne kadar romatolojik hastalıklardaki verisi yeterli olmasa da rekombinant VZV aşısının etkinliği solid organ transplantasyonu, otolog kök hücre nakilli ve hematolojik maligniteli immünosüpresif hastalarda gösterilmiştir.[20-23]

Rekombinant VZV aşısı uygulanırken ilk dozdan 2-6 ay sonra ikinci dozu uygulanır. Immünosüpresif tedavi alanlarda iki aşı arasındaki süre 4 haftaya da çekilebilir.

2.4. HPV aşısı: Daha önce HPV aşılama süreci tamamlanmamış, 18-45 yaş arası romatoloji hastalarına HPV aşısı önerilir.

HPV enfeksiyonları serviks, vajina, vulva, penis, anüs ve orofarengeal kanserler gibi çeşitli kanser türlerine neden olabilmektedir. HPV sadece kadınlarda değil erkeklerde de

Tablo 5. Pnömokok aşılama önerileri

Önceki aşılama durumu	Seçenek 1	Seçenek 2
Hiç aşılanmamış	PCV 20/PCV 21	PCV 13/15 → ≥8 hafta → PPSV 23
Yalnızca PPSV 23	≥1 yıl → PCV 20/PCV 21	≥1 yıl → PCV 13/15
Yalnızca PCV 13	≥1 yıl → PCV 20/PCV 21	≥8 hafta → PPSV 23 → ≥5 yıl → PPSV 23 Hasta 65 yaşına geldiğinde pnömokok aşılama önerilerini değerlendir
PCV 13 ve 1 doz PPSV 23	≥5 yıl → PCV 20/PCV 21	≥5 yıl → PPSV 23 Hasta 65 yaşına geldiğinde pnömokok aşılama önerilerini değerlendir
PCV 13 ve 2 doz PPSV 23	≥5 yıl → PCV 20/PCV 21	Mevcut bilgilerle aşı yapılması önerilmez Hasta 65 yaşına geldiğinde pnömokok aşılama önerilerini değerlendir

*PPSV 23 uygulanması için en kısa aralık: PCV 13/15 dozundan sonra en az 8 hafta, son PPSV 23 dozundan sonra en az 5 yıl olmalıdır.
Ülkemizde henüz PCV 21 bulunmamaktadır. ABD'de Haziran 2024'te FDA onayı almıştır. PCV 15 ülkemizde bulunmamaktadır.
ABD: Amerika Birleşik Devletleri, FDA: *Food and Drug Administration*

önemli enfeksiyon ve kanser nedenidir. Virüs ile karşılaşmadan önce aşılanmak daha etkili olduğundan cinsel olarak aktif olmadan aşılanma önerilir.[10] Romatoloji hastalarında HPV ile ilgili çalışmalar kısıtlıdır. Immünosüpresif tedavi alan SLE hastalarında, sadece hidroksiklorokin kullananlara oranla daha fazla yüksek dereceli servikal displazi ve servikal kanser saptanmıştır.[24] HPV aşılaması sonrasında SLE hastalarında yeterli serokonversiyon geliştiği gösterilmiştir.[25,26] On beş yaş ve üzerinde 0, 2 ve 6. aylarda olmak üzere üç doz aşı önerilmektedir. Aşılama için üst yaş sınırı 45 olarak belirtilir; nedeni çalışmalarda yaşla birlikte HPV enfeksiyonuna maruz kalma olasılığının daha azaldığının düşünülmesi ve FDA onayının bu yaşla sınırlamasıdır.[27] HPV aşısı henüz ulusal çocuk ve erişkin aşı takviminde yer almamakla birlikte kullanımda olan dokuz valanlı HPV aşısı eczanelerden ücretli temin edilebilmektedir.

2.5. Hepatit B virüs (HBV) aşısı: Tüm erişkin romatoloji hastalarına HBsAg, anti-HBs ve anti-HBc'den oluşan tam serolojik değerlendirme yapılmalıdır. Anti-HBs düzeyinin 10 IU/mL'nin altında olması ve aktif enfeksiyon bulunmaması halinde aşılama yapılmalıdır. HBsAg negatif, anti-HBc pozitif, HBV DNA negatif ve anti-HBs <10 IU/mL olan hastalarda hatırlatma dozu (booster) önerilir. Immünosüpresif tedavi almayan hastalarda 0, 1 ve 6. aylarda tek doz aşı yapılması önerilir. Immünosüpresif tedavi alanlarda ise 0, 1, 2 ve 6. aylarda çift doz aşı yapılması önerilir. B hücre deplesyonu tedavisi alan hastalar, riskli temas varlığında aşılamayla birlikte hepatit B immünoglobulin uygulaması yönünden değerlendirilmelidir.

HBV enfeksiyonu, romatoloji hastalarında immünosüpresif tedaviler nedeniyle reaktivasyon açısından klinik sorun oluşturmaktadır. Rituksimab (RTX), yüksek doz kortikosteroidler, tümör nekrozis faktör (TNF) inhibitörleri ve diğer biyolojik hastalık modifiye edici antiromatizmal ilaçların (DMARD) HBV reaktivasyon riskini artırdığı çok sayıda çalışmada gösterilmiştir. Avrupa Romatoloji Dernekleri Birliği (EULAR) ve ACR kılavuzları, immünosüpresif tedavi planlanan tüm hastalarda HBV taramasının önemini vurgulamaktadır.[7,28] Anti-HBs ≥10 IU/mL düzeyinin koruyuculuğu kabul edilmekle birlikte immünsüpresyon altında antikor titresi azalmaktadır. Çift doz veya hızlandırılmış şemalar, immün yanıtı güçlendirmek amacıyla romatoloji pratiğinde giderek daha fazla tercih edilmekte; bazı çalışmalarda çift doz rejimlerinin serokonversiyon oranlarını artırdığı gösterilmiştir.[29-32] Ayrıca B hücre deplesyonu yapan

tedaviler sonrası aşılama yanıtının belirgin şekilde azaldığı bildirilmiş olup, bu durum immunsüpresif tedavi öncesi aşılama stratejilerinin önemini vurgulamaktadır.

2.6. Hepatit A virüs (HAV) aşısı: Anti-HAV immünoglobulin G negatif romatoloji hastalarında hepatit A aşısının 0 ve 6. aylarda iki doz olarak yapılması önerilir.

HAV enfeksiyonu erişkinlerde genellikle daha ağır seyretmekte, hepatik enflamasyon ve iyileşme sürecinin uzaması, immünosüpresif tedavi alan hastalarda belirgin risk oluşturmaktadır. Romatoloji hastalarının önemli bir bölümü metotreksat (MTX), azatiyoprin, JAK inhibitörleri veya biyolojik ajanlar gibi hepatotoksisite potansiyeli olan ilaçlar kullandığından, HAV enfeksiyonu karaciğer fonksiyonlarında belirgin bozulmaya yol açabilir. Literatürde immünosüpresif tedavi altındaki hastalarda HAV aşısına serokonversiyon oranlarının sağlıklı bireylere göre daha düşük olduğu bildirilmektedir; ancak bağışıklık yanıtının klinik olarak yeterli koruma sağladığı gösterilmiştir.[33,34] EULAR ve CDC önerileri, hepatik hastalık riski taşıyan veya immünsüpresyon altındaki tüm erişkinlerde HAV bağışıklama durumunun değerlendirilmesini güçlü şekilde önermektedir. Endemik bölgelerde yaşayan veya seyahat öyküsü bulunan hastalarda aşılamanın geciktirilmemesi önemlidir.[7,28,32-34] Eğer hepatit B aşısıyla birlikte yapılacaksa (kombine aşı) 0, 1 ve 6. aylarda 3 doz uygulanabilir.

2.7. Tetanoz-difteri/Td-asellüler boğmaca (Td/Tdap) aşısı: Çocukluk dönemi tetanoz, difteri ve boğmaca aşılarını tamamlamış romatoloji hastalarında her 10 yılda bir Td veya Tdap ile rapel uygulanması; aşılanma durumu bilinmeyen erişkinlerde önce Tdap verilerek primer aşılama serisinin Td/Tdap ile tamamlanması önerilir. Gebelerde 27-36. haftalar arasında Tdap aşısının yapılması önerilir.

Tetanoz ve difteri aşıları inaktif olup immünsüpresyon altında güvenle uygulanabilmektedir. Bununla birlikte, immün yanıtın şiddeti kullanılan tedaviye göre değişiklik gösterir. Özellikle RTX gibi B hücre deplesyonu oluşturan ajanlar, humoral yanıtı belirgin şekilde azaltarak aşı yanıtını engeller.[35,36] Bu nedenle RTX tedavisi planlanan hastalarda aşılamanın mümkünse tedaviden en az 4 hafta önce yapılması önerilir. Boğmaca bileşeninin yer aldığı Tdap aşısı ise erişkinlerde boğmaca kontrolünde kritik öneme sahip olup, immünosüpresif hastalarda ağır boğmaca enfeksiyonu ve uzun süreli öksürük ataklarının görülme riski daha yüksektir. Gebe romatoloji hastalarında Tdap uygulanması, yenidoğanın pasif korunmasını sağlayarak neonatal boğmaca riskini belirgin azaltmaktadır.[7,28,32,35,36]

2.8. Respiratuvar sinsityal virüs (RSV) aşısı: Romatoloji hastalarında 75 yaş ve üzerindekilere RSV aşısı uygulanması önerilir. 60-74 yaş arasında olup ağır RSV hastalığı açısından artmış risk taşıyan (örneğin kronik obstrüktif akciğer hastalığı, kalp yetmezliği gibi kronik kardiyopulmoner hastalığı bulunan veya immünosüpresif tedavi alan) bireylere RSV aşısı önerilir.

RSV, erişkinlerde özellikle ileri yaşta, kardiyopulmoner hastalığı olanlarda ve immünsüpresyon altında ağır alt solunum yolu enfeksiyonlarına neden olabilir. Yakın zamanda yapılan meta-analizde RSV aşılarının hem hastaneye yatışı hem de ciddi seyri anlamlı düzeyde azalttığı gösterilmiştir. İmmünkompromize bireylerde aşılamayla sağlanan koruyuculuk sağlıklı erişkinlere kıyasla bir miktar daha düşük olsa da klinik açıdan bu etkinin anlamlı seviyede olduğu bildirilmiştir.[37] Romatoloji hastalarında biyolojik DMARD'ler, JAK inhibitörleri ve yüksek doz kortikosteroid kullanımının solunum yolu enfeksiyonlarına duyarlılığı artırmaktadır. Bu nedenle RSV aşısı, özellikle ileri yaş romatoloji hastaları için influenza ve koronavirüs hastalığı-2019 (COVID-19) aşılarıyla birlikte solunum yolu enfeksiyonlarının önlenmesinde önemli bir koruyucu strateji sunmaktadır.[7,32]

RSV'ye bağlı alt solunum yolu hastalığı ve hastaneye yatış riskini azaltmak amacıyla prefüzyon F proteinini hedefleyen iki rekombinant aşı bulunmaktadır. Bunlardan ilki adjuvanlı monovalan, diğeri ise adjuvansız, bivalan yapıdaki prefüzyon F protein aşılarıdır. Her iki aşı da RSV-A ve RSV-B'ye karşı koruma sağlamakta olup tek doz şeklinde intramüsküler olarak uygulanır. Etkinlik verileri doğrudan karşılaştırılabilir olmasa da randomize kontrollü çalışmalar ve gerçek yaşam verileri, her iki aşının da RSV ilişkili alt solunum yolu enfeksiyonuna bağlı hastaneye yatışları anlamlı ölçüde azalttığını göstermektedir. Klinik çalışmalarda ilk RSV sezonunda koruma %60-80 aralığında olup, etkinlik zamanla azalmaktadır. Mevcut veriler, koruyuculuğun en az iki sezon sürdüğünü ve üçüncü sezonda azalmış düzeyde devam edebildiğini göstermektedir.[38-41] Adjuvanlı aşının daha yüksek immün yanıt oluşturduğu gösterilmiş olmakla birlikte, immünosüprese bireylerde klinik üstünlüğünü ortaya koyan doğrudan veri bulunmamaktadır. Her iki aşı da şu an için ülkemizde geri ödeme kapsamında değildir ancak eczanelerden ücretli temin edilebilmektedir.

2.9. Kuduz aşısı: Kuduz açısından riskli temas yaşayan romatoloji hastalarında ulusal aşı algoritmasına uyulması; immünosüpresif hastalarda aktif aşının yanı sıra kuduz immünoglobulininin de uygulanması önerilir.

Kuduz, ölümcül seyri nedeniyle temas sonrası hızlı ve doğru profilaksinin zorunlu olduğu bir enfeksiyondur. Immünosüpresif tedavi altındaki hastalarda kuduz aşı yanıtının zayıflayabileceği gösterilmiştir; özellikle RTX ve diğer B hücre hedefli ajanlar sonrasında humoral yanıt belirgin biçimde azalmaktadır. Bu nedenle immünosüpresif hastalarda hem aktif aşı hem de spesifik immünoglobulin uygulaması standart yaklaşım haline gelmiştir.[42] İmmünosüprese bireylerde aşı serisi (0, 3, 7, 14 ve

28. günlerde) tamamlandıktan 2-4 hafta sonra nötralizan antikor düzeyine bakılması önerilmektedir. Temaslı hayvanın gözlem süresinde kuduz olmadığının gösterilmesiyle aşılama daha erken sonlandırılabilir.[43]

2.10. Seyahat aşıları: Romatoloji hastalarında aşılama gidilecek bölgenin riskine göre planlanmalı; sarı humma, meningokok ve diğer seyahat ile ilişkili aşılar ulusal ve uluslararası önerilere göre uygulanmalıdır. Canlı sarı humma aşısı ileri derecede immünosüpresif hastalarda kontrendike olduğundan zorunlu seyahat durumunda tedavi düzenlemesi için değerlendirilme yapılmalıdır.

Seyahat aşıları romatoloji hastalarında özel değerlendirme gerektirir, çünkü canlı aşıların büyük bölümü orta-ağır immünsüpresyon altında kontrendikedir. Sarı humma aşısı bu açıdan en kritik aşılardan biridir; DSÖ ve CDC rehberleri ileri düzey immün yetmezlikte aşının kesin kontrendike olduğunu vurgulamaktadır.[44,45] İnaktif aşılar ise genellikle güvenli olup meningokok, hepatit A/B ve poliomiyelit inaktif aşıları romatoloji hastalarında uygulanabilir. Seyahat başlangıcına 1 aydan kısa süre varsa hepatit A/B kombine aşı ile hızlandırılmış şema (0, 7, 21-30. gün kombine aşı ve 12. ayda hepatit B rapel) uygulanabilir.[32,46]

2.11. Şiddetli akut solunum sendromu koronavirüsü-2 (SARS-CoV-2) aşısı: İmmünosüprese olmayan romatoloji hastalarında daha önceki aşılanma durumuna bakılmaksızın; 18-64 yaş aralığında bir doz, 65 yaş ve üzerinde altı ay ara ile iki doz güncel sezon aşısının uygulanması önerilir. Orta-ağır derecede immünosüprese kabul edilen 18 yaş ve üzeri romatoloji hastalarında aşılama, önceki aşılanma durumuna göre planlanmalıdır. Daha önce COVID-19 aşısı yapılmamış erişkinlerde üçlü aşılama şeması tamamlanmalıdır. Daha önce aşılanmış immünosüprese hastalarda ise güncel sezon aşısı ile iki doz aşı önerilir. Doz sayısı ve aralıklar hastanın önceki aşı öyküsüne ve kullanılan aşıya göre belirlenmelidir.

SARS-CoV-2 enfeksiyonu romatoloji hastalarında ağır seyretme, hastaneye yatış ve ölüm riskinin artmasıyla ilişkilidir. Immünosüpresif tedaviler—özellikle RTX, mikofenolat mofetil, siklofosfamid ve JAK inhibitörleri—hem enfeksiyon gelişme riskini artırmakta hem de aşı yanıtını azaltabilmektedir. Yapılan son meta-analizde, XBB.1.5 uyarlanmış haberci ribonükleik asit (mRNA) aşılarının erişkinlerde hastaneye yatış riskini %46-50, ≥65 yaşta %51-60 ve immünkompromize bireylerde ise %37 azalttığı gösterilmiştir. Ayrıca KP.2 varyantına karşı aşılarda etkinliğin %68'e kadar çıktığı bildirilmiştir.[37] RTX tedavisi alan hastalarda rapel aşıların zamanlaması kritik öneme sahiptir. ACR ve ACIP, immünosüpresif tedavi alan bireylerde düzenli aralıklarla güncel mRNA aşılarının uygulanmasını önermektedir.[47-50] Ayrıca RTX planlanan hastalarda aşılamanın tedavi öncesine alınması, aşı yanıtını anlamlı derecede artırmaktadır. Geçirilecek COVID-19 enfeksiyonunun romatolojik hastalığı alevlendirme riski göz önünde bulundurulduğunda, etkin aşılama stratejisinin hem enfeksiyon kontrolü hem de hastalık yönetimi açısından önem taşıdığı açıktır.

Erişkin romatoloji hastalarında COVID-19 aşılaması değerlendirilirken, aşılamanın nadir kardiyovasküler riskleri ile enfeksiyonun yaratacağı ağır kardiyovasküler yük arasındaki denge gözetilmelidir. mRNA aşıları nadir de olsa miyokardit ve perikardit olguları ile ilişkilendirilmiştir; bu durum genellikle genç erkeklerde (12-24/30 yaş arası) ve sıklıkla ikinci dozdan sonraki birkaç gün içinde ortaya çıkmakta olup, çoğunlukla hafif seyirli, geçici ve konservatif tedaviye iyi yanıt veren klinik tablolar şeklindedir.[51-53] Özellikle bu durumun genç erkeklerde aşının ilk iki dozu arasındaki süre ile ilişkisi olduğunu düşündüren veriler bulunmaktadır.[54,55] Ancak bunu desteklemeyen çalışmalar da olduğundan konuyla ilgili daha fazla veriye ihtiyaç vardır. COVID-19 aşılarının kardiyovasküler koruyucu etkileri, potansiyel risklerinden çok daha ağır basmaktadır.[53,56] SARS-CoV-2 enfeksiyonunun miyokardit geliştirme riski, aşıya kıyasla 15 kat daha fazladır.[57-59] Ayrıca COVID-19 enfeksiyonu; akut miyokard enfarktüsü, inme, kalp yetmezliği ve venöz tromboemboli gibi majör kardiyovasküler olayların insidansını ciddi şekilde artırmaktadır.[60,61] Araştırmalar, COVID-19 aşılarının olası bir enfeksiyon sonrası kalp yetmezliği ve tromboz gelişme ihtimalini önemli ölçüde azalttığını göstermiştir.[52,62] Aşılanmış bireylerin SARS-CoV-2 ile enfekte olmaları durumunda bile, aşılanmamış olanlara kıyasla majör advers kardiyovasküler olay insidansının ve tüm nedenlere bağlı mortalitenin belirgin bir şekilde düştüğü saptanmıştır.[51,52,63] Sistemik enflamasyon nedeniyle yüksek aterosklerotik kardiyovasküler hastalık riskine sahip olan romatoloji hastalarında, aşıların COVID-19'un neden olduğu vasküler hasara ve tromboenflamasyona karşı güçlü bir koruma sağlayacağı varsayılabilir.

3. Canlı Aşı Uygulama Önerileri

3.1. Canlı aşılar mümkünse immünosüpresif tedavi başlanmadan en az 4 hafta önce uygulanmalıdır. Immünosüpresif tedavi alan hastalarda canlı aşı genellikle kontrendikedir; mutlak uygulanması gereken durumlarda, kullanılan ilacın yarı ömrüne göre aşı öncesi ve sonrası ilaca ara verme süresi bireysel olarak planlanmalıdır. Canlı aşının inaktif aşı alternatifi varsa tercih edilmelidir. Yüksek doz intravenöz Ig (IVIG) (0,4-2 gr/kg) tedavisi sonrasında canlı aşı yapılacaksa, aşının 8-11 ay ertelenmesi önerilir.

Romatizmal hastalıkların seyri ve bu süreçte kullanılan immünosüpresif tedaviler enfeksiyon duyarlılığını artırdığından, canlı aşıların (kızamık-kızamıkçık-kabakulak, suçiçeği, sarı humma vb.) uygulanmasında immünolojik zamanlama ve güvenlik protokollerine uyulması büyük önem arz etmektedir.

Canlı zayıflatılmış mikroorganizmaların replikasyon yeteneği, immünosüpresif tedavi altındaki bireylerde kontrolsüz çoğalma neticesinde "aşı suşu enfeksiyonu" riskini doğurabildiği için, bu aşıların tercihen immünosüpresif tedavi başlangıcından en az 4 hafta önce tamamlanması, hem viral/bakteriyel klirensin sağlanması hem de optimal immünojenik yanıtın oluşması açısından temel gerekliliktir.

Immünosüpresif tedavi başlanmış hastalarda canlı aşılar genel olarak kontrendike kabul edilmekle birlikte; uygulamanın zorunlu olduğu istisnai durumlarda karar, hastalığın aktivitesi, kullanılan ilacın farmakokinetik profili ve biyolojik etki süresi (genellikle yarı ömrün 5 katı süre baz alınarak) dikkate alınarak bireyselleştirilmeli ve mümkünse inaktif veya rekombinant alternatifler öncelikle tercih edilmelidir. Ayrıca, yüksek dozc IVIG (0.4-2 g/kg) gibi pasif antikor içeren ürünlerin aşı içeriğindeki replikasyonu baskılayarak immün yanıtı zayıflatma potansiyeli nedeniyle, IVIG sonrası canlı aşı uygulamalarının literatürle uyumlu şekilde 8 ila 11 ay süreyle ertelenmesi önerilmektedir.[7,28,64]

4. Romatoloji Hastalarında Aşıların İmmünojenisite ve Etkinliği Açısından Uygulanma Zamanlarının Planlanması

4.1. Canlı olmayan aşıların uygulanma zamanlamasında hastalık aktivitesi göz ardı edilebilir.

4.2. Hastalık aktivitesi izin veriyorsa influenza aşısından sonra MTX tedavisine 2 hafta ara verilmesi önerilir.

4.3. Immünosüpresif tedavi alan hastalarda, influenza aşısı yapılacak ise MTX dışı immünosüpresif tedavilere devam edilebilir.

4.4. Immünosüpresif tedavi alan hastalarda, influenza dışı canlı olmayan aşı yapılacak ise RTX dışındaki immünosüpresif tedavilere devam edilebilir.

4.5. RTX tedavisi alan hastalarda, influenza dışı canlı olmayan aşıların uygulanmasının bir sonraki RTX tarihine ertelenmesi ve o RTX tedavisinin de aşılamadan 2 hafta sonra yapılması önerilir.

4.6. <20 mg/gün prednizon eşdeğeri glukokortikoid kullananlarda canlı olmayan aşılar istenilen zamanda uygulanabilir.

4.7. ≥20 mg/gün prednizon eşdeğeri glukokortikoid kullananlarda influenza aşısı mevsimsel olarak zamanında uygulanabilir.

4.8. ≥20 mg/gün prednizon eşdeğeri glukokortikoid kullananlarda influenza dışı canlı olmayan aşıların mümkünse glukokortikoid dozunun 20 mg/gün dozunun altına ininceye kadar ertelenmesi önerilir.

Yapılan çalışmalar, yüksek hastalık aktivitesinin aşıya karşı gelişen bağışıklık yanıtını engellemediğini göstermektedir. Örneğin, 340 RA hastasını kapsayan bir çalışmada, hastaların %14,5'i yüksek hastalık aktivitesine (DAS 28>5,1) sahip olmasına rağmen, bu durumun koruyucu antikor seviyelerine (seroproteksiyon) ulaşmayı engellemediği tespit edilmiştir.[65]

Ayrıca canlı olmayan aşıların uygulanmasının altta yatan hastalığı alevlendirdiğine dair kanıtlar oldukça sınırlıdır. İnfluenza, pnömokok ve HPV gibi aşılar üzerine yapılan geniş çaplı incelemelerde, aşılamanın hastalık aktivitesini artırmadığı veya klinik seyri olumsuz etkilemediği sonucuna varılmıştır.[66]

Metotreksat

MTX romatizmal hastalıklarda sık kullanılan ajanlardan biri olup özellikle 15,8 mg/hafta ve üzeri MTX kullanımında influenza aşılamasında aşı yanıtını azaltabileceğini gösteren çalışmalar mevcuttur.[67] Yapılan bir çalışmada, aşı sonrası 2 hafta MTX'e ara veren hastalarda tatmin edici aşı yanıtı oranı %75,5 iken, tedaviye kesintisiz devam edenlerde bu oran %54,5'te kalmıştır.[68] Ayrıca ara verme stratejisi, farklı influenza suşlarına karşı seroproteksiyon oranlarını %11 ile %16 arasında artırmaktadır.[69,70] Bu sebeple MTX tedavisinin kesilemediği durumlarda hastalar aşılamadan mahrum bırakılmamalıdır.

Benzer şekilde COVID-19 aşılamasından sonra MTX tedavisine 2 hafta ara verilmesinin aşı yanıtını artırdığını gösteren çalışmalar mevcuttur, ancak burada da hastalık aktivasyonu açısından hasta ile konuşularak ortak karar alınmalıdır.[71]

Yakın zamanda yapılan bir çalışmada tek başına MTX tedavisinin 13 valanlı PCV'de aşı yanıtını azaltmaz iken, JAK inhibitörleri ile kombine kullanımda aşı yanıtını azalttığı gösterilmiştir. Kombine tedavi alanlarda aşı döneminde iki hafta MTX'a ara verilerek JAK inhibitörüne devam edilmesi mantıklı olabilecek bir yaklaşımdır.[72]

Romatizmal hastalığı olan bireylerde, hastalık aktivitesi izin veriyorsa influenza ve COVID-19 aşısından sonra MTX tedavisine 2 hafta ara verilmesi önerilmektedir.[7,71,73] Romatizmal hastalığı olup, immünosüpresif tedavi alan hastalarda, influenza aşısı yapılacak ise MTX dışı immünosüpresif tedavilere devam edilebilir.

Glukokortikoid

10 mg ve altı eşdeğeri prednizon kullanımının aşı yanıtına olumsuz etkilemezken 20 mg ve üzeri prednizon dozunun ise aşı yanıtını azalttığı gösterilmiştir.[74,75] Glukokortikoid tedavisinin aşı yanıtını azalttığını gösteren yayınlar olduğu gibi az sayıda da olsa etkilemediğini gösteren yayınlar da vardır.[76,77]

10 mg ve daha düşük prednizon tedavisi alan romatoloji hastalarında canlı olmayan aşılar istenilen zamanda yapılabilir. 20 mg ve üzeri prednizon tedavisi alan bireylerde influenza dışı canlı olmayan aşılar mümkünse prednizon dozu 20 mg'ın altına inilinceye kadar ötelenmesi önerilir. İnfluenza aşısı her dozdaki glukokortikoid kullanımında yapılabilir.

Prednizon eşdeğeri ≥20 mg/gün dozda ve ≥14 gün süreyle sistemik kortikosteroid kullanan hastalarda canlı aşı uygulaması önerilmemektedir. Bu hastalarda yüksek doz kortikosteroid tedavisi sonlandırıldıktan sonra canlı aşı uygulaması için en az 1 ay beklenmelidir. Buna karşılık, kısa süreli (<14 gün) veya düşük-orta doz (<20 mg/gün) sistemik kortikosteroid kullanımı klinik olarak anlamlı immünsüpresyon oluşturmadığından, bu hastalarda canlı aşılar genellikle güvenle uygulanabilir. Ayrıca topikal, inhaler veya intraartiküler steroid uygulamaları sistemik immünsüpresyon oluşturmadığından canlı aşılar açısından kontrendikasyon oluşturmaz.[78,79]

Biyolojik DMARD'ler

B hücre deplesyonu yapan biyolojik ajanlar dışındaki biyolojik DMARD'ler, inaktif aşıların immünojenisitesi üzerine olumsuz etkisi bulunmadığından aşılar zamanında yapılabilir. Örneğin anti-TNF ajanların pnömokok aşı yanıtını olumsuz etkilemediğini gösteren yayınlar mevcuttur.[80] Anti-TNF tedavi altında iken canlı aşı yapılması ile ilgili sonuçlar da tartışmalıdır. Bazı çalışmalarda hiç yan etki gözlenmezken, enfeksiyon gelişimi izlenen çalışmalar da vardır.[81-83]

HBV aşı yanıtı anti-TNF alanlarda diğer biyolojik tedavi (RTX, abatasept ve tosilizumab) alan gruba göre daha yüksek saptanmıştır. Anti-TNF tedavi alan hastalar arasında da infliksimab kullananlarda, etanersept kullananlara göre aşı yanıtı daha düşük bulunmuştur.[84] İnterlökin 12-23 tedavisinin hepatit B aşı yanıtını azalttığını gösteren çalışmalar mevcuttur.[85]

Rituksimab

RTX B hücre deplesyonu yaparak antikor oluşumunu ve aşıların immünojenisitesini en çok etkileyen ajanlardan birisidir. Yapılan bir çalışmada RTX tedavisinden 4-8 hafta sonra influenza aşısı olanlarda, RTX'tan 6-10 ay sonra olanlara göre aşı yanıtının daha kötü olduğu gözlenmiştir.[86] Prospektif gözlemsel bir çalışmada RTX tedavisi alan hastalarda hiç hepatit B aşı yanıtı izlenmemiştir.[84]

Romatizmal hastalığı olup RTX tedavisi alan hastalarda influenza aşısını ötelemek yerine normal döneminde yapılması önerilir. İnfluenza dışı canlı olmayan aşıların yapılması bir sonraki RTX dozuna ertelenmesi ve o RTX tedavisinin de aşılamadan en az iki hafta sonra yapılması önerilir. İnfluenza dışı canlı olmayan aşı yapılacak ise RTX dışındaki immünosüpresif tedavilere devam edilebilir. Ardışık aşılama gerektiren ve RTX tedavisi alan bireylerde, eğer tedavi fazla ötelenmek istenmiyorsa: İki dozluk aşılamalarda (örneğin rekombinant VZV aşısı) ilk dozun 5. ayda, 2. dozun 6. ayda verilmesi, RTX tedavisinin 2 hafta ertelenmesi önerilir. Üç dozlu aşılamalarda ise (örneğin HPV gibi) 6. ayda 3. doz aşısı yapılıp yine en az 2 hafta sonra RTX uygulanmalıdır. Böylece RTX dozu en fazla 2 hafta ertelenmiş olacaktır. Ancak RTX'i ertelemenin mümkün olduğu hastalarda veya tek doz uygulamalı aşılarda; tedavinin 6. ayında yapılması tercih edilmelidir.

JAK İnhibitörleri

JAK inhibitörü ile tedavi edilen hastalarda pnömokok ve influenza aşıları sonrası pnömokok aşı yanıtında azalma gözlenirken, influenza aşı yanıtında değişiklik izlenmemiştir.[87] Pnömokok ve tetanoz aşı yanıtının değerlendirildiği bir başka çalışmada JAK inhibitörü alan hastalarda yeterli aşı yanıtının oluştuğu gözlenmiştir.[77] JAK inhibitörü ile MTX'i birlikte kullananlarda aşı yanıtının azaldığı ancak, JAK inhibitörü monoterapisinin aşı yanıtını etkilemediğini gösteren yayınlar mevcuttur.[72] Rekombinant VZV aşısı yapılan ve JAK inhibitörü kullanan bireylerde de yine aşı yanıtının etkilenmediği gösterilmiştir.[88]

5. Immünosüpresif Tedavi Alan Gebe Romatoloji Hastalarının Bebeklerinin Aşılanması

5.1. Tüm aşılar (inaktif/canlı), intrauterin konvansiyonel sentetik DMARD maruziyeti olan bebeklere uygulanabilir.

5.2. İnaktif aşılar, intrauterin biyolojik DMARD maruziyeti olan bebeklere uygulanabilir.

5.3. İkinci ve/veya üçüncü trimesterde intrauterin TNF inhibitörlerine maruz kalan bebeklerde rotavirüs aşılaması ilk 6 ay içinde yapılabilir.

5.4. İkinci ve/veya üçüncü trimesterde intrauterin TNF inhibitörleri dışında biyolojiklere maruz kalan bebeklere, rotavirüs aşısının, ilk 6 aydan sonraya ertelenmesi önerilir.

5.5. İkinci ve/veya üçüncü trimesterde intrauterin TNF inhibitörlerine ya da diğer biyolojik DMARD'lere maruz kalan bebeklerde bacillus Calmette-Guérin (BCG) aşılamasının 6. aydan sonraya bırakılması önerilir.

5.6. Biyolojik tedavilerin emzirme döneminde kullanılması, bebek aşılama programını etkilemez.

Gebelik sırasında kullanılan biyolojik ilaçlara intrauterin maruz kalan bebeklerde, doğumdan sonra kanda aylarca tespit edilebilir ilaç düzeylerinin bebeklerde bağışıklık sisteminin baskılaması ve özellikle canlı aşıların güvenliği ile ilgili endişelere yol açmaktadır.[89] İnfiksimab, adalimumab ve golimumab için 20. gestasyonel hafta sonrası; etanersept için 32. gestasyonel hafta sonrası maruziyet, intrauterin maruziyet olarak kabul edilmektedir. Sertolizumab pegolün plasental geçişinin minimal ya da tespit edilemeyecek düzeyde olduğu kabul edildiğinden, bebek aşılama programını etkilememektedir. Gebeliğin ikinci yarısında annenin B hücre deplesyonu yapan ajanları kullanması (RTX, belimumab) yenidoğanda geçici B hücre azalmasına veya diğer sitopenilere neden olduğu gösterilmiştir.[90]

Bebeklere uygulanan BCG ve rotavirüs aşıları, doğumdan sonraki ilk altı ayda uygulanan canlı aşılar arasında yer almaktadır. rotavirüs aşısının canlı aşı olmasına rağmen diyareye bağlı çocuk ölümlerini azaltması ve intussusepsiyon riski nedeniyle 6. aydan önce yapılması, ertelenecekse de en geç 8. ayda tamamlanmış olması önerilmektedir. İntrauterin 2. veya 3. trimesterde RTX maruziyetinde ilk 6 aydan sonra; ikinci 6 ay içinde çok da geciktirmeden rotavirüs aşısının yapılması önerilmektedir.[90,91] Literatürde gebeliğin ikinci yarısında intraüterin TNF inhibitörlerine maruz kalan bebeklerde BCG aşısına bağlı nadir de olsa fatal dissemine BCG olguları bildirilmiştir.[92] Gebeliğin ikinci ya da üçüncü trimesterinde TNF inhibitörleri ve TNF inhibitörleri dışındaki biyolojiklere maruz kalan infantlarda BCG aşısının 6. aydan sonraya bırakılması önerilmektedir.[93]

Mevcut kanıtlar, biyolojik ilaçların anne sütüne geçişinin olmadığını veya minimal düzeyde olduğunu desteklemektedir. Ayrıca biyolojik ilaçların oral biyoyararlanımları yok denecek kadar azdır. Bu nedenlerle emziren ve biyolojik ilaç kullanan annelerin bebeklerine, belirtildiği şekilde ve önerilen aşılama takvimine göre canlı virüs aşıları da dahil olmak üzere tüm aşıların yapılması önerilmektedir.[93,94]

Tartışma

Yaşadığımız pandemi sırasında hızla ve farklı bir teknolojiyle geliştirilen COVID-19 mRNA aşıları sonrasında bildirilen advers olaylar, aşıyla nedensellik ilişkisi olmamasına rağmen, aşı güvenliğine yönelik kamuoyu algısının olumsuz etkilenmesine ve genel aşı kararsızlığında artışa katkıda bulunmuştur. Oysa COVID-19 mRNA aşılarının, milyonlarca kişinin hayatını kurtardığı hem pandemi sırasında gözlemlendi hem de pandemiden bu yana çıkan geniş serili çalışmalarla kanıtlandı. Dört yıllık takipte COVID-19 aşısı uygulanan bireylerin değerlendirildiği bir çalışmada, aşıların 2,5 milyon ölümü engellediği, yaklaşık 15 milyon yaşam yılı kazancı sağladığı ve bu kazancın büyük kısmının (%76) 60 yaş üzeri kişilerde olduğu bildirilmiştir.[95]

Aşı tereddüdünün artması ve aşıların sorgulanması, sağlık politikalarını etkileyerek halk sağlığı otoritelerini harekete geçirmiş ve olası salgınları önlemek amacıyla daha kapsamlı ve güven tazeleyici çalışmalar yapmaya yönlendirmiştir. Bu çerçevede COVID-19, RSV ve influenza aşılarına ilişkin güncel meta-analizler, bu aşıların etkinlik ve güvenlik profillerini yeniden ortaya koyarak mevcut kanıtları güçlendirmiştir.[37] Bununla birlikte, özellikle 12-24 yaş arasındaki erkeklerde, COVID-19 mRNA aşısının iki dozu arasındaki sürenin 6 aydan kısa olduğu durumlarda miyokardit riskinin arttığı gösterilmiştir. Bu da aşılama şemalarının belirli hasta alt gruplarında dikkatle planlanması gerektiğini ortaya koymaktadır.[96] Güncel veriler ışığında, immünosüprese olmayan bireylerde yıllık tek doz aşılama önerisi sürdürülmekle birlikte; önemli varyant değişikliklerinin olmadığı durumlarda, gelecekte daha uzun aralıklı aşılama stratejilerinin gündeme gelebileceği öngörülmektedir. İmmünosüprese bireylerde ise eksikse aşılama şemasının tamamlanması ve güncel aşıyla rapel doz uygulanması önerilmektedir.[50]

Güncellemeler kapsamında yapılan son meta-analizde, RSV aşılarıyla ilişkili olarak, daha önce hiç rastlanmadığı söylenen Guillain-Barré sendromunun, çok nadir de olsa özellikle adjuvansız formlarla ilişkili olabileceği gösterilmiş, influenza aşılarına ait etkinlik ve güvenlik verilerinin ise önceki verilerle uyumlu olduğu bildirilmiştir.[37] Bu sonuçlar, değişen çevresel faktörler ve bireysel farklılıkların aşı yanıtını etkileyebileceğini göstermekle birlikte aşılarla ilgili kanıtların geniş kapsamlı çalışmalar ve meta-analizlerle dinamik bir şekilde güncellenmesi gerektiğinin de altını çizmektedir.

Bağışıklık sistemi baskılanmış ya da immün yanıtın değişkenlik gösterebildiği romatoloji hastalarında aşılama, enfeksiyon riskini azaltmak ve hastaların yaşam kalitesini artırmak için önemli bir stratejidir. Aile hekimleri, kayıtlı nüfusun düzenli izlenmesi ve aşılama durumunun kayıt altına alınarak takip edilmesi açısından önemli bir sağlık hizmeti sunmaktadır. Aşıların etkinliği ve güvenliği, hastaların düzenli takibi ve hekim önerilerine uyumla en üst düzeye çıkarılabilir. Erişkin romatoloji hastalarının bağışıklanması, romatologlar ve aile hekimlerinin iş birliği içinde yürütmesi gereken bir koruyucu sağlık hizmetidir. Bu iş birliğinin etkin bir şekilde yapılandırılması, aşılama oranlarının artırılması ve hastaların enfeksiyonlardan korunması için kritik öneme sahiptir.

Aşıların etkinlik ve güvenliğine ilişkin kanıtların giderek güçlendiği bilinmeli; buna karşın aşı tereddüdü ve bireysel risk algısının klinik karar süreçlerini etkilemeye devam ettiği unutulmamalıdır. Romatoloji hastaları gibi özel değerlendirme gerektiren hasta gruplarında aşılamanın, güncel bilimsel veriler ışığında bireyselleştirilerek yapılması büyük önem taşımaktadır. Aşılama, romatoloji hastalarının sağlığını korumak ve yaşam kalitelerini artırmak için vazgeçilmezdir.

Dipnotlar

Yazarlık Katkıları

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Ek 1: https://d2v96fxpocvxx.cloudfront.net/00df66f2-5bbf-4336-8ecd-25d1bc79ad25/content-images/34cefe4b-09ec-426d-861e-8deb7a822561.pdf

Ek 2: https://d2v96fxpocvxx.cloudfront.net/bfe6b059-1982-481c-8e2f-073cbc0b054a/content-images/564ff753-53dc-4d46-ae8a-c812c454e566.pdf

Ek 3: https://d2v96fxpocvxx.cloudfront.net/bfe6b059-1982-481c-8e2f-073cbc0b054a/content-images/3812145e-e8f2-4841-a04e-8bb4ebddc530.pdf

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Cross-cultural adaptation and psychometric evaluation of the Turkish P4 pain intensity scale

Türkçe P4'ün kültürlerarası uyarlanması ve psikometrik değerlendirmesi

Kardem Ulaş[1], Nazemin Gilanlıoğulları[2], Murat Güçtekin[1]

[1]Department of Physiotherapy and Rehabilitation, Girne American University Faculty of Health Sciences, Kyrenia, Northern Cyprus, TR-10 Mersin, Türkiye
[2]Department of Physiotherapy and Rehabilitation, European University of Lefke Faculty of Health Sciences, Lefke, Northern Cyprus, TR-10 Mersin, Türkiye

Abstract

Objective: Pain assessment is "an important part of the healthcare system" as it contributes to improving patients' quality of life, especially for people who have chronic pain such as fibromyalgia. There are many tools that help to assess pain, but they have some limitations. The P4 pain intensity scale is a tool that helps assess pain using four questions that are easy to understand and use. However, it has not yet been translated into Turkish. This study aimed to cross-culturally adapt the P4 into Turkish and evaluate its psychometric properties in individuals with fibromyalgia.

Methods: Two phases were conducted to cross-culturally adapt and psychometrically test the Turkish version of P4 for people with fibromyalgia. In phase one, an expert panel meeting (n=8) and cognitive debriefing interviews (n=10) were conducted to translate P4 into Turkish and to make it understandable and relevant for people with fibromyalgia. In phase two, classical test theory (CTT) was used to assess the reliability and cross-cultural validity of the P4 in individuals with fibromyalgia (n=40) by comparing it with the visual analogue scale or the numeric pain rating scale.

Results: The expert panel meeting and cognitive debriefing interviews confirmed that the Turkish version of the P4 was understandable and relevant to individuals with fibromyalgia. CTT showed that the Turkish version of P4 has good reliability and validity for use in people with fibromyalgia, there is no gold-standard measure to compare its results.

Conclusion: The Turkish version of P4 has the ability to detect true daily pain intensity in people with fibromyalgia in a simple and inexpensive manner.

Keywords: P4, pain, fibromyalgia, cross-cultural adaptation, validity, reliability

Özet

Amaç: Ağrı değerlendirmesi, özellikle fibromiyaljiye bağlı kronik ağrısı olan kişilerde hastanın yaşam kalitesini iyileştirmeye yardımcı olması nedeniyle "sağlık sisteminin önemli bir parçasıdır". Ağrıyı değerlendirmeye yardımcı olan birçok araç bulunmakla birlikte, bunların bazı sınırlamaları vardır. P4 ağrı şiddeti ölçeği, anlaşılması ve kullanımı kolay, dört soruyla ağrıyı değerlendirmeye yardımcı olan bir araçtır. Ancak Türkçeye çevirisi bulunmamaktadır. Bu çalışma, P4'ü Türkçeye kültürlerarası uyarlamayı ve fibromiyalji hastaları için psikometrik olarak test etmeyi amaçlamaktadır.

Yöntem: Fibromiyaljili bireyler için P4'ün Türkçe versiyonunu kültürlerarası uyarlamak ve psikometrik olarak test etmek amacıyla iki aşama yürütülmüştür. Birinci aşamada, uzman paneli toplantısı (n=8) ve bilişsel değerlendirme görüşmeleri (n=10) gerçekleştirilerek P4'ün Türkçeye çevrilmesi ve fibromiyaljili bireyler için anlaşılır ve anlamlı hale getirilmesi amaçlanmıştır. İkinci aşamada, fibromiyaljili bireyler (n=40) için P4'ün güvenilirliği ve kültürlerarası geçerliliği, klasik test teorisi (CTT) kullanılarak, görsel analog skala ve numerik ağrı derecelendirme skalası ile karşılaştırılarak değerlendirilmiştir.

Bulgular: Uzman paneli toplantısı ve bilişsel değerlendirme görüşmeleri, P4'ün Türkçe versiyonunun fibromiyaljili bireyler için anlaşılabilir ve uygun olduğunu göstermiştir. CTT, P4'ün Türkçe versiyonunun fibromiyaljili bireyler için kullanılabilecek iyi bir güvenilirlik ve geçerliliğe sahip olduğunu göstermiştir.

Sonuç: P4'ün Türkçe versiyonu fibromiyalji hastalarında günlük ağrı şiddetini pratik bir şekilde değerlendirmek için güvenilir şekilde kullanılabilir.

Anahtar Kelimeler: P4, ağrı, fibromiyalji, kültürlerarası adaptasyon, geçerlilik, güvenilirlik

Correspondence / İletişim: Kardem Ulaş Dr. Asst. Prof.,
Department of Physiotherapy and Rehabilitation, Girne American University Faculty of Health Sciences, Kyrenia, Northern Cyprus, TR-10 Mersin, Türkiye
E-mail: soyerkardem@gmail.com **ORCID ID:** orcid.org/0000-0002-6136-6124
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Introduction

The assessment and management of pain are recognized as crucial aspects of healthcare, and significant investment continues to be directed toward improving these processes.[1,2] The development of new tools that enable more accurate and efficient assessment of pain has been identified as a key target in this endeavor.[3,4]

Patients with fibromyalgia experience chronic widespread pain and tenderness. Fibromyalgia-related pain will change over time. Many people have good days and bad days. This fluctuating course of fibromyalgia often complicates pain assessment.[5]

There are many tools available to quantify pain. They range from a simple 1-10 verbal rating scale for intensity to the McGill pain questionnaire, which attempts to characterize the quality and intensity of pain in much greater depth.[6,7] Probably the most widely used and understood tool among those with fibromyalgia is the pain visual analogue scale (VAS) or the numeric pain rating scale (NPRS). This involves a 10 cm line with terminal descriptors "no pain" and "worst pain imaginable". Patients are asked to place a mark on the line to represent the overall intensity of their pain and to do the same to indicate pain "at its best". The difference between the two marks represents the perceived change in pain and is an indirect measure of pain relief.[6]

The VAS and NPRS allow good quantification of pain intensity and are relatively sensitive to changes over time. However, they have disadvantages. Some patients have difficulty understanding or using a 10 cm line. Those scales do not assess different components of pain (e.g., intensity, duration, and quality). This is important, as treatment may differentially affect these components. The VAS and NPRS are also criticized for a lack of clear categorization of pain intensity. This can render decisions based on baseline pain intensity unreliable, because changes in perceived pain intensity can be skewed across different levels of severity.[8-10]

Because the pain management system was effectively transitioned into a clinical practice setting and demonstrated a significant improvement in patient well-being, the P4 pain scale is to be used. It has great potential to supersede the NPRS and VAS scales.[11,12]

The first consideration regarding the scope of the P4 scale is that the panel must develop a scale capable of assessing pain in any situation, regardless of the severity or cause of the pain. Therefore, the scale needs to be simply worded and easily understood so that it can be used by a wide range of people, from patients to medical staff. The impact of this may be a wide-ranging standardization of pain assessment and improved recognition of pain.[12,13]

Our aim in this study was to translate the P4 into Turkish and to pave the way for its use among Turkish fibromyalgia patients, thereby shortening the decision-making process regarding pain during activities of daily living.

Materials and Methods

Recommended guidelines should be followed when conducting the cross-cultural adaptation and psychometric testing of a questionnaire.[14-16] Cross-cultural adaptation includes five steps: double translations, synthesis, reverse translation, expert panel review (including various members) to produce the pre-final version, and pretesting with the target population to assess the understandability of the items. As P4 was developed in another language, and after obtaining permission from the original developer of P4, recommended guidelines were followed to cross-culturally adapt P4 into Turkish and to make it understandable and relevant for people with fibromyalgia. Psychometric properties and pragmatic outcome measures are important for monitoring the success of implementation efforts and comparing the effectiveness of other rehabilitation techniques.[17] People aged over 18 who were able to write and speak Turkish, lived in Northern Cyprus, had a diagnosis of fibromyalgia, and could provide written consent were recruited for this study. After agreeing to participate in this study and providing written consent, participants were given three questionnaires to complete: the Turkish versions of the P4, VAS, and NPRS, to enable comparison of the P4 results with those of other questionnaires that aim to assess the same content.

Translation

The English version of the P4 was intended to be translated into Turkish to make the items understandable for people with fibromyalgia. After written permission was taken from the developers of P4, two translators used forward translation method to translate the English version of P4 into Turkish.[15] An expert panel, including the translator, synthesis recorder, healthcare professionals who work with people with fibromyalgia (such as a doctor, physiotherapist, and dietitian), research team members, and a lay person who spoke both Turkish and English, discussed the two forward translations for each item to ensure that they were understandable and agreed on a single Turkish version of the P4.

The draft Turkish version of the P4 was then reverse-translated into English; the items were checked and compared with the original P4. Following the translation process, the items of the translated Turkish version of the P4 were discussed by the expert panel members to ensure that they were understandable to people with fibromyalgia, and the panel reached a consensus.

After the expert panel review, ten participants who were diagnosed with fibromyalgia using exactly the same criteria were recruited to assess whether the items of the Turkish version of the P4 were understandable and relevant to their condition. Finally,

after completing the Turkish version of the P4, participants were asked to take part in a cognitive debriefing interview to provide feedback on the relevance, understandability, ease of completion, and structure of the P4. The understandability and relevance of the items were evaluated using a five-point rating scale. In addition, open-ended questions were asked about the ease of completion, structure, and items of the questionnaire to obtain more detailed information about the P4. Following the completion of interviews, the P4 was edited, and the final version was sent back to the expert panel members to gain further advice on the final Turkish version of the P4.

Statistical Analysis

Participants with fibromyalgia were recruited to evaluate the psychometric properties of the P4 using classical test theory (CTT). This will include concurrent validity, acceptability, contrast validity, minimal detectable difference, and test-retest reliability. To obtain descriptive and meaningful data, the sample size needs to be large enough for CTT.[18] A rule of thumb for sample size calculation is to include ten participants per item for confirmatory factor analysis.[18] As the P4 includes four items, the rule of thumb was used, and 40 participants will provide sufficient information for assessing psychometric properties. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 27.0; IBM Corp., Armonk, NY, 2020). Descriptive values for numerical demographic variables were expressed as mean ± standard deviation, and frequency (number and percent) for categorical variables. Statistical significance was set at p-values of <0.05 and <0.01.

Determination of Reliability

The intraclass correlation coefficient (ICC) and Cronbach's alpha were calculated as measures of internal consistency. Cronbach's alpha coefficient should be higher than 0.70 ($\alpha \geq 0.70$) to be accepted as very good.[19]

Determination of Validity

The Pearson correlation coefficient was calculated to determine the validity of the Turkish version of P4.

Ethical Consideration

Ethical approval was obtained from European University of Lefke Non-Interventional Clinical Researches Ethics Board (approval number: BAYEK038.12, date: 28.12.2023). Before collecting the data, informed written consent was obtained from the participants. All data were anonymized and kept strictly confidential.

Results

First Phase

Recruitment for phase-one started after receiving ethics approval from the Ethics Committee and lasted three months. The expert panel included eight people: a methodologist, two translators, a lay person, a physiotherapist, a doctor, a psychologist, and a dietitian. As a result of expert panel meetings, the English version of the P4 was translated into Turkish, and all items were found to be relevant and understandable to people with fibromyalgia. After the expert panel meeting, the first draft of the Turkish version of the P4 was used in cognitive debriefing interviews.

In total, 10 people diagnosed with fibromyalgia were recruited. All participants were female and aged between 23 and 47 years. Overall, all participants found the P4 survey to be good and relevant to their condition. They reported that there was nothing they would like to change or add. Only one participant thought that the date on the questionnaire, which is given as (year/month/day), could be reordered as (day/month/year), as this is the common format used in North Cyprus. This was edited after obtaining agreement from the expert panel members. The results of the cognitive debriefing interview were shared with the expert panel members, and the panel reached a consensus to use the translated version of the P4 for the second phase of the research to assess its psychometric properties.

Second Phase

Psychometric Properties

To assess the psychometric properties, 40 participants were recruited for this study. Table 1 provides a summary of the participants' demographic details. To quantify the reliability and validity, each participant was asked to complete VAS, NPRS and P4 twice (two weeks apart).[20] The VAS first measurement and the NPRS first measurement mean scores of the participants were 4.30 ± 1.40 and 4.0 ± 1.35 respectively. The VAS second measurement and the NPRS second measurement mean scores of the participants were 3.81 ± 1.2 and 3.51 ± 1.16 respectively. Participants' responses to P4 items for the first and second measurements are listed in Table 2.

Reliability

The test-retest reliability for the first measurements of the P4 total score was 0.81 [95% confidence interval (CI)]. Table 3 demonstrates Cronbach's alpha values for each item. The ICC value was calculated as a mean of 0.98 (0.979 to 0.994), $p<0.001$, which was above the acceptable level of 0.70.

Validity

The Pearson's r values were 0.824 for the P4 total score at the first measurement, 0.839 for NPRS and VAS at the first measurement, and 0.806 and 0.741 for the second measurements, respectively. Table 4 presents the analysis of item validations.

Discussion

The Turkish version of P4 used in the current study was considered statistically reliable and valid for measuring pain intensity in patients with fibromyalgia. Although not all questions needed to be adapted, changed, or removed for the 4th item, activity might affect pain changes in fibromyalgia patients, so Pearson's r was found to have fair validity.

Our goal in translating the P4 into Turkish was to obtain a practical clinical measure that is as sensitive as the single-item NPRS and VAS, yet more sensitive at indicating changes throughout the day and across activities. Norman[21] has shown that the test-retest reliability of a measure affects its sensitivity to change. Spadoni et al.[12] developed the P4 to measure pain intensity and change. They also examined whether the test-retest reliability and validity of the P4 were higher than those of the single-item NPRS. They found that the reliability and longitudinal validity of the P4 were statistically higher than those of the NPRS.[13] Similarly, our initial findings showed that the test-retest reliability and validity of the P4 were both statistically significant and higher than those of the NPRS and VAS.

In their research, they investigated patients not labelled as having chronic pain. In our research, we prefer to assess P4 in fibromyalgia patients because we can obtain a brief report. We believe that most of the questionnaires and scales for fibromyalgia are quite long and sometimes confusing.

No gold standard exists for pain assessment, and investigators must rely on a construct validation process. When we examine the reliability and validity of VAS [ICC=0.99 (95% CI 0.989 to 0.992)] and NPRS (r=0.79-0.96), they are both highly reliable and valid tools for measuring pain intensity.[22,23] However, the most important disadvantage is that they are single-item. For example, during the assessment of pain, when we ask the patients to score their pain with VAS and/or NPRS, they sometimes experience difficulty to detect exact value and ask "In general the severity of my pain is 3/10 but at nights it rises to 6/10, so which one should I circle?". Our study has shown, through item validation, that P4 serves to resolve that dilemma.

Previous studies have shown that the Turkish versions of the VAS and NPRS are reliable tools for assessing pain.[24,25] However, unlike VAS and NPRS, the P4 provides a more multidimensional assessment of pain by helping to analyze pain levels at different times of the day. For example, patients may experience low pain in the morning but significant pain in the evening. This cannot be captured using the VAS or NPRS, as they assess a single time point. However, this kind of detailed information can help healthcare professionals adapt the rehabilitation timeline or guide people with fibromyalgia to self-manage their daily activities by adapting those activities according to their pain, which can vary throughout the day.

Table 1. Participant descriptive

	n (40) n ± SD	n (40) n (%)
Age	33.4±13.3 years	
Gender		
Female		34 (85%)
Male		6 (15%)
Duration of disease	4.4±2.9 years	

n: Number, SD: Standard deviation, %: Percentage

Table 2. Descriptive of items

	n ± SD		n ± SD
NPRS (first)	4.0±1.35	**NPRS (second)**	3.51±1.16
VAS (first)	4.3±1.40	**VAS (second)**	3.81±1.2
P4.1 (first)	5.37±2.31	**P4.1 (second)**	4.95±2.3
P4.2 (first)	4.35±2.0	**P4.2 (second)**	4.47±1.9
P4.3 (first)	4.7±2.18	**P4.3 (second)**	5.35±2.2
P4.4 (first)	2.65±2.38	**P4.4 (second)**	2.19±1.9
P4. score (first)	16.98±6.77	**P4. score (second)**	16.95±6.7

First indicates test measures, second indicates re test measures, n: Number, NPRS: Numeric pain rating scale, P4: Pain intensity scale, SD: Standard deviation, VAS: Visual analogue scale

Table 3. Cronbach's alpha analyses of P4

	Cronbach's alpha analysis	
Items	**Total correlation**	**Cronbach's alpha if item deleted**
Item 1	0.892	0.744
Item 2	0.939	0.753
Item 3	0.769	0.775
Item 4	0.416	0.832
Total score	0.999	0.825

Cronbach's alpha of total scale: 0.817, P4: Pain intensity scale

Study Limitations

The study has several limitations. There is no other linguistic translation of P4, so we were not able to compare and discuss from the perspective of cross-cultural validation. Moreover, the sample size was limited because the number of fibromyalgia cases in TRNC is not known exactly, so it had to be determined using the rule of thumb. In addition, most participants were female, as fibromyalgia is more common in women. However, these limitations made it difficult to generalize the results, and further studies should be conducted with a larger sample of fibromyalgia patients and should include more detailed demographic information, such as participants' education level, to allow analyses across different subgroups.

Table 4. Item validation

		P4.1 (first)	P4.2 (first)	P4.3 (first)	P4.4 (first)	P4.score (first)	P4.1 (second)	P4.2 (second)	P4.3 (second)	P4.4 (second)	P4.score (second)	NPRS (first)	NPRS (second)	VAS (first)	VAS (second)
P4.1 (first)	r		0.750**	0.852**	0.188	0.899**	0.932**	0.787**	0.971**	0.032	0.862**	0.897**	0.868**	0.969**	0.910**
	p		0.000	0.000	0.227	0.000	0.000	0.000	0.000	0.839	0.000	0.000	0.000	0.000	0.000
P4.2 (first)	r			0.567**	0.500**	0.913**	0.864**	0.925**	0.782**	0.492**	0.950**	0.700**	0.721**	0.673**	0.613**
	p			0.000	0.001	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.000
P4.3 (first)	r				-0.195	0.709**	0.720**	0.611**	0.818**	-0.167	0.633**	0.715**	0.731**	0.878**	0.862**
	p				0.211	0.000	0.000	0.000	0.000	0.286	0.000	0.000	0.000	0.000	0.000
P4.4 (first)	r					0.518**	0.292	0.540**	0.176	0.840**	0.552**	0.289	0.212	0.096	0.068
	p					0.000	0.058	0.000	0.258	0.000	0.000	0.060	0.173	0.541	0.664
P4.score (first)	r						0.902**	0.932**	0.890**	0.415**	0.977**	0.824**	0.801**	0.839**	0.791**
	p						0.000	0.000	0.000	0.006	0.000	0.000	0.000	0.000	0.000
P4.1 (second)	r							0.781**	0.944**	0.194	0.922**	0.855**	0.829**	0.874**	0.825**
	p							0.000	0.000	0.213	0.000	0.000	0.000	0.000	0.000
P4.2 (second)	r								0.762**	0.451**	0.924**	0.790**	0.792**	0.746**	0.661**
	p								0.000	0.002	0.000	0.000	0.000	0.000	0.000
P4.3 (second)	r									0.047	0.872**	0.828**	0.819**	0.921**	0.862**
	p									0.767	0.000	0.000	0.000	0.000	0.000
P4.4 (second)	r										0.498**	0.137	0.126	-0.039	-0.015
	p										0.001	0.382	0.422	0.806	0.922
P4.score (second)	r											0.821**	0.806**	0.794**	0.741**
	p											0.000	0.000	0.000	0.000
NPRS (first)	r												0.929**	0.931**	0.855**
	p												0.000	0.000	0.000
NPRS (second)	r													0.894**	0.838**
	p													0.000	0.000
VAS (first)	r														0.937**
	p														0.000
VAS (second)	r														
	p														

First indicates test measures, second indicates retest measures, *: p<0.05, correlation is significant at the 0.05 level, **: Correlation is significant at the 0.01 level, NPRS: Numeric pain rating scale, P4: Pain intensity scale, r: Pearson correlation coefficient, VAS: Visual analogue scale

Conclusion

The validity of measures intended to assess symptom-related quality of life and pain will always be incomplete because there are no gold standards for these attributes. The current study demonstrates P4's ability to detect true daily pain intensity in a simple and inexpensive manner.

Ethics

Ethics Committee Approval: Ethical approval was obtained from European University of Lefke Non-Interventional Clinical Researches Ethics Board (approval number: BAYEK038.12, date: 28.12.2023).

Informed Consent: Before collecting the data, informed written consent was obtained from the participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.U., N.G., M.G., Concept: K.U., N.G., M.G., Design: K.U., N.G., Data collection and analysis: M.G., Analysis or Interpretation: K.U., Literature Search: K.U., N.G., M.G., Writing: K.U., N.G.

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Real-world experience of rituximab therapy in ANCA-associated vasculitis according to renal involvement

ANCA ilişkili vaskülitte renal tutuluma göre rituksimab tedavisi: Gerçek yaşam deneyimi

Rabia Deniz[1], Pınar Akyüz Dağlı[2], Akın Işık[3], Tuğba Ocak[4], Burcu Ceren Ekti Uludoğan[5], Kübra Uğur[6], Batuhan Erdir[6], Mehmet Ali Enlice[7], Ebru Aşıcıoğlu[8], Yavuz Pehlivan[4], Nazife Şule Yaşar Bilge[5], Timuçin Kaşifoğlu[5], Fatma Alibaz Öner[3], Şükran Erten[9], Ahmet Omma[2], Haner Direskeneli[3], Cemal Bes[1], Nilüfer Alpay Kanıtez[10]

[1]*University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye*
[2]*University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye*
[3]*Marmara University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye*
[4]*Bursa Uludağ University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Bursa, Türkiye*
[5]*Eskişehir Osmangazi University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Eskişehir, Türkiye*
[6]*University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Internal Medicine, İstanbul, Türkiye*
[7]*Koç University Faculty of Medicine, Department of Internal Medicine, İstanbul, Türkiye*
[8]*Marmara University Faculty of Medicine, Department of Internal Medicine, Division of Nephrology, İstanbul, Türkiye*
[9]*Ankara Yıldırım Beyazıt University, Ankara City Hospital, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye*
[10]*Koç University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye*

Abstract

Objective: To evaluate treatment persistence, efficacy, and safety of rituximab (RTX) in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV), with a specific focus on the impact of renal involvement.

Methods: In this multicenter, retrospective cohort study, 214 AAV patients who received at least one RTX dose between 2012 and 2024 were analyzed. Patients were stratified based on renal involvement. The primary endpoint was RTX retention, defined as the time from the first infusion to permanent discontinuation for any cause. Secondary endpoints included remission, relapse, and infection-related discontinuations. Clinical characteristics, treatment indications (induction or maintenance), cumulative RTX doses, and safety outcomes were compared between renal and non-renal groups using descriptive statistics and survival analyses.

Results: Among the cohort, 132 patients (61.7%) had renal involvement and 82 (38.3%) had non-renal involvement. The median RTX treatment duration was 24 months. RTX was used for maintenance in 72.4% of patients and for induction in 49% of patients. Drug retention did not differ

Özet

Amaç: Bu çalışmada, antinötrofil sitoplazmik antikor ilişkili vaskülit (AAV) hastalarında rituksimab (RTX) tedavisinin sürekliliği, etkililiği ve güvenliliği değerlendirilmiş; özellikle renal tutulumun tedavi sonuçlarına etkisi araştırılmıştır.

Yöntem: 2012-2024 yılları arasında en az bir kür RTX uygulanmış 214 AAV hastasının verileri çok merkezli, retrospektif kohort tasarımında analiz edildi. Hastalar renal tutulum varlığına göre sınıflandırıldı. Birincil sonlanım noktası, herhangi bir nedenle tedavinin kalıcı olarak sonlandırılmasına kadar geçen süre olarak tanımlanan RTX tedavisinde kalımdı. İkincil sonlanım noktaları arasında remisyon, relaps ve enfeksiyon ilişkili tedavi kesilmeleri yer aldı. Klinik özellikler, tedavi endikasyonları (indüksiyon veya idame), kümülatif RTX dozları ve güvenlilik sonuçları renal ve non-renal gruplar arasında tanımlayıcı ve sağkalım analizleriyle karşılaştırıldı.

Bulgular: Kohortun 132'sinde (%61,7) renal, 82'sinde (%38,3) non-renal tutulum mevcuttu. Ortanca RTX tedavi süresi 24 aydı. RTX hastaların %72,4'ünde idame, %49'unda indüksiyon amacıyla kullanıldı. Renal ve non-renal gruplar arasında ilaçta kalım açısından anlamlı fark saptanmadı

Correspondence / İletişim: Nilüfer Alpay Kanıtez MD,
Koç University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye
E-mail: nilalpay@gmail.com **ORCID ID:** orcid.org/0000-0003-1185-5816
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Abstract

significantly between renal and non-renal groups (log-rank p=0.608). Infections were the most frequent cause of RTX discontinuation (38.2% vs. 34.8%). Hypogammaglobulinemia occurred in 17.4% and 15.9% of patients, respectively (p=0.460). Mortality rates were comparable between groups (9.8% vs. 8.5%, p=0.475). Despite higher prior cyclophosphamide exposure in renal patients (12.1% vs. 3.7%, p=0.026), overall treatment outcomes were similar.

Conclusion: RTX demonstrated sustained treatment persistence and an acceptable safety profile across AAV phenotypes, independent of renal involvement. These findings emphasize that RTX can serve as a phenotype-independent long-term therapeutic option, although vigilant infection monitoring remains crucial in all patients.

Keywords: ANCA-associated vasculitis, rituximab, renal involvement, drug retention, real-world data

Özet

(log-rank p=0,608). RTX tedavisinin kesilmesinin en sık nedeni enfeksiyondu (%38,2'ye karşı %34,8). Hipogamaglobulinemi oranları sırasıyla %17,4 ve %15,9 olup gruplar arasında anlamlı farklılık göstermedi (p=0,460). Mortalite oranları da benzerdi (%9,8'e karşı %8,5; p=0,475). Renal grupta siklofosfamid maruziyeti daha yüksek olmasına rağmen (%12,1'e karşı %3,7; p=0,026), genel tedavi sonuçları iki grup arasında benzer bulundu.

Sonuç: RTX, renal tutulumdan bağımsız olarak AAV fenotiplerinde uzun dönemli tedavi sürekliliği ve kabul edilebilir güvenlilik profili sergilemiştir. Bu bulgular, RTX'in fenotipten bağımsız uzun süreli bir tedavi seçeneği olabileceğini, ancak tüm hastalarda enfeksiyonların dikkatle izlenmesinin gerekli olduğunu vurgulamaktadır.

Anahtar Kelimeler: ANCA-ilişkili vaskülit, rituksimab, renal tutulum, ilaçta kalım, gerçek yaşam verisi

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises a group of necrotizing small-vessel vasculitides, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (eGPA).[1,2] These conditions are characterized by diverse clinical presentations that range from renal involvement to severe pulmonary manifestations, necessitating tailored therapeutic strategies.[3]

Historically, combination regimens of cyclophosphamide (CYC) and corticosteroids significantly improved survival by inducing remission in up to 90% of cases.[4] However, the long-term toxicity of CYC, including infertility, malignancy, and opportunistic infections has led to a shift toward less toxic yet effective alternatives.[5]

Rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, has transformed AAV management by enabling selective B-cell depletion and sustained ANCA suppression.[6-9]

Large randomized trials such as RTX in ANCA-AAV (RAVE) and RTX versus CYC in ANCA-AAV (RITUXIVAS) established RTX as non-inferior to CYC for induction therapy, even in patients with severe renal involvement.[7,10] Furthermore, the maintenance of remission using RTX in systemic ANCA-AAV (MAINRITSAN) and RTX versus azathioprine (AZA) for maintenance of remission in ANCA-AAV (RITAZAREM) trials confirmed RTX's superiority over AZA in relapse prevention during maintenance.[11-13]

Despite these advances, how renal involvement influences RTX efficacy and safety remains insufficiently characterized. Renal disease is associated with worse prognosis and typically warrants aggressive immunosuppression to prevent irreversible kidney damage and end-stage renal disease.[14] Conversely, patients without renal involvement, often with upper respiratory tract or pulmonary disease, may both tolerate and require less intensive regimens. Importantly, relapse risk is influenced not only by the extent of organ involvement but also by ANCA subtype, with PR3-ANCA-positive patients (commonly GPA) exhibiting a higher relapse propensity compared to myeloperoxidase (MPO)-ANCA-positive patients (often MPA with renal-limited disease).[15] While several trials have evaluated induction and maintenance strategies in AAV broadly, few have specifically addressed how the presence or absence of renal involvement influences long-term outcomes under RTX maintenance.

Most pivotal trials were not designed to directly compare long-term RTX durability and safety between renal and non-renal AAV phenotypes, e.g., RAVE excluded patients with advanced renal failure and RITUXVAS enrolled exclusively renal disease, while MAINRITSAN and RITAZAREM primarily focused on relapse prevention rather than phenotype-stratified drug survival or cumulative exposure.[4,6,9,16] In real-world cohorts under RTX maintenance, kidney involvement has been associated with longer relapse-free survival and a lower relapse risk, whereas other series suggest kidney involvement may increase the risk of severe hypogammaglobulinaemia leading to RTX discontinuation.[17] Therefore, direct comparative evidence on treatment retention, cumulative dosing, and safety between renal and non-renal AAV remains limited.

Furthermore, the real-world performance of RTX including dosing schedules, drug survival, adverse events, and reasons for discontinuation remains incompletely characterized in stratified populations.[18,19] Additionally, the risk of serious infections remains a key consideration, particularly in patients undergoing long-term maintenance therapy.[20,21] Understanding these distinctions is essential for optimizing personalized treatment pathways in AAV and for refining maintenance strategies to balance efficacy with safety.[22]

This multicenter study aimed to evaluate the real-world outcomes of RTX maintenance therapy in patients with AAV, specifically comparing those with and without renal involvement. We investigated treatment persistence, cumulative dosing, relapse and remission patterns, and adverse events in these two phenotypes to determine whether renal disease influences

the long-term effectiveness and safety of RTX in routine clinical practice.

Materials and Methods

Study Population and Data Collection

This was a multicenter, retrospective, observational cohort study including adult patients (≥18 years) with a diagnosis of AAV; GPA, MPA, or EGPA, according to the 1990 American College of Rheumatology criteria. Patients were recruited from six tertiary rheumatology centers in Türkiye between September 2012 and September 2024.

Patients were eligible if they had a diagnosis of AAV and received at least one course of RTX for either induction or maintenance therapy during the study period. Patients with concomitant autoimmune diseases, active malignancies, insufficient follow-up (<6 months), or missing essential clinical or laboratory data required for outcome assessment were excluded from the analysis. Data were extracted from electronic medical records using standardized case-report forms to ensure uniformity across centers. No statistical imputation was performed, as cases with incomplete essential data were excluded at the time of cohort assembly. In all centers, ANCA was determined by testing for PR3-ANCA and MPO-ANCA using an enzyme-linked immunosorbent assay. Patients with ANCA-negative (double-negative) serology were not excluded if they fulfilled clinical criteria for AAV diagnosis.

Renal involvement was defined as biopsy-proven pauci-immune necrotizing and/or crescentic glomerulonephritis and/or clinical and laboratory findings consistent with active renal vasculitis, including proteinuria >500 mg/day, and/or persistent microscopic hematuria on at least two consecutive assessments, unexplained elevation in serum creatinine attributed to AAV, and/or rapidly progressive renal dysfunction (e.g., rapidly rising serum creatinine levels or dialysis-requiring acute kidney injury) in accordance with established AAV and glomerular disease guidelines.[3,23] Kidney biopsy was performed whenever clinically feasible. In cases where biopsy could not be obtained due to clinical instability or advanced renal failure, classification was based on compatible clinical findings, ANCA positivity, and active urinary sediment. Patients fulfilling any of these criteria were categorized as "renal", while those without renal manifestations were classified as "non-renal".

Induction and Maintainance Strategies

In routine clinical practice across participating centers, remission induction was performed with CYC and/or RTX, depending on disease severity and prevailing treatment standards during the study period. In selected severe cases, both agents were used sequentially or in combination at the physician's discretion. The RTX induction regimen consisted of 1000 mg administered intravenously on days 0 and 15 (total 2000 mg). After achieving remission, patients were transitioned to maintenance therapy tailored according to clinical phenotype, relapse risk, comorbidities, and treatment tolerance. Maintenance options included RTX, AZA, or mycophenolate mofetil. Thus, "induction" and "maintenance" represent sequential treatment phases rather than mutually exclusive patient categories, and reported proportions may overlap.

Pneumocystis jirovecii pneumonia prophylaxis with trimethoprim/sulfamethoxazole was administered to all patients receiving induction therapy unless contraindicated (e.g., by a drug allergy or persistent hyperkalemia). Dosage adjustments were made according to renal function. Prophylaxis was applied in accordance with standard clinical practice guidelines.

Outcomes and Definitions

The primary endpoint was drug retention, defined as the time from the first RTX infusion to permanent discontinuation for any reason. Temporary treatment interruptions lasting less than 6 months were not considered discontinuation events. Censoring occurred at the last clinical visit, upon loss to follow-up, or at death unrelated to RTX discontinuation. Causes of discontinuation were categorized as remission, relapse, adverse event, infection, allergy, physician's decision, or patient request.

Secondary endpoints included:

- Frequency and causes of discontinuation,
- Occurrence of infections (classified as serious if hospitalization or intravenous antibiotic therapy was required),
- Incidence of hypogammaglobulinemia,
- Mortality during follow-up.

Remission and relapse definitions were adapted from established AAV management guidelines and major clinical trials.[3,4,6] Refractory disease was defined according to European Alliance of Associations for Rheumatology recommendations.[3] Renal dysfunction was defined based on standard laboratory reference ranges in accordance with KDIGO guidelines.[23,24]

Remission was defined as the absence of clinical signs of active vasculitis, as assessed by the treating physician, with no new or worsening organ involvement and stabilization of laboratory parameters. All patients accepted as being in the remission phase had a Birmingham vasculitis activity score of 0. Low-dose glucocorticoid therapy was permitted during remission; however, patients requiring moderate-to-high-dose glucocorticoids due to active disease were not considered in remission. Relapse was defined as new or recurrent organ involvement attributed to AAV. Refractory disease refers to persistent or worsening disease activity despite standard induction therapy. Renal dysfunction was defined as creatinine levels >1.1 mg/dL in women and >1.3 mg/dL in men.

Serum immunoglobulin G (IgG) levels were routinely measured prior to RTX initiation in all patients. No patient had hypogammaglobulinemia before the first RTX course. Hypogammaglobulinemia observed during follow-up that developed after at least one RTX cycle and was therefore considered treatment-related. Intravenous immunoglobulin (IVIG) replacement therapy was initiated in patients with clinically significant hypogammaglobulinemia, based on serum IgG levels and the presence of recurrent or severe infections. IVIG was administered following formal approval for off-label use by the Turkish Medicines and Medical Devices Agency. Hypogammaglobulinemia was defined as serum IgG <7 g/L. Persistent hypogammaglobulinaemia was defined as the absence of improvement six months after RTX treatment.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median (range), while categorical variables were summarized as frequencies and percentages. Differences between renal and non-renal groups were analyzed using the Mann-Whitney U test for continuous data and the chi-square or Fisher's exact test for categorical data. Drug retention was assessed using Kaplan-Meier survival analysis, and survival curves were compared by the log-rank test. All statistical analyses were performed using SPSS version 30.0 (SPSS Inc., Chicago, IL, USA), with a p-value <0.05 considered statistically significant. Given the retrospective, descriptive design, no multivariate adjustment or time-dependent modeling was applied.

Ethical Approval and Funding

The study was approved by the Marmara University Faculty of Medicine Non-Drug and Medical Device Research Ethics Committee (project no. 09.2024.1382, date: 11.03.2025) and conducted in accordance with the Declaration of Helsinki. Written informed consent was waived due to the retrospective design. No external funding was received.

Results

Baseline Characteristics of Study Groups

Baseline Characteristics

A total of 214 patients with AAV were included in the analysis: 132 had renal involvement and 82 did not. The overall cohort comprised 67.3% GPA, 23.4% MPA, and 9.3% EGPA. MPA was significantly more frequent in the renal group than in the non-renal group (32.6% vs. 8.5%, p<0.001), whereas EGPA was more common in the non-renal group (3.5% vs. 18.3%, p=0.004). The distribution of GPA was comparable across groups (Table 1).

Demographic characteristics, including sex, age, and disease duration, were similar across groups. Thirty patients (22.7%) in the renal group required hemodialysis during their disease course. Over a median follow-up of four years, mortality rates were comparable (9.8% vs. 8.5%, p=0.475). Cardiac involvement was more frequent in non-renal patients (7.2% vs. 2.8%, p=0.037), whereas involvement of other organs did not differ significantly (Table 1).

Rituximab Treatment Patterns

RTX was used as maintenance therapy in 72.4% of patients and as induction therapy in 49% of patients. The proportion of refractory cases receiving RTX was higher among renal patients (25.8% vs. 15.6%, p=0.038). CYC exposure was more common in the renal group (12.1% vs. 3.7%, p=0.026), whereas methotrexate (MTX) exposure was more common in the non-renal group (19.5% vs. 4.5%, p<0.001). The frequency of concomitant glucocorticoid or AZA use did not differ significantly between groups.

The median cumulative RTX dose was approximately 7 g in both renal and non-renal patients, with a median treatment duration exceeding 24 months (Table 2). The minimum and maximum cycle doses ranged from 500 mg to 2 g, and the intervals between cycles varied from 4 to 65 months, reflecting wide heterogeneity in real-world regimens. The longest RTX exposure was 144 months in a patient without renal disease. In patients with prolonged treatment, maintenance regimens were frequently de-escalated. Instead of repeated full 2000-mg cycles every 6 months, reduced dosing strategies were applied, including single 500-1000-mg infusions every 6 months or infusions at extended intervals (e.g., 1000-2000 mg annually), according to clinical stability and relapse risk.

Drug Retention and Discontinuation

Kaplan-Meier analysis demonstrated comparable RTX retention rates between renal and non-renal groups, with no statistically significant difference (log-rank p=0.608) (Figure 1). Median drug survival exceeded two years in both cohorts.

The most frequent cause of RTX discontinuation was infection in both renal (38.2%) and non-renal (34.8%) patients, followed by remission (14.7% and 8.7%, respectively) and allergic reactions (14.7% and 8.7%, respectively). Only one patient in the renal group discontinued due to disease relapse. Three patients in the renal group stopped RTX because of hypogammaglobulinemia, and none in the non-renal group did (Table 3).

Safety Outcomes

Infection remained the leading adverse event and the leading cause of treatment discontinuation, but its incidence was similar between groups. Most infections were respiratory or urinary in origin. The rate of serious infection—defined as requiring hospitalization or intravenous antibiotic therapy—did not differ significantly.

Hypogammaglobulinemia occurred in 17.4% of renal and 15.9% of non-renal patients (p=0.460). Approximately half of these patients received IVIG replacement therapy. Persistent hypogammaglobulinemia, defined as low IgG persisting for six months or more after RTX exposure, was recorded in 23 cases. Despite higher baseline disease severity and cumulative immunosuppressive exposure in the renal group, no increase in severe infections or mortality was observed.

Table 1. Demographic and clinical characteristics of patients based on renal involvement

	Renal (n=132)	Non-renal (n=82)	p-values
Diagnosis (n, %)			
Granulomatosis with polyangiitis	84 (63.6)	60 (73.2)	0.148
Microscopic polyangiitis	43 (32.6)	7 (8.5)	<0.001
Eosinophilic granulomatosis with polyangiitis	5 (3.8)	15 (18.3)	0.004
Gender (male, n, %)	78 (59.1)	39 (47.6)	0.120
Age (mean ± SD, years)	53.49±14.9	50.62±14.1	0.082
Disease duration (median, range, years)	4.0 (0.5-24)	4.0 (0.5-24)	0.391
Death (n, %)	13 (9.8)	7 (8.5)	0.475
Clinical findings (n, %)			
Musculoskeletal	60 (45.5)	43 (52.4)	0.329
Mucocutaneous	35 (26.5)	17 (20.7)	0.413
Eye involvement	9 (6.8)	11 (13.4)	0.146
Upper respiratory	71 (53.8)	54 (65.9)	0.089
Lower respiratory	106 (80.3)	62 (75.6)	0.494
Alveolar hemorrhage	34 (25.8)	13 (15.9)	0.061
Cardiac	2 (2.8)	6 (7.3)	0.037
Central nervous system	6 (4.5)	4 (4.9)	0.994
Peripheral nervous system	19 (14.4)	18 (22)	0.109
Gastrointestinal	7 (5.3)	5 (6.1)	0.771
Hemodialysis	30 (22.7)	0	<0.001
Renal dysfunction	86 (65.2)	0	<0.001
Persistent HGG (n, %)	23 (17.4)	13 (15.9)	0.460
Postponing RTX due to HGG (n, %)	21 (16.0)	9 (11.5)	0.247
Autoantibody positivity (n, %)			
Anti-PR3	80 (60.6)	51 (62.2)	0.886
Anti-MPO	42 (31.8)	18 (22.0)	0.159
Double-negative	10 (7.6)	13 (15.8)	0.059
Indication for RTX use (n, %)			
Induction of remission	59 (44.7)	46 (56.1)	0.069
Relapse	24 (18.2)	17 (20.7)	0.386
Refractory disease	34 (25.8)	12 (14.6)	0.038
Maintenance of remission	97 (73.5)	58 (70.7)	0.753
Concurrent therapies with RTX (n, %)			
Glucocorticoid	128 (97)	77 (93.9)	0.309
Methotrexate	6 (4.5)	16 (19.5)	<0.001
Mycophenolate mophetil	9 (6.8)	11 (13.4)	0.087
Cyclophosphamide	16 (12.1)	3 (3.7)	0.026
Azathioprine	27 (20.5)	21 (25.6)	0.238
Intravenous immunoglobulin	17 (12.9)	11 (13.4)	0.533
Plasmapheresis	14 (10.6)	3 (3.7)	0.054

Anti-PR3: Anti-proteinase 3 antibodies, HGG: Hypogammaglobulinemia, MPO: Myeloperoxidase, RTX: Rituximab, SD: Standard deviation

Table 2. Treatment duration and dose schedule of rituximab in maintenance treatment			
	Renal (n=132)	Non-renal (n=82)	p-value
Treatment duration (median, range, months)	26 (3-141)	31 (6-144)	0.381
Cumulative dose (median, range, g)	7 (1-34)	7.75 (1-36)	0.622
Dose per cycle (median, range, g)			
Minimum	1 (0.5-2)	2 (0.5-2)	0.403
Maximum	2 (0.5-2)	2 (0.5-2)	0.081
Interval between cycles (median, range, months)			
Minimum	6 (4-24)	6 (4-8)	0.597
Maximum	7 (4-65)	7 (4-30)	0.498

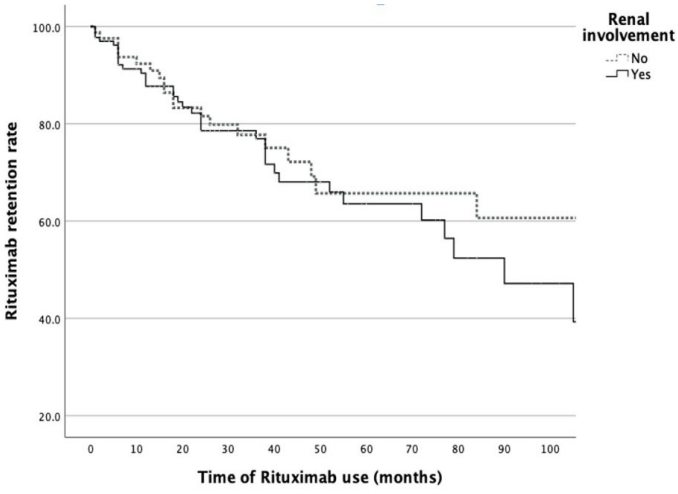

Figure 1. Rituximab retention rates based on renal involvement. The Kaplan-Meier curve shows the rituximab retention rates according to the presence of renal involvement

Table 3. Reasons for discontinuation of rituximab			
Discontinuation reasons n (%)	Renal (n=34)	Non-renal (n=23)	p-values
Infection	13 (38.2)	8 (34.8)	0.929
Remission	5 (14.7)	2 (8.7)	0.689
Rituximab allergy	5 (14.7)	2 (8.7)	0.689
Non-response	3 (8.8)	3 (13.0)	0.677
Physician's decision	1 (2.9)	3 (13.0)	0.292
Hypogammaglobulinemia	3 (8.8)	0	0.265
Flare	1 (2.9)	0	0.980
Other	3 (8.8)	5 (21.7)	0.247

Discussion

This multicenter real-world study compared the long-term outcomes of RTX therapy in patients with AAV, stratified by the presence of renal involvement. Our main finding was that RTX demonstrated comparable drug retention, efficacy, and safety across renal and non-renal disease phenotypes, despite renal patients having higher baseline severity and cumulative immunosuppressive exposure, including CYC. These results suggest that renal involvement does not adversely influence RTX persistence or tolerability in clinical practice.

Our findings are consistent with previous randomized trials demonstrating the efficacy of RTX for remission induction and maintenance in AAV, including patients with renal involvement.[4,6,10,25] However, these studies did not specifically analyze whether renal involvement modifies RTX outcomes. Our study fills this gap by providing dedicated comparative data, indicating that renal involvement does not negatively impact RTX retention, efficacy, or safety in the maintenance phase. Our findings complement this literature by providing phenotype-specific real-world evidence, showing that RTX remains equally effective and safe regardless of renal status.

Although patients with renal involvement had greater prior exposure to CYC and a higher baseline inflammatory burden, rates of drug survival, infection, and hypogammaglobulinemia were comparable to those in patients without renal disease. This indicates that RTX can be used as a phenotype-independent maintenance strategy even in individuals with reduced renal function who may not tolerate other immunosuppressants such as MTX. In contrast to conventional maintenance agents such as AZA or MTX, which may be contraindicated or less effective in patients with impaired renal function, RTX offers a phenotype-independent option with both immunological and clinical durability.[16,26] While MTX is often limited to non-renal disease due to nephrotoxicity, and MMF shows higher relapse rates particularly in PR3-ANCA patients, RTX appears to offer a more balanced efficacy-to-toxicity ratio across subtypes.[13,27]

Based on clinical experience and established practice patterns, the presence of renal involvement in vasculitis is a poor prognostic indicator. Mortality rates in our group with renal involvement and in the non-renal group are similar. One of the most important reasons for this is that non-renal patients with RTX indications are likely to have more severe disease than other non-renal patients. The similarity of retention rates, dosing schedules, and discontinuation rates due to hypogammaglobulinemia and infection in both groups suggests that RTX does not pose an additional risk for patients with renal involvement or those at risk of renal dysfunction. This aligns with findings from registry-based studies and elderly cohorts, where RTX maintained a favorable safety profile even among immunosenescent or comorbid patients.[28,29]

Infections represented the leading cause of RTX discontinuation in both groups, aligning with data from long-term RTX cohorts.[30] Most infections were respiratory or urinary, and the rate of serious infections requiring hospitalization was not elevated among patients with renal disease. Given that almost one in five patients develops persistent hypogammaglobulinemia, these infection rates should be considered in conjunction with

it. Therefore, monitoring immunoglobulin levels and providing IVIG therapy when necessary may improve outcomes. Our study shows that we were able to administer IVIG to only half of the patients with persistent hypogammaglobulinemia. As outlined in the literature, monitoring gamma globulin levels and providing IVIG replacement therapy when necessary are important, particularly for AAV patients receiving RTX, regardless of renal involvement.[26,27,31,32]

In our study, the long-term retention and cumulative dosing patterns suggest clinicians tend to individualize RTX regimens over time, with adjusted intervals and dosages based on relapse history and tolerance, an approach supported by MAINRITSAN2 and newer ANCA-guided re-treatment protocols.[19,33] Maintenance treatment intervals of up to 65 months are a consequence of the chronic nature of the disease. Therefore, individualisation of maintenance treatment protocols is inevitable. Our findings demonstrate equal drug survival and tolerability in renal and non-renal groups and highlight RTX as a reliable first-line treatment not only for refractory disease or induction but also for long-term disease suppression, independent of renal phenotype.

Study Limitations

This study has several limitations. Its retrospective design may introduce selection and information biases. Variability in RTX maintenance protocols across participating centers might affect the generalizability of dose and interval findings. Data on disease activity and more detailed information on the nature and severity of infections could not be provided because insufficient data were available. Nevertheless, the multicenter nature of the study enhances external validity, and the large, well-characterized cohort allows clinically meaningful comparisons. Although the RTX-treated cohort included patients receiving induction, relapse, refractory, and maintenance therapies, such heterogeneity reflects real-world clinical practice. The primary objective of this study was to evaluate outcomes according to renal involvement rather than treatment indication. Therefore, analyses were performed across the entire RTX-exposed cohort.

Conclusion

In conclusion, RTX provided sustained efficacy and safety during long-term maintenance therapy in AAV patients, regardless of renal involvement. Drug retention, hypogammaglobulinemia, and infection rates were similar across phenotypes, suggesting that RTX is a reliable maintenance option for both renal and non-renal disease. These results support individualized RTX strategies, emphasizing infection prevention and immunoglobulin monitoring as key components of long-term care.

Ethics

Ethics Committee Approval: The study was approved by the Marmara University Faculty of Medicine Non-Drug and Medical Device Research Ethics Committee (project no. 09.2024.1382, date: 11.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: R.D., N.A.K., Design: R.D., N.A.K.., Data collection and analysis: R.D, P.A.D., A.I., T.O., B.C.E.U., K.U., B.E., M.A.E., E.A., Y.P., N.Ş.Y.B., T.K., F.A.Ö., Ş.E., A.O., H.D., C.B., N.A.K., Literature Search: R.D., N.A.K., Writing: R.D.

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Parotid gland ultrasonographic findings are milder in patients with primary Sjögren's disease-related interstitial lung disease

Primer Sjögren hastalığına bağlı interstisyel akciğer hastalığı olan hastalarda parotis bezi ultrasonografik bulguları daha hafiftir

Tahir Saygın Öğüt[1], Mert Ünal[2], Funda Erbasan[3], Mustafa Ender Terzioğlu[3], Veli Yazısız[3]

[1]*University of Health Sciences Türkiye, Antalya City Hospital, Clinic of Internal Medicine, Divison of Rheumatology, Antalya, Türkiye*
[2]*Akdeniz University Faculty of Medicine, Department of Internal Medicine, Antalya, Türkiye*
[3]*Akdeniz University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Antalya, Türkiye*

Abstract

Objective: To evaluate parotid gland ultrasonography findings in patients with Sjögren's disease (SjD) with interstitial lung disease (ILD) and to compare them with those of SjD patients without ILD.

Methods: This single-center, cross-sectional study included 20 patients with SjD-related ILD and 110 SjD patients without ILD. Parotid gland ultrasonography was graded according to the Outcome Measures in Rheumatology (OMERACT) semiquantitative scoring system (grades 0-3). Parotid gland ultrasonography findings, along with clinical and laboratory characteristics, were compared between the two groups.

Results: Demographic characteristics were largely comparable between groups, with no significant differences in mean age or age at diagnosis (p>0.05). However, the proportion of male patients was significantly higher in the ILD group than in the non-ILD group (20.0% vs. 1.9%, p=0.005). Regarding the primary outcomes, parotid gland ultrasonography scores indicated milder involvement in patients with SjD-related ILD. The proportion of patients with a total OMERACT score ≥2 in both parotid glands was significantly lower in the ILD group than in the non-ILD group (65.0% vs. 84.5%, p=0.03). As a secondary finding, at diagnosis, 70% of patients with ILD (n=14) presented predominantly with pulmonary symptoms, whereas only 30% had sicca manifestations.

Conclusion: This study demonstrates that patients with SjD-related ILD more frequently present with pulmonary symptoms rather than sicca symptoms and exhibit milder parotid-gland involvement on ultrasonography. These findings suggest that SjD-related ILD may represent a distinct clinical subgroup characterized by relatively low-grade parotid gland ultrasonographic changes.

Keywords: Interstitial lung disease, ultrasonography, Sjögren's disease, parotid gland

Özet

Amaç: Bu çalışmanın amacı, interstisyel akciğer hastalığı (İAH) olan Sjögren hastalığı (SH) hastalarda parotis bezi ultrasonografisi bulgularını değerlendirmek ve bu bulguları İAH olmayan SH hastaları ile karşılaştırmaktır.

Yöntem: Bu tek merkezli, kesitsel çalışmaya SH'ye bağlı İAH tanısı olan 20 hasta ve İAH olmayan 110 SH hastası dahil edildi. Parotis bezi ultrasonografisi bulguları, Romatolojide Sonuç Ölçümleri (OMERACT) yarı-kantitatif skorlama sistemine (derece 0-3) göre değerlendirildi. Parotis bezi ultrasonografisi bulguları ile birlikte grupların klinik ve laboratuvar özellikleri karşılaştırıldı.

Bulgular: Gruplar arasında ortalama yaş ve tanı yaşı açısından istatistiksel olarak anlamlı fark saptanmadı (p>0.05). Ancak erkek hasta oranı, İAH grubunda İAH olmayan gruba kıyasla anlamlı derecede daha yüksekti (%20,0 vs. %1,9; p=0,005). Birincil sonuçlar açısından, SH'ye bağlı İAH olan hastalarda parotis bezi ultrasonografisi skorlarının daha hafif olduğu görüldü. Her iki parotis bezinde toplam OMERACT skoru ≥2 olan hasta oranı, İAH grubunda İAH olmayan gruba göre anlamlı olarak daha düşüktü (%65,0 vs. %84,5; p=0,03). İkincil bir bulgu olarak, tanı anında İAH grubundaki hastaların %70'inde (n=14) baskın semptomların pulmoner tutulum ile ilişkili olduğu, yalnızca %30'unda ise kuruluk (sikka) semptomlarının ön planda olduğu saptandı.

Sonuç: Bu çalışma, SH'ye bağlı İAH'si olan hastaların sikka semptomlarından ziyade pulmoner semptomlarla daha sık başvurduğunu ve parotis bezi ultrasonografik tutulumunun daha hafif olduğunu göstermektedir. Bu bulgular, SH'ye bağlı İAH'nin nispeten düşük dereceli parotis bezi ultrasonografik değişiklikleri ile karakterize ayrı bir klinik alt grup olabileceğini düşündürmektedir.

Anahtar Kelimeler: İnterstisyel akciğer hastalığı, ultrasonografi, Sjögren hastalığı, parotis bezi

Correspondence / İletişim: Veli Yazısız Prof. MD,
Akdeniz University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Antalya, Türkiye
E-mail: drvyazisiz@yahoo.com.tr **ORCID ID:** orcid.org/0000-0002-3176-4850
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Introduction

Sjögren's disease (SjD) represents a chronic immune-mediated disorder in which persistent lymphocytic activity predominantly targets exocrine tissues, leading to progressive glandular dysfunction. The incidence of SjD is estimated to be approximately 4-7 per 100,000 individuals, while its prevalence is estimated at around 2-3%.[1] In 30-40% of patients with SjD, extraglandular manifestations may also occur, including arthritis, nephritis, neuropathy, and pulmonary involvement.[2]

Pulmonary involvement is one of the most common extraglandular manifestations of SjD, with a reported prevalence ranging from 9% to 75%.[3] This wide variability in prevalence is mainly attributable to differences in the definitions used to classify pulmonary involvement. Interstitial lung disease (ILD) is, generally, a late complication of SjD, and is associated with significantly increased morbidity and mortality.[3,4]

In a study by Gao et al.[5], 49% of patients with SjD-ILD initially presented with non-sicca symptoms. Another study reported that only 49.4% of SjD-ILD patients had sicca symptoms as their initial complaint.[6] These findings suggest that patients with SjD who present with sicca or non-sicca symptoms may have different initial targets of immune dysregulation and potentially distinct pathogenic mechanisms.[3]

There is growing evidence supporting the use of major salivary gland ultrasonography (SGUS), a non-invasive method, in the diagnosis of SjD.[7] Whether it can replace invasive methods, such as minor salivary gland biopsy, is debated. Furthermore, SGUS could facilitate stratification of heterogeneous SjD phenotypes and provide deeper insights into their distinct pathophysiological pathways. This study was conducted to assess parotid gland ultrasonographic changes in SjD and to examine their relationship with the presence of ILD.

Materials and Methods

Ethical Approval

This study was initially approved by the Akdeniz University Clinical Research Ethics Committee (approval number: KAEK-242, date: 22.03.2023). An additional approval regarding the extension of the data collection period to cover June 2023-May 2024 was subsequently granted by the Akdeniz University Medical Scientific Research Ethics Committee (approval number: TBAEK-623, date: 03.07.2025). Following the ethical guidelines of the Declaration of Helsinki, we secured written informed consent from every participant before enrollment.

Study Population

A total of 130 primary SjD patients (20 with ILD and 110 without ILD) aged over 18 and fulfilling the 2016 American College of Rheumatology and the European League Against Rheumatism (EULAR) SjD classification criteria[8] were enrolled in the study. We excluded individuals with a history of head and neck radiotherapy, sarcoidosis, or viral infections (human immunodeficiency virus and hepatitis C). Furthermore, those with other systemic autoimmune diseases, a history of parotid gland procedures, or technical limitations affecting SGUS assessment were not enrolled.

Descriptive Data and Clinical Assessments

A comprehensive medical history was obtained from all patients, and physical examinations were performed. Clinical and laboratory data were collected from the hospital data system: demographic characteristics (age, sex, and smoking status), disease duration, comorbidities, former and ongoing treatments, complete blood count, inflammatory markers [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)], antinuclear antibody (ANA) patterns and titers, extractable nuclear antigen profiles, minor salivary gland biopsy results, Schirmer test findings, pulmonary function test (PFT) results, and thoracic computed tomography (CT) results. The presence of ILD in patients with SjD was determined based on a combination of clinical features, imaging studies, and PFTs.

Imaging Protocols

Parotid gland imaging was performed with a high-frequency linear transducer (12 MHz) on a LOGIQ S7 EXPERT platform to ensure standardized grayscale image acquisition. Long-axis US images of two parotid glands were obtained while patients were in the supine position. An experienced rheumatologist evaluated all ultrasound images. Significantly, the operator was blinded to the ILD status of the patients at the time of SGUS assessment. The grading was performed according to the 2019 Outcome Measures in Rheumatology (OMERACT) Greyscale Ultrasound Scoring System,[9] which defines the following categories: Grade 0: Normal glandular appearance with homogeneous echotexture and no abnormalities; Grade 1: Mild changes with preserved echogenicity, without anechoic or hypoechoic areas; Grade 2: Moderate alterations, including focal anechoic or hypoechoic lesions; Grade 3: Severe glandular inhomogeneity or signs of fibrosis throughout the glandular tissue. Representative SGUS images corresponding to each grade from our cohort are shown in Figure 1. In this study, only two parotid glands were assessed by ultrasound. The submandibular glands were not included. Therefore, unlike the original OMERACT semi-quantitative score (minimum-maximum: 0-12), the OMERACT score ranged from a minimum of 0 to a maximum of 6 (grades 0-3 for both parotids).

PFT results, including spirometry and diffusing capacity of the lung for carbon monoxide, were retrieved from the institutional electronic medical record system. Thoracic CT images were re-

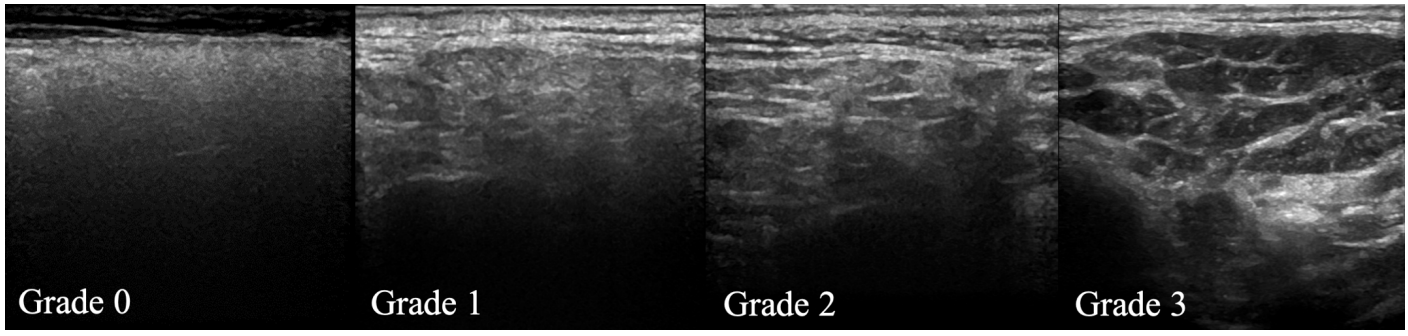

Figure 1. Representative parotid gland greyscale ultrasound images demonstrating Grades 0 to 3 according to the 2019 OMERACT scoring system[9]
OMERACT: Outcome Measures in Rheumatology

evaluated and classified according to American Thoracic Society guidelines[10,11] as follows: definite, probable, and indeterminate usual interstitial pneumonia (UIP); non-specific interstitial pneumonia (NSIP); organizing pneumonia; hypersensitivity pneumonitis (HP); and lymphocytic interstitial pneumonia (LIP).[12,13] The ILD diagnosis was conducted based on clinical features, PFT, and high-resolution CT imaging patterns.

Statistical Analysis

SPSS for Windows version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Patient characteristics and laboratory results were analyzed using descriptive statistics. Categorical data were expressed as frequency (n) and percentage (%). The chi-square test or Fisher's exact test (whichever was appropriate) was used to compare categorical data; the Student's t-test was used for normally distributed numeric data; and the Mann-Whitney U test was used for non-normally distributed numeric data. A p-value <0.05 was considered statistically significant.

Results

The baseline characteristics of patients with SjD-related ILD and non-ILD are presented in Table 1. Patients with an SGUS total OMERACT score for parotid glands ≥2 were less frequent in the ILD group compared to the non-ILD group (65.0% vs. 84.5%, p=0.03). The proportion of patients with a total SGUS score ≥3 was also lower in the ILD group, but the difference was not statistically significant (p=0.09). SGUS scores for the right and left parotid glands were consistent in both groups (Kappa=0.604 and 0.665, respectively; p<0.001) (Table 2). No significant difference was found in biopsy focus scores between SjD-ILD and non-ILD patients (66.7% vs. 77.4%, p=0.37). Medication use data are summarized in Table 1. In the study population, the use of immunosuppressive and immunomodulatory agents differed significantly between patients with SjD and those without ILD. Azathioprine, methotrexate, rituximab, or mycophenolate mofetil were used by 95.0% of patients in the ILD group, compared to 16.2% of patients in the group without ILD (p<0.001). Hydroxychloroquine use was significantly less frequent in the ILD group (40.0% vs. 72.4%, p=0.005). Pilocarpine use was reported only in the non-ILD group (10.6%), whereas none of the ILD patients received this medication. Glucocorticoid use was markedly higher in the ILD group (47.4% vs. 6.7%, p<0.001).

The clinical and functional characteristics of patients with SjD-related ILD are presented in Table 3. At the last clinical visit, respiratory symptoms were not observed in 35.0% of ILD patients; among these, cough (n=7) and dyspnea (n=10) occurred in 50.0% of cases. Based on thoracic CT findings, the most common radiological pattern was UIP, observed in 14 patients (70%); 8 patients (40%) were classified as having definite UIP. An NSIP pattern was observed in 5 patients (25%). One patient had HP, and another showed features of both NSIP and LIP.

There were no significant differences between the ILD and non-ILD groups in mean age or age at SjD diagnosis. Sicca symptoms as the initial manifestation were less common in the ILD group (30.0%), whereas pulmonary symptoms predominated (70.0%). ILD was significantly more prevalent in males than in females (20.0% vs. 1.9%, p=0.005). A higher proportion of patients in the ILD group had a history of smoking (45.0% vs. 22.7%, p=0.008). No significant differences were observed between the groups in terms of age, age at SjD diagnosis, autoantibody positivity (ANA, anti-Ro/SS-A, anti-La/SS-B), hemoglobin or platelet count.

However, leukocyte (8.62±1.76 vs. 6.05±1.79 $\times 10^3/mm^3$) and neutrophil (5.64±1.37 vs. 3.43±1.32 $\times 10^3/mm^3$) counts were significantly higher in the ILD group (both p<0.001). CRP levels were also significantly elevated in ILD patients (7.9±11.6 vs. 3.2±3.7 mg/L, p=0.01). No significant differences were found in ESR or in serum complement levels 3 and 4 (C3, C4).

Discussion

In this study, patients with SjD-related ILD demonstrated milder ultrasonographic involvement of the parotid glands compared with patients without ILD. High-grade parotid SGUS abnormalities were less frequent in the ILD group, suggesting that glandular structural changes may be less pronounced despite the presence of significant extraglandular disease.

Table 1. Baseline characteristics of SjD patients with and without interstitial lung disease			
	SjD-ILD (n=20)	**SjD without ILD (n=110)**	**p**
Age, years (mean ± SD)	59.9±11.2	56.3±12.3	0.10
Age at SjD diagnosis, years (mean ± SD)	54.1±13. 0	49.4±11.4	0.23
Sex (male), n (%)	4 (20.0)	2 (1.9)	***0.005***
Smoking (ever), n (%)	9/20 (45.0)	17/75 (22.7)	***0.008***
ANA positivity, n (%)	12/20 (60.0)	75/110 (68.2)	0.474
Anti-Ro52 positivity, n (%)	8 (40.0)	55 (50.0)	0.43
Anti-Ro/SS-A positivity, n (%)	6 (30.0)	54 (49.1)	0.10
Anti-La/SS-B positivity, n (%)	5 (25.0)	23 (20.1)	0.71
Hemoglobin, gr/dL (mean ± SD)	12.7±1.24	12.7±1.15	0.96
Leucocytes, thousand/mm^3 (mean ± SD)	8.62±1.76	6.05±1.79	***<0.001***
Neutrophils, thousand/mm^3 (mean ± SD)	5.64±1.37	3.43±1.32	***<0.001***
Trombocytes, thousand/mm^3 (mean ± SD)	288.5±62.4	246.4±63.9	0.08
Complement C3 level, g/L (mean ± SD)	1.24±0.2	1.21±0.2	0.52
Complement C4 level, g/L (mean ± SD)	0.24±0.06	0.23±0.09	0.48
CRP, mg/L (mean ± SD)	7.9±11.6	3.2±3.7	***0.01***
ESR, mm/hour (mean ± SD)	17.2±8.9	18.3±9.4	0.63
Medications used, n (%)			
Azathioprine, methotrexate, mycophenolate mofetil, rituximab	19 (95.0)	17/105 (16.2)	***<0.001***
Hydroxychloroquine sulfate	8 (40.0)	76/105 (72.4)	***0.005***
Pilocarpine	0	11/104 (10.6%)	0.21
Glucocorticoid	9 (47.4)	7/104 (6.7)	***<0.001***
Schirmer test <5 mm, n (%)	8 (40.0)	26 (23.6)	0.12
MSGB Focus score ≥1, n (%)	10/15 (66.7)	65/84 (77.4)	0.37
SGUS OMERACT for parotid glands			
≥2 points, n (%)	13 (65.0)	93 (84.5)	***0.03***
≥3 points, n (%)	2 (10.0)	32 (29.1)	0.09

ANA: Antinuclear antibody, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ILD: Interstitial lung disease, MSGB: Minor salivary gland biopsy, OMERACT: Outcome Measures in Rheumatology, SD: Standard deviation, SGUS: Salivary gland ultrasonography, SjD: Sjögren's disease

Table 2. Comparison of right and left parotid gland ultrasonographic OMERACT grades between SjD patients with and without interstitial lung disease

SjD-ILD							**SjD without ILD**						
		Right parotid gland (n)						**Right parotid gland (n)**					
		Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Total**			**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Total**
Left parotid gland (n)	**Grade 0**	4	0	0	0	4	**Left parotid gland (n)**	**Grade 0**	5	6	0	0	11
	Grade 1	3	11	0	0	14		**Grade 1**	6	61	1	0	68
	Grade 2	0	1	1	0	2		**Grade 2**	0	5	16	1	22
	Grade 3	0	0	0	0	0		**Grade 3**	0	1	0	8	9
	Total	7	12	1	0	20		**Total**	11	73	17	9	110
Kappa value: 0.604, p<0.001							Kappa value: 0.665, p<0.001						

ILD: Interstitial lung disease, OMERACT: Outcome Measures in Rheumatology, SjD: Sjögren's disease

These findings point to a dissociation between salivary gland involvement and pulmonary manifestations in SjD.

SjD-related ILD is associated with increased morbidity and mortality. Numerous observational studies have investigated demographic, clinical, and serological features in patients with SjD-related ILD; however, the results have been inconsistent.[14] Studies specifically examining the relationship between SGUS findings and organ involvement in SjD remain limited. In this context, our study compared SGUS grades, clinical features, and radiological features between SjD patients with and without ILD, and demonstrated that the ILD group had lower parotid OMERACT scores.

Table 3. Clinical and functional characteristics of SjD patients with interstitial lung disease

	Age	Gender	Age at ILD/type of ILD		Age at pSS	Smoking (ever)	Respiratory symptoms	FVC (%)	FEV_1 (%)	FEV_1/FVC	DLCO (%)	Focus score ≥1	Treatment
Patient 1	80	M	76	Definite UIP	76	(+)	--	85	95	82	49	+	AZA, GC
Patient 2*	55	F	47	Ind. UIP	35	(-)	D	81	84	87	95	--	MMF, GC
Patient 3	61	F	59	NSIP	59	(-)	--	66	73	92	53	-	MMF, GC
Patient 4*	61	F	57	Possible UIP	47	(+)	D	66	70	89	53	+	MTX, GC
Patient 5	56	F	54	NSIP	54	(-)	--	85	97	96	58	+	HCQ, GC
Patient 6	62	F	53	Definite UIP	53	(+)	C, D	74	69	78	36	-	MMF
Patient 7	30	F	29	NSIP	29	(+)	C, D	75	78	87	57	+	MMF, GC
Patient 8	65	F	57	Possible UIP	61	(-)	C	63	69	91	39	-	MMF, RTX, GC
Patient 9	72	M	70	Definite UIP	70	(+)	D	53	64	91	39	-	MMF
Patient 10	77	F	64	Possible UIP	65	(-)	--	100	109	84	66	+	MTX, HCQ, GC,
Patient 11	62	M	60	Definite UIP	60	(+)	--	71	80	88	74	-	MMF, GC
Patient 12*	61	F	57	Definite UIP	51	(-)	D	46	55	100	24	+	MMF, HCQ, GC
Patient 13*	44	F	44	Ind. UIP	30	(-)	--	101	107	90	84	-	MMF
Patient 14	62	M	57	NSIP	57	(-)	C	76	90	92	45	+	MMF, HCQ, GC
Patient 15	61	F	56	Definite UIP	56	(-)	D	61	63	86	69	-	MMF, HCQ, GC
Patient 16	50	F	48	HS	48	(-)	C	74	79	89	50	+	MMF, HCQ, GC
Patient 17	69	F	66	Definite UIP	66	(+)	C, D, OC	42	50	76	38	--	MMF, HCQ
Patient 18	59	F	49	Definite UIP	49	(+)	C, D	48	42	71	48	+	RTX
Patient 19*	71	F	62	Ind. UIP	57	(+)	--	142	158	87	75	--	MMF, HCQ
Patient 20*	49	F	42	NSIP, LIP	38	(-)	D	60	65	89	49	--	AZA, GC

Cases marked with * had sicca onset, whereas the others presented with ILD as the initial manifestation
AZA: Azathioprine, C: Cough, D: Dyspnea, DLCO: Diffusing capacity of the lung for carbon monoxide, F: Female, FEV_1: Forced expiratory volume in 1 second, FEV_1/FVC, Ratio of forced expiratory volume in 1 second to forced vital capacity, FVC: Forced vital capacity, GC: Glucocorticoid, HCQ: Hydroxychloroquine, HS: Hypersensitivity pneumonitis, ILD: Interstisial lung disease, Ind: Indeterminate, LIP: Lymphoid interstitial pneumonia, M: Male, MMF: Mycophenolate mofetil, MSGBFS: Minor Salivary Gland Biopsy Focus Score, MTX: Methotrexate, NSIP: Non-specific interstitial pneumonia, OC: Oxygen concentrator, RTX: Rituximab, SjD: Sjögren's disease, UIP: Usual interstitial pneumonia

The reported prevalence of SjD-related ILD varies widely, ranging from 10% to 20%, depending on ethnicity and diagnostic criteria.[15,16] Consistent with the literature, our cohort had a prevalence of 15.4%. In a meta-analysis by He et al.[15], older age, male sex, and elevated CRP levels were identified as risk factors for SjD-related ILD. Although SjD is more common in females, male patients tend to present with more severe disease and worse outcomes.[17] In our cohort, CRP, leukocyte, and neutrophil levels were significantly higher in the ILD group. These elevated inflammatory markers, which reflect immune activation, may play a critical role in systemic damage, including pulmonary and pleural complications.[5] However, these findings should be interpreted with caution because glucocorticoid use was more frequent in the ILD group; steroid therapy is known to increase circulating leukocyte and neutrophil counts and thus may represent a potential confounding factor.

The proportion of patients with OMERACT scores ≥2 and ≥3 on SGUS was lower in the ILD group compared to the non-ILD group (65.0% vs. 84.5% and 10.0% vs. 29.1%, respectively). La Rocca et al.[3] proposed that in newly diagnosed SjD patients, the presence of pulmonary symptoms may mask classical sicca symptoms. Similarly, in our cohort, patients with SjD-ILD exhibited significantly lower SGUS scores, suggesting that SGUS alone may be insufficient for the diagnosis of SjD in patients being evaluated for ILD.

Immunological differences in organ involvement may explain the variations observed in clinical, histopathological, and radiological findings in SjD. Epithelial cells in salivary glands may, in response to unknown triggers, initiate innate immune responses that lead to acquired immunity against self-antigens. These epithelial cells act as both targets and mediators of the immune response.[18] Ductal epithelial cells produce pro-inflammatory cytokines, including B-cell-activating factor, interleukin-1 (IL-1), IL-6, IL-21, and tumor necrosis factor-α, and express major histocompatibility complex class II, thereby activating both innate and adaptive immune responses. These mechanisms stimulate B-cells within follicular-like structures, promoting the production of autoantibodies and local inflammation.[18] In murine models of SjD, pulmonary lesions were characterized by a predominance of B-cells, distinguishing them from salivary gland lesions.[19] Lung inflammatory infiltrates resembling bronchus-associated lymphoid tissue have been observed, where $CD23^+$ follicular B-cells, under a T helper type 2-polarized immune environment, contribute to pulmonary autoimmune lesions in a $CD4^+$ T-cell-dependent manner.[19]

The presence of anti-Ro antibodies has been associated with more active disease in SjD, including ILD,[20] and higher SGUS scores are more frequently observed in anti-Ro/SSA- and anti-La/SSB-positive patients.[7,21] Dong et al.[22] reported a correlation between anti-Ro52 antibodies and ILD in a SjD cohort. Anti-Ro52 (TRIM21) antibodies have also been detected in a significant proportion of patients with idiopathic interstitial pneumonia.[23] Despite the lower SGUS scores observed in our ILD group, there were no significant differences in autoantibody positivity between groups. This suggests that the difference in SGUS findings in SjD-ILD may be independent of serological autoantibody status.

Consistent with clinical expectations, immunosuppressive therapy was more frequently administered to the SjD-related ILD group than to the non-ILD group. The TEARS[24] and TRACTISS[25] trials evaluated SGUS as an outcome parameter in SjD. In the TEARS trial, 50% of patients treated with rituximab showed improvement in SGUS scores compared to only 7% in the placebo group.[24] Similarly, in the TRACTISS trial, patients treated with rituximab demonstrated significantly lower SGUS scores at weeks 16 and 48 compared to those receiving placebo.[25] In the present study, patients with SjD-related ILD received immunosuppressive agents more frequently, and the observed differences in SGUS findings may reflect treatment-related responses to immunosuppression.

Study Limitations

Our study has several limitations. First, parotid gland US, minor salivary gland biopsy, CT scans, and Schirmer testing were not performed simultaneously. Secondly, there were no SGUS scores available at the time of diagnosis or prior to immunosuppressive therapy; therefore, the effects of such therapy on SGUS findings could not be entirely eliminated. In addition, the ultrasonographic assessment was limited to the parotid glands; the submandibular glands—which may demonstrate earlier or more pronounced involvement in SjD—were not evaluated, representing an important methodological limitation. Additionally, salivary flow rates and overall disease activity (EULAR Sjögren's Syndrome Disease Activity Index and EULAR Sjögren's Syndrome Patient-Reported Index) were not assessed. Moreover, the single-center study design limits the generalizability of the results, and multicenter studies are essential to validate these results.

Conclusion

Parotid gland ultrasonographic changes were milder in SjD patients with ILD compared with patients without ILD. These findings suggest that SjD may comprise distinct clinical subgroups, including predominantly glandular and predominantly non-glandular phenotypes, with differing parotid ultrasonographic characteristics when systemic organ involvement is present. Diagnostic approaches relying solely on parotid gland imaging via SGUS may underdiagnose SjD, particularly in patients with significant extraglandular manifestations but limited involvement of the major salivary gland. Further studies employing comprehensive salivary gland assessments are essential to elucidate the diagnostic utility of SGUS across the diverse clinical phenotypes of SjD, characterized by varying degrees of glandular and systemic involvement.

Ethics

Ethics Committee Approval: This study was initially approved by the Akdeniz University Clinical Research Ethics Committee (approval number: KAEK-242, date: 22.03.2023). An additional approval regarding the extension of the data collection period to cover June 2023-May 2024 was subsequently granted by the Akdeniz University Medical Scientific Research Ethics Committee (approval number: TBAEK-623, date: 03.07.2025).

Inform Consent: We secured written informed consent from every participant before enrollment.

Footnotes

A preliminary version of this work was presented at the XXIV National Rheumatology Congress (26-30 October 2024) and published in the supplementary issue of Journal of Turkish Society for Rheumatology (2025).

Authorship Contributions

Surgical and Medical Practices: T.S.Ö., M.Ü., F.E., M.E.T., V.Y., Concept: T.S.Ö., M.Ü., F.E., M.E.T., V.Y., Design: T.S.Ö., M.Ü., F.E., M.E.T., V.Y., Data Collection and Processing: T.S.Ö., M.Ü., F.E., M.E.T., V.Y., Analysis or Interpretation: T.S.Ö., M.Ü., F.E., M.E.T., V.Y., Literature Search: T.S.Ö., M.Ü., F.E., M.E.T., V.Y., Writing: T.S.Ö., M.Ü., F.E., M.E.T., V.Y.

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Reluctance and its determinants in managing fibromyalgia patients among Moroccan rheumatologists

Faslı romatologlar arasında fibromiyalji hastalarının yönetiminde isteksizlik ve belirleyicileri

Rajaa Bensaid, Fatima Zahrae Taik, Nihad Takhrifa, Anass Adnine, Fatima Ezzahra Abourazzak

Abdelmalek Essaadi University, Mohammed Vi University Hospital, Life and Health Sciences Laboratory, Faculty of Medicine and Pharmacy of Tangier, Department of Rheumatology, Tangier, Morocco

Abstract

Objective: Fibromyalgia is a complex and disabling chronic pain condition with poorly understood mechanisms and limited treatment efficacy. These uncertainties often lead to skepticism and reluctance among healthcare professionals. This study aimed to assess Moroccan rheumatologists' willingness to manage fibromyalgia patients and to identify influencing factors, with the goal of improving physician-patient relationships and overall care.

Methods: A cross-sectional survey was conducted among rheumatologists affiliated with the Moroccan Society of Rheumatology. Participants completed an electronic questionnaire that included socio-demographic and professional data, willingness to manage fibromyalgia patients, and validated tools assessing frustration (Difficult Doctor-Patient Relationship Questionnaire), illness perception (Brief Illness Perception Questionnaire, BIPQ), personality traits (Big Five Inventory-10), and burnout (abbreviated Maslach Burnout Inventory).

Results: Seventy-one rheumatologists participated. Forty-four (62%) reported reluctance to manage fibromyalgia patients, mainly due to difficult interactions (n=39; 70%) and perceived therapeutic inefficacy (n=31; 56%). High frustration scores were observed in 62 participants (87%). Fibromyalgia was perceived as a severe and impactful condition (mean BIPQ=44.5±16.9). In multivariate analysis, older age was independently associated with lower resistance to care [odds ratio (OR): 1.072; 95% confidence interval (CI): 1.010-1.138; p=0.021], as was the perception that patients were concerned about their illness (OR: 1.274; 95% CI: 1.033-1.571; p=0.024).

Conclusion: Reluctance to manage fibromyalgia patients is frequent among Moroccan rheumatologists, mainly driven by challenging interactions and perceived therapeutic limitations. Targeted training for younger physicians and communication-centered approaches may improve physician-patient relationships and patient outcomes.

Keywords: Fibromyalgia, physician-patient relations, professional burnout, personality traits, surveys and questionnaires

Özet

Amaç: Fibromiyalji, mekanizmaları tam olarak anlaşılamayan ve tedavi etkinliği sınırlı olan, karmaşık ve yeti yitimine yol açan kronik bir ağrı durumudur. Bu belirsizlikler, sağlık çalışanları arasında sıklıkla şüpheciliğe ve isteksizliğe yol açmaktadır. Bu çalışma, Faslı romatologların fibromiyalji hastalarını yönetme konusundaki istekliliklerini değerlendirmeyi, etkileyen faktörleri belirlemeyi ve böylece hekim-hasta ilişkisini ve genel bakım kalitesini iyileştirmeyi amaçlamıştır.

Yöntem: Fas Romatoloji Derneği'ne bağlı romatologlar arasında kesitsel bir anket çalışması yürütülmüştür. Katılımcılar; sosyo-demografik ve profesyonel verileri, fibromiyalji hastalarını yönetme istekliliğini ve şu valide edilmiş araçları içeren elektronik bir anketi doldurmuştur: Zor Hekim-Hasta İlişkisi Ölçeği, Hastalık Algısı Ölçeği (BIPQ), Kişilik Özellikleri Ölçeği ve Tükenmişlik Ölçeği.

Bulgular: Çalışmaya 71 romatolog katılmıştır. Kırk dört katılımcı (%62), temel olarak zor etkileşimler (n=39; %70) ve algılanan terapötik yetersizlik (n=31; %56) nedeniyle fibromiyalji hastalarını yönetmede isteksizlik bildirilmiştir. Katılımcıların 62'sinde (%87) yüksek hayal kırıklığı puanları gözlemlenmiştir. Fibromiyalji, şiddetli ve etkisi yüksek bir durum olarak algılanmıştır (ortalama BIPQ=44.5±16.9). Çok değişkenli analizde, ileri yaşın bakım direncini azalttığı [risk oranı (OR): 1.072; %95 güven aralığı (GA): 1.010-1.138; p=0.021] ve hastaların hastalıkları konusundaki endişe algısının isteklilikle ilişkili olduğu (OR: 1.274; %95 GA: 1.033-1.571; p=0.024) saptanmıştır.

Sonuç: Faslı romatologlar arasında fibromiyalji hastalarını yönetme konusundaki isteksizlik yaygındır ve temel olarak zorlu iletişimler ile terapötik sınırlamalardan kaynaklanmaktadır. Genç hekimlere yönelik hedeflenmiş eğitimler ve iletişim odaklı yaklaşımlar, hekim-hasta ilişkisini ve hasta sonuçlarını iyileştirmeye yardımcı olabilir.

Anahtar Kelimeler: Fibromiyalji, hekim-hasta ilişkileri, mesleki-tükenmişlik, kişilik özellikleri, anketler ve soru formları

Correspondence / İletişim: Rajaa Bensaid MD,
Abdelmalek Essaadi University, Mohammed Vi University Hospital, Life and Health Sciences Laboratory, Faculty of Medicine and Pharmacy of Tangier, Department of Rheumatology, Tangier, Morocco
E-mail: raja.masensen@gmail.com **ORCID ID:** orcid.org/0000-0001-5767-2148

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Introduction

Fibromyalgia (FM) is a chronic widespread pain syndrome frequently associated with fatigue, sleep disturbances, cognitive dysfunction, and multiple somatic symptoms. Although it is officially recognized by the World Health Organization and included in the 11th revision of the International Classification of Diseases, FM remains a controversial nosological entity, both in terms of its pathophysiology and its clinical management.[1] The absence of specific biomarkers and the subjective nature of symptoms make the diagnosis essentially clinical, often leading to diagnostic uncertainty and therapeutic delays. This medically unexplained profile may also create tensions in the physician-patient relationship.[2]

Several studies have shown that patients with FM are often perceived as "difficult" by healthcare professionals, due to the chronicity of symptoms, poor response to conventional treatments, and the emotional burden they impose. Such negative perceptions can impair the therapeutic relationship, reduce patient satisfaction, and compromise treatment adherence.[3]

While numerous studies have been conducted in Western and Asian countries, data from North Africa remain scarce. To our knowledge, this study provides the first regional data on physicians' reluctance to manage FM patients. It is also the first to examine healthcare providers' personality traits as potential determinants of reluctance, offering novel insights into the psychological and professional factors influencing FM management.

The objective of this study was to assess Moroccan rheumatologists' reluctance to manage FM patients and identify associated factors through a cross-sectional survey. By generating data from North Africa, this study clarifies the situation on the continent, complements existing evidence from other regions, and supports the development of strategies to strengthen the physician-patient relationship and improve FM care.

Materials and Methods

Study Design and Population

This cross-sectional survey was conducted in April and May 2024 among Moroccan rheumatologists who are members of the Moroccan Society of Rheumatology. The study was approved by the Tangier Hospital-University Ethics Committee (approval date: 06.03.2024, approval number: AC76V/2024). Participation was entirely voluntary, and informed consent was obtained electronically. Specifically, the first question of the online questionnaire asked participants whether they agreed to complete the survey. Only those who answered "yes" were able to proceed to the subsequent questions. Before answering the questionnaire, participants were informed of the study objectives, the estimated time required to complete the questionnaire (5 minutes), and the guarantee of anonymity.

The questionnaire was designed using the Google Forms platform and distributed to 270 rheumatologists via WhatsApp. To optimize participation, six reminders were sent through the same platform during the data collection period. A technical restriction within Google Forms ensured that each participant could submit the questionnaire only once, thereby preventing duplicate responses (Supplementary File 1).

Socio-demographic and Professional Characteristics

The first section of the questionnaire collected information on age, sex, professional status (resident or practicing rheumatologist in the public, private, or academic sector), years of clinical experience, and the number of FM patients seen weekly (<1, 1-5, or >5).

Reluctance to Accept FM Patients

To evaluate willingness to manage FM patients, the following question was asked: "If a known or suspected FM patient wishes to consult you, do you feel reluctant to accept them in your practice?" Respondents who answered "yes" were invited to select one or more reasons from a predefined list: persistent doubts about FM as a valid condition; belief that psychiatrists or pain specialists are more appropriate for these patients; perceived difficulties in interaction or time-consuming consultations; perceived inefficacy of treatments; or other reasons.

Frustration

Physician frustration was assessed using the 10-item Difficult Doctor-Patient Relationship Questionnaire (DDPRQ-10), a validated tool for evaluating frustration with patients suffering from chronic illness. Each item was rated on a 6-point Likert scale (1="not at all" to 6="very much"). A total score ≥30 indicates that the patient is perceived as difficult to manage.[4,5]

Illness Perception

Illness perception was assessed using the physician version of the Brief Illness Perception Questionnaire (BIPQ). This 9-item tool evaluates the cognitive, emotional, and comprehensibility dimensions of illness perception, with each item rated from 0 to 10. Higher scores indicate greater perceived severity. An additional item assessed causal attribution by asking participants to list the top three perceived causes of FM, including biological, psychological, or social factors.[6-10]

Burnout

Burnout was assessed using the abbreviated Maslach Burnout Inventory (aMBI) comprising nine items. This instrument

explores three dimensions: emotional exhaustion (EE; items 1-3), depersonalization (DP; items 4-6), and personal accomplishment (PA; items 7-9). Participants rated the frequency of symptoms on a 7-point Likert scale ranging from 0 ("never") to 6 ("every day"): 0=never, 1=a few times a year, 2=at least once a month, 3=a few times a month, 4=once a week, 5=a few times a week, 6=every day.

Each subscale score was calculated as the sum of its corresponding items. Higher EE/DP scores and lower PA scores indicated greater burnout. For EE and DP, scores of 0-9 indicate no or low burnout, whereas scores of 10-18 indicate moderate or high burnout. For PA, scores of 0-9 indicated moderate to high burnout, while scores of 10-18 indicated no burnout. Participants were classified as experiencing burnout if they scored in the moderate/high range on at least two of the three subscales, in accordance with established definitions.[11]

Personality Traits

Personality traits were assessed using the 10-item Big Five Inventory (BFI-10), which covers five domains: extraversion, agreeableness, conscientiousness, neuroticism, and openness. Each domain was represented by two items, one positively phrased and one negatively phrased, rated on a 5-point Likert scale. The most representative trait from each of the five domains was retained for analysis.[12]

Data Collection

Data were collected using Google Forms. The survey link was distributed via WhatsApp to 270 Moroccan rheumatologists and rheumatology residents affiliated with a national Society of Rheumatology. A brief introductory note explained the objectives of the study.

Statistical Analysis

Survey data were extracted to Microsoft Excel and analyzed using SPSS version 21.0. Descriptive statistics were calculated for all variables. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as means with standard deviations or as medians with interquartile ranges, depending on their distribution. Binary logistic regression was performed to identify factors associated with reduced reluctance to manage patients with FM. A p-value <0.05 was considered statistically significant

Results

Demographic Data

A total of 71 responses were collected, representing a response rate of 26% (71/270). Women accounted for 80.3% of the participants. The mean age was 38.9±10.8 years. Private sector practitioners represented 31% of respondents. The median number of years in clinical practice was 7.[3-15] Approximately 36.2% of rheumatologists reported seeing between one and five patients with FM per week (Table 1).

Reluctance to Accept Fibromyalgia Patients

In response to the question "If a patient diagnosed with or suspected of having FM wishes to consult you, do you feel reluctant to accept them in your practice?" more than half of physicians (62%) answered "yes." The most frequently reported reasons were perceived difficulty interacting with FM patients (70.9%), the perceived inefficacy of current treatments (57%), and the time-consuming nature of their management during consultations (46%) (Table 2).

Rheumatologists' Frustration

The mean score on the 10-item DDPRQ-10 was 38.1±8.0. Among the participants, 87.3% perceived patients with FM as frustrating and difficult to manage (Table 3).

Illness Perception

FM was perceived as a severe condition, with a mean score of 44.5±16.9 on the 9-item BIPQ. The highest scores were observed for the items assessing emotional impact, perceived consequences, and chronic timeline. In contrast, the lowest scores were reported for symptom experience and perceived treatment control. Moderate scores were noted for perceived understanding of, and concern about, the illness. Regarding causal attributions, psychological factors were most frequently cited as the perceived causes of FM (Table 4).

Table 1. Demographic characteristics of participants

	n=71
Age (a)	38.86±10.75
Gender (b)	
Female	57 (80.3%)
Male	14 (19.7%)
Professional status (b)	
Rheumatology resident	30 (42.3%)
Private practice rheumatologist	22 (31%)
Public sector rheumatologist	12 (16.9%)
University-affiliated rheumatologist	7 (9.9%)
Years of practice (c)	7 [3-15]
Previous experience in managing FM patients (b)	67 (94.4%)
Number of FM patients seen per week (b)	
Fewer than 1 patient/week	39 (56.5%)
Between 1 and 5 patients/week	25 (36.2%)
More than 5 patients/week	5 (7.2%)

Values are expressed as follows: a mean ± standard deviation. b: Percentage, c: Median and interquartile range. FM: Fibromyalgia

Burnout and Personality Traits

Assessment with the aMBI revealed higher scores on the PA subscale (mean: 10.9±4.3), while scores for EE and DP were lower [8.8±5.2 and 3, (1-5) respectively].

Regarding the BFI-10, the highest personality trait scores were observed for conscientiousness (mean: 8.0±1.6), followed by agreeableness (mean: 7.4±1.4) (Table 5).

Factors Associated with Lower Reluctance to Accept Fibromyalgia Patients

In univariate analysis, older age [odds ratio (OR): 1.062; 95% confidence interval (CI): 1.012-1.114; p=0.015], the perception that patients are concerned about their condition (OR: 1.240; 95% CI: 1.040-1.479; p=0.017), and the personality trait agreeableness (OR: 1.557; 95% CI: 1.048-2.312; p=0.028)

Table 2. Reasons for reluctance to manage fibromyalgia patients, n=71

	n (%)
Feels reluctant to accept an FM patient (a, b)	44 (62%)
Contact with FM patients is often difficult (a, b)	39 (70.9%)
Current treatment options for FM are often ineffective (a, b)	31 (56.4%)
FM management consumes a large part of consultation time (a, b)	25 (45.5%)
Persistent doubt about the legitimacy of the FM diagnosis (a, b)	13 (23.6%)
Pain specialists are more suitable to manage these patients (a, b)	11 (20%)
Psychiatrists are more suitable to manage these patients (a, b)	10 (18.2%)
Other (a, b)	6 (10.9%)

Values are presented as numbers (a) and percentages (b). FM: Fibromyalgia

Table 3. Difficult Doctor Patient Relation Questionnaire (DDPRQ), n=71

	Mean (SD)
How much are you looking forward to a fibromyalgia patient's next visit? (r)	4.79 (1.31)
How "frustrating" you find a fibromyalgia patient?	3.49 (1.60)
How manipulative you find a fibromyalgia patient?	2.94 (1.42)
To what extent are you frustrated by fibromyalgia patient's vague complaints?	3.72 (1.38)
How self-distractive is the fibromyalgia patient?	3.06 (1.35)
Do you find yourself secretly hoping a fibromyalgia patient will not return?	3.08 (1.77)
How at ease you feel with fibromyalgia patients? (r)	4.54 (1.10)
How time consuming is caring for a fibromyalgia patient?	4.11 (1.45)
How enthusiastic do you feel about caring for a fibromyalgia patient? (r)	4.65 (1.25)
How difficult is it to communicate with a fibromyalgia patient?	3.75 (1.47)

DDPRQ Questions ranked 0-6 (r-reverse scale). Values are presented as mean ± standard deviation (SD)

Table 4. Physicians' illness perceptions and causal attribution. Illness perception items (range 0-10), n=71

	Mean (SD)
Consequences: How much does fibromyalgia affect the patient's life? (a)	**7.08 (2.87)**
Timeline: How long do you think fibromyalgia will continue? (a)	**6.87 (2.73)**
Personal control (r): In general, how much control do you think patients have over fibromyalgia in general? (a)	3.96 (2.85)
Treatment control (r): How much do you think general treatment can help fibromyalgia? (a)	6.55 (2.94)
Identity: How much do patients experience symptoms from fibromyalgia? (a)	**2.75 (2.54)**
Concern: In general, how much are patients concerned about their illness? (a)	5.49 (3.05)
Understanding (r): In general, how much do you feel patients understand about their illness? (a)	4.46 (2.82)
Emotional response: In general, how much does fibromyalgia affect patients emotionally? (a) (e.g., anger, fear, confusion depression)	**7.32 (2.94)**
Causal attribution items (b)	
Biologic factors	**59.2%**
Sociologic factors	**38%**
Psychologic factors	**87.3%**

Values are presented as follows: a: Mean ± standard deviation, b: Percentage, r: Stands for reverse items, SD: Standard deviation

were significantly associated with lower reluctance to accept FM patients. In the multivariate analysis, only age (OR: 1.072; 95% CI: 1.010-1.138; p=0.021) and the perception that patients were preoccupied with their illness (OR: 1.274; 95% CI: 1.033-1.571; p=0.024) remained significantly associated with reduced resistance to accepting these patients (Table 6).

Discussion

This study provides new insights into the perceptions and attitudes of rheumatologists toward patients with FM, a population often regarded as challenging to manage. Our findings reveal high levels of frustration and a notable reluctance to accept FM patients in clinical practice, reflecting a physician-patient relationship characterized by uncertainty and emotional burden.

More than 60% of surveyed rheumatologists reported reluctance to treat FM patients, citing difficult interactions (70.9%), limited treatment efficacy (57%), and time-consuming consultations (46%). These findings are consistent with those reported by Homma et al.[13] in Japan, where only 44.2% of rheumatologists were willing to accept new FM patients. In that study, reluctance was mainly attributed to difficulties in controlling symptoms rather than to negative stereotypes toward patients themselves. Symptom management challenges were also identified as the primary source of physician frustration. In our sample, the high mean DDPRQ-10 score (38.1±8.0) further illustrates this resistance, with over 87% of participants perceiving FM patients as "difficult." Similar conclusions were drawn by Walker et al.[14], who reported that somatization, loss of control, and psychiatric comorbidities were significant contributors to physician frustration. Such widespread reluctance, across different contexts, is likely to have negative repercussions for patient care by undermining the therapeutic alliance.

Table 5. Burnout according to the aMBI and personality traits of participants according to the BFI-10 a, n=71

Maslach Burnout Inventory (a BMI)	
Emotional exhaustion (EE) a	8.77±5.19
Depersonalization (DP) b	3 [1-5]
Personal accomplishment (PA) a	**10.86±4.34**
BFI-10 a	
Extraversion	6.59±2.01
Agreeableness	**7.42±1.37**
Conscientiousness	**7.96±1.62**
Neuroticism	5.86±2.17
Openness to experience	6.68±1.50

Values are presented as follows: a: Mean ± standard deviation, b: Median and interquartile range, BFI-10: Big Five Inventory-10

Table 6. Univariate and multivariate analysis of factors associated with lower reluctance to manage FM patients

Variable	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value (multivariate)
Age	**1.062 (1.012-1.114)**	**0.015**	**1.072 (1.010-1.138)**	**0.021**
Gender	1.131 (0.335-3.818)	0.842	-	-
Professional status	1.096 (0.678-1.773)	0.708	-	-
Perception that patients are concerned about their condition	**1.240 (1.040-1.479)**	**0.017**	**1.274 (1.033-1.571)**	**0.024**
Emotional exhaustion (EE)	1.018 (0.928-1.118)	0.702	-	-
Depersonalization (DP)	0.963 (0.851-1.089)	0.546	-	-
Personal accomplishment (PA)	1.019 (0.911-1.139)	0.742	-	-
Agreeableness (BFI-10)	**1.557 (1.048-2.312)**	**0.028**	**1.168 (0.745-1.832)**	**0.498**
Extraversion	1.229 (0.953-1.587)	0.113	-	-
Conscientiousness	0.994 (0.733-1.347)	0.967	-	-
Neuroticism	1.018 (0.815-1.272)	0.874	-	-
Openness to experience	1.250 (0.896-1.744)	0.189	-	-
Causal attribution: Biological factors	0.600 (0.222-1.625)	0.315	-	-
Causal attribution: Psychological factors	3.905 (0.887-17.194)	0.072	-	-
Causal attribution: Social factors	3.905 (0.887-17.194)	0.072	-	-

BFI-10: Big Five Inventory-10, CI: Confidence interval, FM: Fibromyalgia, OR: Odds ratio

The perception of FM among participating rheumatologists reflects a complex and partly contradictory view. FM was generally recognized as a severe and chronic condition, as indicated by the high overall BIPQ score (44.5±16.9). The highest item scores were reported for emotional impact, perceived consequences, and chronic timeline, suggesting that physicians acknowledge the persistent and disabling nature of the disease. In contrast, lower scores were observed for symptom recognition and perceived treatment control, indicating uncertainty regarding the clinical specificity of FM and limited confidence in therapeutic efficacy. Moderate scores for patients' understanding of the illness and for concern about the disease further highlight a perception of FM as poorly understood and emotionally complex. Collectively, these findings suggest that FM is perceived as a disabling condition with ill-defined clinical boundaries, potentially impairing care delivery and undermining trust in the physician-patient interaction.

Regarding causal attributions, 87.3% of surveyed rheumatologists identified psychological factors as the primary cause of FM, followed by biological (59.2%) and sociological (38%) factors. This suggests that physicians tend to conceptualize FM within a biopsychosocial framework. In Uclés-Juárez et al.'s[3] Spanish study, 60% of general practitioners and 66% of internists considered FM a form of somatization, whereas rheumatologists adopted a more biomedical and nuanced perspective. Similarly, in Arshad and Kong's[15] study of Southeast Asian rheumatologists, 92.5% acknowledged FM as a clinical entity, but only 3% considered it purely medical in origin, with most (87%) favoring a psychomedical explanation.[3-15]

In our study, burnout levels among rheumatologists were low according to the aMBI, and no significant association was found between burnout and reluctance to manage FM patients. This contrasts with findings from other studies. For instance, the EPIFFAC study in Spain reported that 25% of family physicians exhibited high levels of burnout, characterized by EE, DP, and reduced PA, and perceived FM patients as burdensome, with more negative impressions associated with higher burnout scores.[16] Thus, while general burnout may be infrequent in our sample, emotional fatigue specifically triggered by FM consultations cannot be excluded.

Multivariate analysis identified two factors independently associated with lower resistance to managing FM patients: physician age and the perception that patients are concerned about their condition. Although certain personality traits, particularly agreeableness, were associated in univariate analysis, none remained significant in the multivariate model, suggesting that personality plays only a secondary role. These findings are consistent with those of Mostafapour et al.[17], who noted that while personality traits may influence the quality of the physician-patient relationship, personal engagement remains one of its strongest determinants.

Study Limitations

This study has several strengths, including its targeted approach, the use of validated assessment tools, and the exploration of a largely understudied context. To our knowledge, it is the first study to examine the association between reluctance to manage FM patients and physicians' personality traits. Nonetheless, some methodological limitations should be acknowledged, particularly the modest response rate (26%), which resulted in a restricted sample size, and the reliance on self-reported data.

Conclusion

Overall, this study reveals a predominantly negative perception of FM among rheumatologists, marked by significant reluctance to provide care, elevated levels of frustration, and an unclear conceptualization of the disease. These factors represent major barriers to establishing a high-quality physician-patient relationship. Our findings highlight the urgent need for continuing medical education focused on chronic pain management, therapeutic communication, and clinical recognition of functional symptoms. Moreover, promoting a biopsychosocial approach to FM care appears essential to rebuilding trust and strengthening the therapeutic alliance.

In-depth qualitative studies are warranted to better understand the underlying factors driving physicians' reluctance to treat FM patients. Such investigations may substantially improve the quality of care, not only for individuals with FM but also for those with other unexplained chronic pain syndromes.

Ethics

Ethics Committee Approval: The study was approved by the Tangier Hospital-University Ethics Committee (approval date: 06.03.2024, approval number: AC76V/2024).

Informed Consent: Participation was entirely voluntary, and informed consent was obtained electronically.

Footnotes

Authorship Contributions

Concept: R.B., F.Z.T., N.T., F.E.A., Design: R.B., F.Z.T., Data Collection and Processing: R.B., F.Z.T., Analysis or Interpretation: R.B., F.Z.T., A.A., Literature Search: R.B., Writing: R.B., F.Z.T., N.T., A.A., F.E.A.

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Supplementary File 1: https://d2v96fxpocvxx.cloudfront.net/2c83d69a-dc5a-476c-9385-2d943ca48693/content-images/e5110db9-1ab3-42bc-a520-61cb5ca3010d.pdf

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Treatment response and retention rates of bDMARDs in advanced spinal ankylosis or bamboo spine: Real-world data from the HUR-BIO registry

İleri spinal ankiloz veya bambu omurga olan hastalarda bDMARD tedavi yanıtı ve ilaç devamlılığı: HUR-BIO kayıt sisteminden gerçek yaşam verileri

Bayram Farisoğulları[1,2], Pedro Machado[2,3,4], Gözde Kübra Yardımcı[1], Emre Bilgin[1], Ertuğrul Çağrı Bölek[1], Emine Sarıyıldız[1], Gizem Ayan[1], Levent Kılıç[1], Ali Akdoğan[1], Şule Apraş Bilgen[1], İhsan Ertenli[1], Sedat Kiraz[1]

[1]Hacettepe University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
[2]University College London, Centre for Rheumatology and Department of Neuromuscular Diseases, London, UK
[3]University College London Hospitals Biomedical Research Centre, Department of Rheumatology, London, UK
[4]Northwick Park Hospital, London North West University Healthcare NHS Trust, Department of Rheumatology, London, UK

Abstract

Objectives: To evaluate clinical characteristics, biological disease-modifying antirheumatic drugs (bDMARD) treatment response and drug retention in patients with axial spondyloarthritis (axSpA) with advanced spinal ankylosis or bamboo spine, compared with patients without syndesmophytes.

Methods: Patients from the Hacettepe University Rheumatology Biologic Registry who had available cervical and lumbar radiographs were classified into three groups: advanced spinal ankylosis, bamboo spine, and a control group with at least ten-year disease duration and without syndesmophytes. Baseline characteristics, treatment responses [Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) and Assessment of Spondyloarthritis International Society partial remission (ASAS-PR)], and retention of first bDMARDs were evaluated.

Results: Of 770 patients, 99 had advanced spinal ankylosis, 78 had bamboo spine, and 92 constituted the control group. Patients with advanced structural damage were older, more often male, and had higher body mass index, greater smoking exposure, and more frequent hip involvement. Baseline disease activity was similar across groups. At follow-up, BASDAI50 and ASAS-PR responses were comparable among advanced spinal ankylosis, bamboo spine, and controls. Median retention of first bDMARDs did not differ significantly between groups (log-rank p=0.86). One-year retention rates were 75% (no syndesmophytes), 84% (advanced spinal ankylosis), and 78% (bamboo spine); at 5 years, retention rates were 67%, 64%, and 60%, respectively; and at 10 years, retention rates were 50%, 41%, and 43%, respectively. Median drug survival ranged from 104 to 126 months across groups.

Özet

Amaç: Bu çalışmanın amacı, ileri spinal ankiloz veya bambu omurgası olan aksiyel spondiloartrit (axSpA) hastalarında klinik özellikleri, biyolojik hastalık modifiye edici antiromatizmal ilaçlara (bDMARD) tedavi yanıtını ve ilaç devamlılığını, sindesmofiti olmayan hastalarla karşılaştırarak değerlendirmektir.

Yöntem: Hacettepe Üniversitesi Romatoloji Biyolojik Kayıt Sistemi'nde yer alan ve servikal ile lomber radyografileri mevcut olan hastalar üç gruba ayrıldı: ileri spinal ankiloz, bambu omurga ve en az 10 yıllık hastalık süresi olup sindesmofiti olmayan kontrol grubu. Başlangıç özellikleri, tedavi yanıtları [Bath Ankilozan Spondilit Hastalık Aktivite İndeksi 50'nin (BASHAİ50) ve Uluslararası Spinal Ankiloz Çalışma Grubu parsiyel remisyon (ASAS-PR)] ve ilk bDMARD tedavisinin devamlılığı değerlendirildi.

Bulgular: Toplam 770 hastanın 99'unda ileri spinal ankiloz, 78'inde bambu omurga saptandı ve 92 hasta kontrol grubunu oluşturdu. İleri yapısal hasarı olan hastalar daha ileri yaşta, daha sıklıkla erkek cinsiyette olup daha yüksek vücut kitle indeksi, sigara maruziyeti ve kalça tutulumu oranına sahipti. Başlangıç hastalık aktivitesi gruplar arasında benzerdi. İzlem sürecinde BASHAİ50 ve ASAS-PR yanıtları ileri spinal ankiloz, bambu omurga ve kontrol grupları arasında benzer bulundu. İlk bDMARD tedavisinin medyan devam süresi gruplar arasında anlamlı farklılık göstermedi (log-rank p=0,86). Bir yıllık ilaç devam oranları sırasıyla %75 (sindesmofit yok), %84 (ileri spinal ankiloz) ve %78 (bambu omurga) idi. Beş yılda bu oranlar sırasıyla %67, %64 ve %60; 10 yılda ise %50, %41 ve %43 olarak bulundu. Medyan ilaç sağkalımı gruplar arasında 104-126 ay arasında değişmekteydi.

Correspondence / İletişim: Bayram Farisoğulları MD,
Hacettepe University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
E-mail: bayramfarisogullari@gmail.com **ORCID ID:** orcid.org/0000-0002-9394-1103
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Abstract

Conclusion: Patients with advanced spinal ankylosis or bamboo spine achieve meaningful clinical improvement with bDMARD therapy and demonstrate long-term drug retention comparable to that of axSpA patients without syndesmophytes, supporting the initiation and continued use of bDMARDs in this population.

Keywords: Ankylosing spondylitis, axial spondyloarthritis, advanced spinal ankylosis, bamboo spine, bDMARDs, treatment response, retention rate

Özet

Sonuç: İleri spinal ankiloz veya bambu omurga varlığı olan hastalar bDMARD tedavisi ile anlamlı klinik iyileşme sağlamakta ve sindesmofiti olmayan axSpA hastalarına benzer uzun dönem ilaç devamlılığı göstermektedir. Bu bulgular, bu hasta grubunda bDMARD tedavisinin başlanmasını ve sürdürülmesini desteklemektedir.

Anahtar Kelimeler: Ankilozan spondilit, aksiyel spondiloartrit, ileri spinal ankiloz, bambu omurga, bDMARD'ler, tedavi yanıtı, ilaç devamlılığı

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that predominantly affects the axial skeletal.[1,2] In axSpA, structural spinal damage may occur through the formation of syndesmophytes.[3] Over time, progressive intervertebral ossification can lead to the development of bony bridges between consecutive vertebrae, ultimately resulting in advanced spinal ankylosis, and, in its most severe form, the characteristic "bamboo spine" appearance.[4] Advanced spinal disease is associated with impaired physical function,[5] reduced mobility,[6] and may lead to permanent disability and decreased quality of life.[7] In advanced spinal ankylosis or bamboo spine, which reflect irreversible structural damage,[8] identifying the presence of active inflammation remains important for disease management.

Biological disease-modifying antirheumatic drugs (bDMARDs) have been shown to be effective in controlling inflammation and disease activity in axSpA in randomized controlled trials (RCTs).[9] Many RCTs of bDMARDs did not include participants with severe spinal structural damage because it was assumed that they would have a lower therapeutic response. To date, two RCTs have shown that adalimumab[10] and etanercept[11] are effective in patients with advanced spinal ankylosis or bamboo spine who have high disease activity. In addition, two other studies have reported the efficacy of infliximab over 54 weeks[12] and adalimumab over 12 weeks[13] in this patient population. Overall, real-world evidence on the use of bDMARDs in patients with advanced spinal ankylosis or bamboo spine remains very limited.

This real-world study aims to compare baseline features, bDMARDs treatment response, and drug retention in patients with advanced spinal ankylosis and bamboo spine versus patients without syndesmophytes, all with at least 10-year disease duration.

Materials and Methods

Database, Study Population and Selection of Control Group

Hacettepe University Rheumatology Biologic Registry (HUR-BIO) is a prospective, single center database of biological treatments, established in 2005, and with a prospective design since 2012.[14] At the time of data collection, the HUR-BIO SpA registry had enrolled 2907 patients. Of these, 770 patients underwent lateral radiographs of the lumbar and cervical spine and were included in the study. Radiographic images of the lumbar and cervical spine were assessed by an experienced physician (UK) using predefined standardised definitions for the presence of syndesmophytes, spinal ankylosis, and bamboo spine. Radiographic data in the registry were recorded categorically (presence or absence of syndesmophytes and predefined structural classifications), and the exact number of syndesmophytes or bridged vertebral units was not systematically documented.

Three subgroups were established: 1) "advanced spinal ankylosis," defined by the presence of at least two intervertebral adjacent bridges and/or fusion at the lumbar and/or cervical spine,[11] without bamboo spine; 2) "bamboo spine," defined by the presence of a Bath Ankylosing Spondylitis Radiologic Index (BASRI)-spine grade 4,[15] with complete fusion of the cervical and lumbar vertebrae; "control group" of patients with at least 10-year disease duration without syndesmophytes at lumbar and cervical spine (BASRI 0, 1 and 2 without syndesmophytes). It was thought that this control group would be very unlikely to ever develop syndesmophytes of the spine.[16] Hip involvement was defined as BASRI-hip grade 2, 3, or 4.[17]

Data Collection, Outcome Measures and Response to bDMARD Treatment

Baseline (at the start of bDMARD treatment) demographic, clinical, laboratory, treatment and imaging data were collected from the HUR-BIO database: age, gender, age at disease onset, disease duration, body mass index (BMI), SpA family history (first-degree), human leukocyte antigen (HLA)-B27, history of uveitis, enthesitis, dactylitis, peripheral joint involvement, use of bDMARDs, use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and corticosteroid treatment.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score,[18] Bath Ankylosing Spondylitis Functional Index (BASFI) score,[19] axSpA Disease Activity Score containing C-reactive protein (ASDAS-CRP),[20] visual analogue scale (VAS)-patient global assessment (PGA) (0-100 mm), pain-VAS (0-100 mm), fatigue-VAS (0-100 mm),[21] erythrocyte sedimentation rate (ESR; mm/h)

and CRP (mg/L) levels were evaluated as outcome measures, at baseline (start of bDMARD treatment) and last visit.

bDMARDs evaluated in the study included anti-tumor necrosis factor (TNF) agents (adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab) and the anti-interleukin-17 (IL-17) agent secukinumab. During the follow-up period, bDMARD use, bDMARD switching (if yes, reasons for switching), and response to bDMARDs were assessed at each outpatient visit. Treatment response to bDMARDs was evaluated by the BASDAI50 response (defined as a 50% improvement of the initial BASDAI score)[22] and achievement of Assessment of Spondyloarthritis International Society partial remission (ASAS-PR) (defined as a value ≤2 for each of the following four domains on a 0-10 scale: PGA of disease activity, pain, function (assessed by BASFI), and inflammation [a mean of the BASDAI questions 5 and 6)][23] at the last visit. Drug retention was assessed as the time to treatment discontinuation of the first bDMARD, including switching to another bDMARD or loss to follow-up.

Ethics Committee Approval

Ethics committee approval was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: 2021/03-16, date: 02.02.2021). The study was conducted in accordance with the Declaration of Helsinki. This was a retrospective study. Written informed consent was obtained from all patients at enrolment into the HUR-BIO cohort.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) to determine whether they were normally distributed. Descriptive analyses were presented using medians and interquartile range (IQR) for the non-normally distributed and ordinal variables, and mean ± standard deviation for normally distributed. One-way analysis of variance was used to compare normally distributed variables. Levene's test was used to assess the homogeneity of variances. Kruskal-Wallis tests were conducted to compare non-normally distributed parameters. The Mann-Whitney U test was performed to test the significance of pairwise differences, using the Bonferroni correction to adjust for multiple comparisons. The chi-square or Fisher's exact test, where appropriate, was used to compare proportions between groups. A 5% type-I error level was used to infer statistical significance.

Results

Characteristics of the Patient Subgroups

Among 770 axSpA patients with lumbar and cervical radiographs, 78 (10.1%) had bamboo spine, 99 (12.8%) had advanced spinal ankylosis, and 92 (11.9%) had at least 10-year disease duration and no syndesmophytes; these patients were included in the study (Figure 1). Detailed quantification of the extent of syndesmophytes or the number of bridged vertebral units was not available in the database, as radiographic data were recorded categorically.

Compared to the without syndesmophytes subgroup, both the advanced spinal ankylosis and bamboo spine subgroups had higher age (42.2±8.8, 51.3±10.2 and 55.5±9.3 years, respectively, p<0.001), higher age at disease onset [25.01 (IQR 11), 36.6 (IQR 19.7) and 33.3 (IQR 17.7), respectively, p<0.001], longer delay in diagnosis [12.02 (IQR 43.01), 36.01 (IQR 89) and 36.01 (IQR 100.5) months, respectively, p=0.013], more males (59.8%, 78.8% and 84.6%, p<0.001), higher BMI [26.3 (IQR 8.1), 29.7 (IQR 7.4) and 29.4 (IQR 6.8), respectively, p<0.001], more smoking packages-years [1.6 (IQR 7.6), 10 (IQR 18.9) and 14 (IQR 30), respectively, p<0.001] and more hip involvement (3.1%, 39.5% and 49.3%, p<0.001). There were no differences between the advanced spinal disease and bamboo spine subgroups in these parameters, except for age, with the bamboo spine subgroup being older than the advanced spinal disease subgroup.

Disease duration was higher in the bamboo spine subgroup compared with both the advanced spinal ankylosis subgroup and the subgroup without syndesmophytes [17.6 (IQR 13.1), 12.3 (IQR 14.6) and 13.8 (IQR 4.9) years, respectively, p<0.001; there was no difference between the advanced spinal ankylosis and without syndesmophytes subgroups]. However, tender joints at the start of the bDMARDs treatment were more common in the subgroup without syndesmophytes than in the advanced spinal ankylosis and bamboo spine subgroups (p<0.001), with no difference between the latter two subgroups. No significant differences were observed between the subgroups in terms of swollen joints, HLA-B27 positivity, enthesitis, dactylitis, uveitis, and concomitant use of methotrexate and sulfasalazine (Table 1).

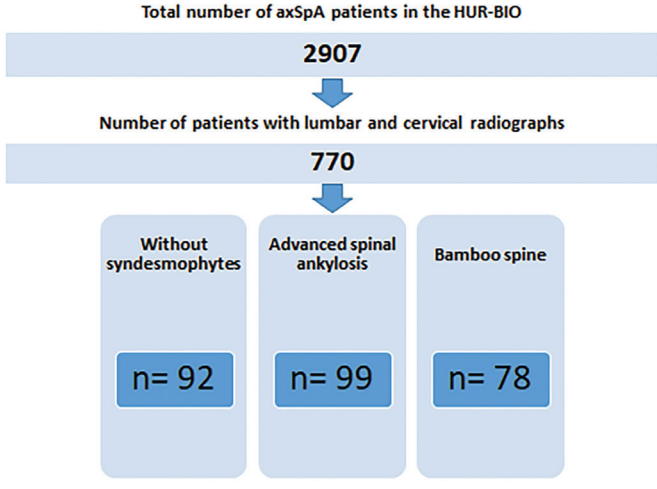

Figure 1. Study flow chart
axSpA: Axial spondyloarthritis, HUR-BIO: Hacettepe University Rheumatology Biologic Registry

Baseline Outcome Measures and Treatment Response of bDMARDs

The time from diagnosis to the start of bDMARD therapy was longer in the bamboo spine subgroup than in the advanced spinal ankylosis subgroup and the subgroup without syndesmophytes [118.7 (IQR 135), 59.7 (IQR 154) and 88.1 (IQR 102) months, respectively, p=0.007; there was no difference between the advanced spinal ankylosis and the subgroup without syndesmophytes].

ASDAS-CRP, BASDAI, BASFI, ESR, CRP, PGA-VAS, pain-VAS and fatigue-VAS levels were similar at the start of bDMARD treatment in all subgroups.

At the last visit, there was a significant difference among the three subgroups (without syndesmophytes, advanced spinal ankylosis, and bamboo spine) in terms of median CRP [0.35 (IQR 0.5), 0.65 (IQR 1), and 0.65 (IQR 0.7), respectively, p=0.001], median BASFI score [1.5 (IQR 3.7), 2.9 (IQR 4.8), and 3.9 (IQR 4.4), respectively, p=0.002], and percentage of patients with BASFI score >4 (23%, 29.8%, and 44.6%, respectively, p=0.01). The bamboo spine and advanced spinal ankylosis subgroups had significantly higher scores than the non-syndesmophyte subgroup for these parameters.

No significant differences were observed between subgroups in terms of ASDAS-CRP, BASDAI50 response, ASAS-PR, BASFI50 response, PGA-VAS, pain-VAS, and fatigue-VAS at the last visit (Table 2).

Distribution and Retention Rate of bDMARDs in the Subgroups

The median total bDMARDs usage time was longer in the bamboo spine subgroup compared to the advanced spinal ankylosis subgroup [110.02 (IQR 93.5) vs. 84.9 (IQR 82.5) months, respectively, p=0.004]; however, there was no significant difference

Table 1. Demographic and clinical characteristics of the study subgroups at baseline

	Without syndesmophytes (n=92)	Advanced spinal ankylosis (n=99)	Bamboo spine (n=78)	p-value
Age, years°	42.2±8.8*^	51.3±10.2*$^{\Sigma\times}$	55.5±9.3^$^{\Sigma\pi}$	**<0.001**
Age at onset of symptoms, years~	22.9 (11.6)*^$^{\infty}$	28 (19.4)*	27.01 (12.5)^	**<0.001**
Age at disease diagnosis, years~	25.01 (11)*^$^{\infty}$	36.6 (18.7)*	33.3 (18)^	**<0.001**
Delay in diagnosis, months~	12.5 (43)	36.01 (82)	36.01 (103)	0.054
Male, n (%)	55 (59.8)*^	78 (78.8)*$^{\times}$	66 (84.6)^$^{\pi}$	**<0.001**
Disease duration, years~	14.8 (5)^$^{\infty}$	13.4 (14.4)$^{\Sigma\times}$	18.9 (12.4)^$^{\Sigma\pi}$	**<0.001**
Family history of SpA (first-degree), positivity/total (%)	13/70 (18.6)^	21/67 (31.3)	25/61 (41)^$^{\pi}$	**0.013**
HLA-B27 positivity/total, (%)	21/42 (50)	31/45 (69)	16/28 (57)	0.19
BMI~	26.3 (8.1)*^	29.7 (7.4)*	29.4 (6.8)^	**<0.001**
Smoking, packages-year~	1.6 (7.6)*^	10 (18.9)*	14 (30)^	**<0.001**
Smoking, n (%)	*	*		**0.03**
Current	35 (38)	48 (48.5)	31 (39.7)	
Ex-smoker	21 (22.8)	32 (32.3)	27 (34.6)	
Never	36 (39.1)	19 (19.2)	20 (25.6)	
Enthesitis, positivity/total, n (%)	8/33 (24.2)	6/35 (17.1)	5/26 (19.2)	0.76
Dactylitis, positivity/total, n (%)	2/69 (3)	1/68 (1.5)	1/58 (1.7)	0.82
Uveitis, n (%)	16 (17.4)	24 (24.2)	26 (33.3)	0.055
Swollen joints, positivity/total (%)	5/43 (11.6)	2/53 (3.8)	0/29	0.08
Tender joints, positivity/total (%)	16/43 (37.2)*^	5/53 (9.4)*	0/29^	**<0.001**
Hip involvement, positivity/total (%)	11/84 (13.1)*^	34/86 (39.5)*	37/75 (49.3)^	**<0.001**
Corticosteroid use before bDMARDs, n(%)	24 (26.1)	13 (13.1)	13 (16.7)	0.06
Concomitant csDMARDs use, n (%)				
Sulfasalazine	19 (20.7)	19 (19.2)	17 (21.8)	0.91
Methotrexate	2 (2.2)	4 (4)	7 (9)	0.11

$^{\pi}$ Patients with syndesmophytes without advanced spinal ankylosis or patients without syndesmophyte with <10-year disease duration, $^{\circ}$ mean ± SD, ~ median (IQR), * p<0.05 for comparison between subgroups "without syndesmophytes" and "advanced spinal ankylosis," ^ p<0.05 for comparison between subgroups "without syndesmophytes" and "bamboo spine," $^{\Sigma}$ p<0.05 for comparison between subgroups "advanced spinal ankylosis" and "bamboo spine," $^{\infty}$ p<0.05 for comparison between subgroups "without syndesmophytes" and remaining subgroups, $^{\times}$ p<0.05 for comparison between subgroups "advanced spinal ankylosis" and remaining subgroups, $^{\pi\times}$ p<0.05 for comparison between subgroups "bamboo spine" and remaining subgroups

bDMARDs: Biological disease-modifying antirheumatic drugs, BMI: Body mass index, csDMARDs: Conventional synthetic DMARD, HLA: Human leukocyte antigen, IQR: Interquartile range, SD: Standard deviation, SpA: Spondyloarthritis

compared to the subgroup without syndesmophytes [110.02 (93.5) vs. 105.03 (89.03) months, respectively, p=0.2]. Additionally, there was no significant difference between subgroups in the duration of use of the first bDMARD. Switching rates for bDMARDs were 42.4%, 43.4%, and 46.2% in the subgroups without syndesmophytes, with advanced spinal ankylosis, and with bamboo spine, respectively (p=0.88). The distribution of the first and last bDMARD treatments among subgroups is shown in Figure 2; no significant differences were observed between subgroups.

Retention rates for first bDMARDs in patients without syndesmophytes, advanced spinal ankylosis, and bamboo spine were 75%, 84%, and 78% at 1 year; 67%, 64%, and 60% at 5 years; and 50%, 41%, and 43% at 10 years, respectively. Median bDMARD therapy survival times in patients without syndesmophytes, without advanced spinal ankylosis, and without bamboo spine were 126.2 (104.2-148.1), 106.9 (80.8-133.1), and 104.0 (72.2-135.8) months, respectively. There was no difference between subgroups the retention rates of the first bDMARDs (log-rank test p-value=0.86) (Figure 3).

Discussion

In this real-world study, patients with advanced spinal ankylosis and bamboo spine demonstrated treatment responses and bDMARD retention rates comparable to those of patients without syndesmophytes. These findings provide important evidence supporting the continued and timely use of bDMARDs in patients with advanced structural spinal damage who exhibit high disease activity.

An important methodological consideration is the potential heterogeneity within the advanced spinal ankylosis group. The definition used (≥2 adjacent intervertebral bridges) may encompass a spectrum of structural severity, ranging from limited bridging to more extensive ankylosis. As the extent of structural involvement was not systematically quantified in the registry, this heterogeneity could not be explored further and may have influenced subgroup comparisons. In addition, the distinction between advanced spinal ankylosis and bamboo spine is based on a categorical threshold (BASRI-spine grade 4), which may introduce a threshold effect between near-complete and complete fusion. Patients with very similar structural burden may therefore be classified into different groups. Accordingly, these categories should be interpreted as pragmatic classifications rather than as strictly distinct biological states.

In the HUR-BIO cohort, treatment responses in patients with advanced spinal ankylosis and bamboo spine, including achievement of ASAS-PR and BASDAI50 responses, were

Table 2. Follow-up period and disease assessments at baseline and last visit, stratified by subgroup

	Without syndesmophytes (n=92)		Advanced spinal disease (n=99)		Bamboo spine (n=78)		p-value	
Time between diagnosis to start of bDMARD therapy˜	88.1 (102)^		59.7 (154)$^{\Sigma}$		118.7 (135)^$^{\Sigma}$		**0.007**	
Follow-up duration, months˜	94.6 (79.9)		78.8 (80.1)$^{\Sigma}$		102.3 (94.1)$^{\Sigma}$		**0.017**	
First bDMARD usage time, months˜	61.7 (103)		46 (77)		59.2 (95)		0.76	
Total bDMARD usage time, months˜	105.03 (89.03)		84.9 (82.5)$^{\Sigma}$		110.02 (93.5)$^{\Sigma}$		**0.013**	
bDMARD switch, n (%)	39 (42.4)		43 (43.4)		36 (46)		0.88	
	Baseline	**Last visit**	**Baseline**	**Last visit**	**Baseline**	**Last visit**	**Baseline**	**Last visit**
ESR, mm/h˜	21.5 (34)	11 (13.5)	25.5 (29)	14 (16)	23 (31)	14 (13.5)	0.6	0.47
CRP, mg/dL˜	1.5 (4)	0.35 (0.5)*^	1.7 (2)	0.65 (1)*	1.8 (3)	0.65 (0.7)^	0.4	**<0.001**
ASDAS-CRP˜	3.6 (0.8)	1.86 (1)	3.4 (0.9)	2 (1.2)	3.4 (0.8)	1.87 (1.4)	0.4	0.23
BASDAI˜	5.7 (2.6)	2 (4)	5.6 (3.3)	2.5 (3)	5.6 (3.2)	2.4 (3)	1	0.23
BASDAI50 response, positive/ total, n (%)		41/68 (60.3)		36/68 (52.9)		27/52 (51.9)		0.58
BASFI˜	5.4 (4)	1.5 (3.7)^	4.5 (4)	2.9 (4.8)	6.5 (3)	3.9 (4.4)^	0.1	**0.002**
BASFI >4, n (%)	29 (59)	20 (23)^	29 (56)	28 (29.8)	27 (75)	33 (44.6)^	0.1	**0.012**
ASAS-PR, n (%)		26 (29.9)		15 (16)		17 (23)		0.08
PGA-VAS˜	70 (30)	30 (40)	60 (30)	37.5 (30)	60 (20)	35 (40)	0.88	0.26
Pain-VAS˜	70 (30)	40 (50)	70 (30)	40 (40)	70 (35)	40 (40)	0.87	0.54
Fatigue-VAS˜	60 (37.5)	30 (45)	60 (50)	30 (30)	55 (52.5)	30 (50)	0.85	0.97

˜ Median (IQR), * p<0.05 between subgroup 1 and 2, ^ p<0.05 between subgroup 1 and 3, $^{\Sigma}$ p<0.05 between subgroup 2 and 3. Four patients from the bamboo subgroup, 5 patients from each of the advanced spinal ankylosis subgroup and without syndesmophytes subgroup were excluded from the last visit evaluation because of missing data at final visit

ASAS-PR: Assessment in spondyloarthritis international society partial remission, ASDAS: Axial spondyloarthritis disease activity score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, bDMARD: Biological disease-modifying antirheumatic drug, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IQR: Interquartile range, PGA: Patient global assessment, SD: Standard deviation, VAS: Visual analogue scale

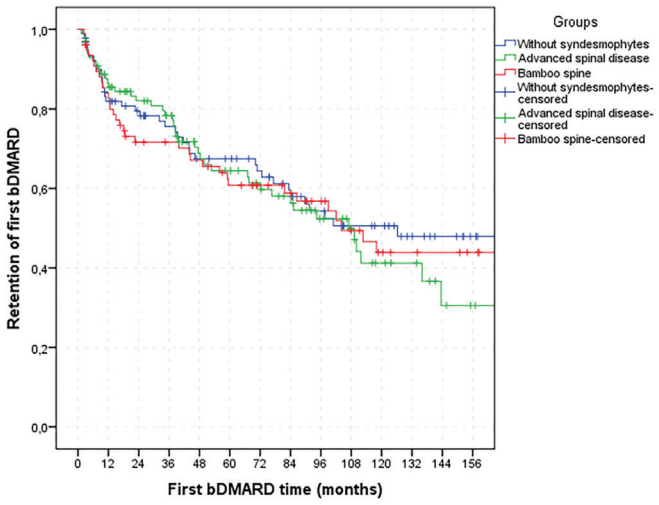

Figure 2. Retention rates of first bDMARDs treatment in the different subgroups. Log rank test p-value=0.86
bDMARD: Biological disease-modifying antirheumatic drug

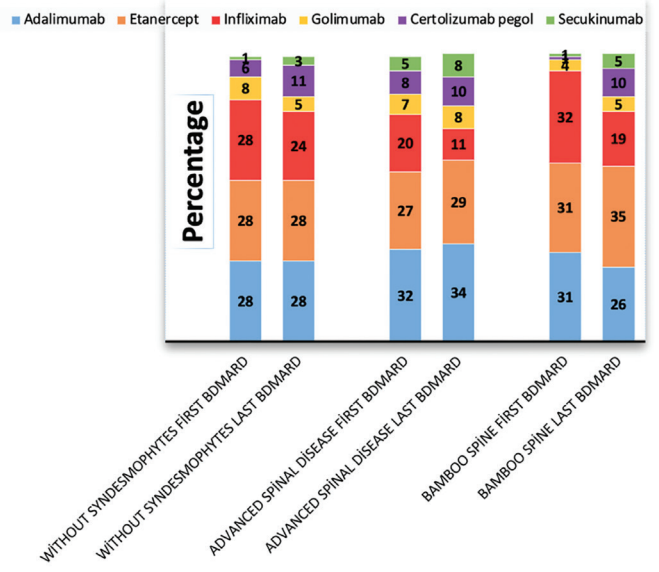

Figure 3. Distribution of bDMARDs treatment at the first and last visit
bDMARD: Biological disease-modifying antirheumatic drug

comparable to those observed in the overall HUR-BIO axSpA population. Among individuals with advanced spinal ankylosis and bamboo spine, ASAS-PR was achieved by 16% and 23%, respectively, and a BASDAI50 response was achieved by 53% and 52%, respectively. Across randomised controlled trials and real-world studies of TNFi and IL-17i therapies in raxSpA, the proportion of patients achieving ASAS-PR ranged from 15% to 50.8%, and BASDAI50 responses ranged from 48% to 63% at various time points.[13,24-30] Only a few studies have specifically investigated treatment efficacy in advanced spinal axSpA. In a post-hoc analysis of an RCT assessing adalimumab treatment over two years in 11 patients with ≥50% spinal involvement, 62.5% achieved a BASDAI50 response (60% among those with bamboo spine), although ASAS-PR results were not reported.[10] In an observational study evaluating infliximab at week 54 in advanced spinal axSpA (≥50% spinal involvement), ASAS-PR and BASDAI responses were achieved in 18% and 82% of patients, respectively.[12] Another observational study assessing adalimumab at week 12 across different stages of spinal involvement, namely stages I-III (<50% of the spine; n=891), stage IV (50 to <80%; n=31), and stage V (≥80%, including bamboo spine; n=41), reported ASAS-PR rates of 30%, 26%, and 7%, and BASDAI responses of 57%, 58%, and 66%, respectively.

Another observational study assessing adalimumab at week 12 across different stages of spinal involvement—stages I-III (<50% of the spine; n=891),stage IV (50-<80%; n=31), and stage V (≥80%, including bamboo spine; n=41)—reported ASAS-PR rates of 30%, 26%, and 7%, and BASDAI responses of 57%, 58%, and 66%, respectively.[13] In a 12-week RCT investigating etanercept in advanced AS (defined by multiple intervertebral adjacent bridges: ≥2 in the lumbar or cervical spine or ≥3 in the thoracic spine), patients receiving etanercept (n=43) showed significantly higher BASDAI50 response rates than placebo (46% vs. 23%, p=0.031). However, ASAS-PR rates did not differ significantly between groups (18% vs. 5%, p=0.073).[11] Differences across studies likely reflect variation in definitions of advanced disease, disease severity, and study methodology. Collectively, these studies, including the present analysis, reinforce that bDMARDs remain effective in advanced structural disease.

Physical function as assessed by the BASFI followed the expected patterns. BASFI improved in all groups, but patients with bamboo spine had persistently higher scores at follow-up compared with individuals without syndesmophytes. This aligns with earlier findings that BASFI correlates with radiographic damage, particularly syndesmophytes and ankylosis.[31] Studies of bDMARDs in advanced disease have shown improvement in BASFI but consistently report higher absolute BASFI scores in those with bamboo spine or extensive ankylosis.[11-13] These observations support the concept that functional impairment in this population reflects both reversible inflammatory activity and irreversible structural damage. In our cohort, improvements in BASFI likely reflect suppression of inflammation with bDMARD therapy, whereas residual functional limitation is attributable to established ankylosis.[5,6,32]

A key strength of this study is the evaluation of long-term bDMARD retention in advanced spinal disease, an area with virtually no published evidence. Retention rates at 12 months (81-85%), 5 years (60-67%), and 10 years (41-51%) were similar across all groups and closely aligned with those reported in real-world axSpA cohorts.[26,28,29,33-35] These findings indicate that individuals with advanced spinal ankylosis or bamboo spine maintain long-term adherence to bDMARD therapy and derive sustained benefit comparable to that of patients without structural progression.

Baseline phenotypic characteristics of the advanced spinal ankylosis and bamboo spine groups differed markedly from those without syndesmophytes. Patients with advanced structural damage were older, were more often male, had higher BMI, greater smoking exposure, and more frequent hip involvement—factors known to predict accelerated spinal radiographic progression. Bamboo spine was associated with longer disease duration, consistent with the cumulative nature of damage formation, whereas advanced ankylosis occurred despite a disease duration similar to that in those without syndesmophytes, suggesting more rapid structural progression in this subgroup. These patterns are in line with previous studies reporting that syndesmophyte development is associated with male sex, older age, and longer disease duration.[31,36-40] Furthermore, baseline differences between groups, including age, sex, BMI, smoking exposure, disease duration, and hip involvement, may contribute to residual confounding. As this was a registry-based observational study, analyses were not fully adjusted for all potential covariates, and findings should therefore be interpreted with appropriate caution.

Study Limitations

This study has limitations. First, some variables had missing data because of the cohort's long duration. Second, patients were grouped according to lumbar and cervical radiographs because most patients did not undergo thoracic radiography, and thoracic vertebrae could not be clearly evaluated on chest radiographs. Third, only 770 of 2,907 patients had both cervical and lumbar radiographs, and individuals with radiographs differed in some characteristics from those without them. Fourth, radiographic data were recorded categorically, and the exact number of syndesmophytes or bridged vertebral units was not available, limiting detailed assessment of structural severity. Therefore, potential heterogeneity within this subgroup could not be further explored. Additionally, the definition of advanced spinal ankylosis may include heterogeneous structural severity, and the categorical distinction between advanced ankylosis and bamboo spine may introduce a threshold effect. Fifth, radiographs were assessed by a single reader, and formal inter- and intra-observer reliability analyses were not performed. Sixth, although patients with radiographs represented a substantial proportion of the registry (26.4%), selection bias cannot be excluded; it may be related to indications for imaging—particularly neck pain or restricted movement—and to changes in patterns of radiograph use over time. Because analyses were not adjusted for all potential confounders, residual confounding cannot be excluded. Nonetheless, the study's strengths include its sizeable cohort of patients with advanced spinal ankylosis and bamboo spine, a population rarely captured in RCTs or observational studies, and the provision of long-term real-world treatment response and drug survival data.

Conclusion

In conclusion, this study contributes important evidence demonstrating that patients with advanced spinal ankylosis or bamboo spine can achieve meaningful clinical improvement with bDMARD therapy and maintain long-term treatment adherence comparable to that of patients without syndesmophytes.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: 2021/03-16, date: 02.02.2021).

Informed Consent: This was a retrospective study. Written informed consent was obtained from all patients at enrolment into the HUR-BIO cohort.

Footnotes

Authorship Contributions

Concept: B.F., G.K.Y., L.K., A.A., Ş.A.B., İ.E., S.K., Design: B.F., G.K.Y., L.K., A.A., Ş.A.B., İ.E., S.K., Data Collection and Processing: B.F., G.K.Y., E.B., E.Ç.B., E.S., G.A., L.K., A.A., Ş.A.B., İ.E., S.K., Analysis or Interpretation: B.F., P.M., Literature Search: B.F., P.M., Writing: B.F., P.M., G.K.Y., E.B., E.Ç.B., E.S., G.A., L.K., A.A., Ş.A.B., İ.E., S.K.

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Diagnostic and immunophenotypic contribution of ultrasound-guided synovial biopsy in inflammatory arthritis: Real-world experience from a tertiary rheumatology center

Enflamatuvar artritte ultrasonografi eşliğinde sinovyal biyopsinin tanısal ve immünofenotipik katkısı: Üçüncü basamak bir romatoloji merkezinden gerçek yaşam deneyimi

Gülnur Çelik Yılmaz[1], Hakan Apaydın[1], Halit Üner[2], Gözde Elif Taşar Kapaklı[2], Mehmet İhsan Başkaya[1], Cem Özişler[1], Alper Sarı[1], Sevinç Can Sandıkçı[1], Emine Gözde Aydemir Gülöksüz[1], Ekin Başak Doğancı[1], Melih Pamukcu[1]

[1]University of Health Sciences Türkiye, Ankara Etlik City Hospital, Department of Rheumatology, Ankara, Türkiye
[2]University of Health Sciences Türkiye, Ankara Etlik City Hospital, Department of Pathology, Ankara, Türkiye

Abstract

Objective: Synovial tissue-based assessment has re-emerged as a useful approach for characterizing disease heterogeneity in inflammatory arthritis; however, real-world data on the diagnostic and immunophenotypic contribution of ultrasound-guided synovial biopsy (USGSB) in routine rheumatology practice remain limited. We aimed to evaluate the diagnostic contribution, procedural feasibility, and immunophenotypic characteristics of USGSB in patients undergoing tissue sampling for suspected inflammatory arthritis at a tertiary rheumatology center.

Methods: This single-center retrospective observational study included 53 consecutive adults who underwent USGSB for persistent synovitis and diagnostic uncertainty. Histopathological evaluation was performed using hematoxylin-eosin staining and Krenn synovitis scoring. Immunohistochemical analyses included CD3, CD20, CD68, CD138, and CD31. Synovial pathotypes were classified as lympho-myeloid, diffuse-myeloid, or pauci-immune/fibroid when tissue and staining qualities were sufficient. Biopsy contribution was defined as biopsy-supported diagnostic reclassification or the identification of a clinically actionable alternative etiology beyond standard clinical, laboratory, and imaging assessments.

Results: Final diagnostic attribution was available for 51 of 53 patients. Inflammatory arthritis was the most frequent diagnostic category (39/51,

Özet

Amaç: Sinovyal doku temelli değerlendirme, enflamatuvar artritte hastalık heterojenitesini karakterize etmek için yararlı bir yaklaşım olarak yeniden önem kazanmıştır; ancak ultrasonografi eşliğinde sinovyal biyopsinin (USGSB) rutin romatoloji pratiğindeki tanısal ve immünofenotipik katkısına ilişkin gerçek yaşam verileri sınırlıdır. Bu çalışmada, üçüncü basamak bir romatoloji merkezinde enflamatuvar artrit şüphesiyle doku örneklemesi yapılan hastalarda USGSB'nin tanısal katkısını, prosedürel uygulanabilirliğini ve immünofenotipik özelliklerini değerlendirmeyi amaçladık.

Yöntem: Bu tek merkezli retrospektif gözlemsel çalışmaya, persistan sinovit ve tanısal belirsizlik nedeniyle USGSB uygulanan ardışık 53 erişkin hasta dahil edildi. Histopatolojik değerlendirme hematoksilen-eozin boyama ve Krenn sinovit skorlaması kullanılarak yapıldı. İmmünohistokimyasal analizlerde CD3, CD20, CD68, CD138 ve CD31 değerlendirildi. Doku ve boyama kalitesi yeterli olduğunda sinovyal patotipler lenfo-miyeloid, diffüz-miyeloid veya pauci-immün/fibroid olarak sınıflandırıldı. Biyopsi katkısı, standart klinik, laboratuvar ve görüntüleme değerlendirmelerinin ötesinde biyopsi destekli tanısal yeniden sınıflandırma veya klinik olarak eyleme geçirilebilir alternatif bir etiyolojinin saptanması olarak tanımlandı.

Bulgular: Elli üç hastanın 51'inde nihai tanısal değerlendirme mevcuttu. Enflamatuvar artrit en sık tanı kategorisiydi (39/51, %76,5) ve romatoid artrit en büyük alt grubu oluşturdu (25/51, %49,0). Enfeksiyöz artrit, dejeneratif

Correspondence / İletişim: Gülnur Çelik Yılmaz MD,
University of Health Sciences Türkiye, Ankara Etlik City Hospital, Department of Rheumatology, Ankara, Türkiye
E-mail: gulnurcelik61@gmail.com **ORCID ID:** orcid.org/0000-0001-8397-6815
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Abstract

76.5%), with rheumatoid arthritis representing the largest subgroup (25/51, 49.0%). Alternative diagnoses or management-relevant diagnostic reclassifications were identified in 12 of 51 patients (23.5%), including infectious arthritis, degenerative joint disease, systemic inflammatory diseases, crystal-induced arthritis, and synovial lipoma. Among histologically assessable specimens (n=50), high-grade synovitis was observed in 34 cases (68.0%). CD68-positive macrophage infiltration was the most frequent immunohistochemical finding (48/53, 90.6%), followed by CD3-positive T lymphocytes (42/53, 79.2%), CD20-positive B cells (26/53, 49.1%), CD138-positive plasma cells (21/53, 39.6%), and CD31 positivity (37/53, 69.8%). Definitive pathotype classification was possible in 44/53 cases (83.0%). No major procedure-related complication was documented.

Conclusion: In this real-world cohort, USGSB provided useful diagnostic refinement and tissue-level immunophenotypic characterization in selected patients with suspected inflammatory arthritis. Biopsy-based treatment stratification remains exploratory and requires validation.

Keywords: Inflammatory arthritis, ultrasound-guided synovial biopsy, synovial tissue, immunophenotype, histopathology, diagnostic yield

Özet

eklem hastalığı, sistemik enflamatuvar hastalıklar, kristal artropati ve sinovyal lipom dahil olmak üzere 12/51 hastada (%23,5) alternatif tanılar veya tedavi açısından anlamlı tanısal yeniden sınıflandırma saptandı. Histolojik olarak değerlendirilebilir örnekler arasında (n=50), 34 olguda (%68,0) yüksek dereceli sinovit izlendi. En sık immünohistokimyasal bulgu CD68-pozitif makrofaj enfiltrasyonuydu (48/53, %90,6); bunu CD3-pozitif T lenfositler (42/53, %79,2), CD20-pozitif B hücreleri (26/53, %49,1), CD138-pozitif plazma hücreleri (21/53, %39,6) ve CD31 pozitifliği (37/53, %69,8) izledi. Kesin patotip sınıflandırması 44/53 olguda (%83,0) yapılabildi. Majör işlem ilişkili komplikasyon kaydedilmedi.

Sonuç: Bu gerçek yaşam kohortunda USGSB, enflamatuvar artrit şüphesi olan seçilmiş hastalarda yararlı tanısal netleştirme ve doku düzeyinde immünofenotipik karakterizasyon sağladı. Biyopsi temelli tedavi sınıflandırması halen araştırma düzeyindedir ve doğrulanmaya ihtiyaç duymaktadır.

Anahtar Kelimeler: Enflamatuvar artrit, ultrasonografi eşliğinde sinovyal biyopsi, sinovyal doku, immünofenotip, histopatoloji, tanısal verim

Introduction

Inflammatory arthritis comprises a heterogeneous group of disorders in which clinical phenotype, serology, and imaging do not always enable confident etiological classification at presentation. In real-world practice, this diagnostic uncertainty is particularly pronounced in seronegative, oligoarticular, monoarticular, or undifferentiated presentations and may delay appropriate disease-modifying treatment or obscure alternative diagnoses such as infection, crystal-associated disease, degenerative disease, or atypical systemic inflammatory disorders. In this context, synovial tissue offers direct assessment of the target organ in which immune activation, stromal remodeling, and vascular changes converge.[1]

Historically, synovial tissue acquisition was largely restricted to arthroscopy. Over the last decade, however, ultrasound-guided minimally invasive synovial biopsy has improved feasibility in routine rheumatology practice. Ultrasound guidance allows targeted sampling of clinically involved synovium across large and small joints and can provide tissue suitable for histopathology and immunohistochemistry (IHC).[2-4] Methodology-focused studies and European Alliance of Associations for Rheumatology (EULAR) points to consider have also emphasized standardized reporting, transparent sampling procedures, and harmonized histological evaluation in synovial tissue research.[3,5]

Standardized histopathological assessment provides a structured framework for interpreting synovial inflammation. The Krenn synovitis score evaluates lining layer hyperplasia, stromal cellularity, and inflammatory infiltrates and can help distinguish inflammatory from low-grade or degenerative patterns.[6] In parallel, immunohistochemical profiling has shown that synovial inflammation is not uniform but includes distinct immune-cell patterns, commonly described as lympho-myeloid, diffuse-myeloid, and pauci-immune/fibroid pathotypes.[7-9]

Although synovial pathotypes are increasingly discussed in precision medicine frameworks, their role in routine treatment selection has not been established in most clinical settings. Trials and translational programs have examined tissue-based treatment-response prediction, but prospective validation is still required before synovial biopsy can be used confidently as a therapeutic decision tool.[8-10] Therefore, real-world studies should clearly distinguish between diagnostic contribution, biological characterization, and unproven treatment-predictive utility.

The present study aimed to evaluate the diagnostic and immunophenotypic contributions of ultrasound-guided synovial biopsy (USGSB) in patients with suspected inflammatory arthritis who were managed at a tertiary rheumatology center. The primary focus was the role of biopsy in diagnostic refinement and tissue-level characterization in clinically challenging cases. Associations with clinical, serological, ultrasonographic, and patient-reported measures were considered descriptive and hypothesis-generating rather than confirmatory.

Materials and Methods

Study Design and Patients

This study was a single-center, retrospective, observational study conducted at a tertiary rheumatology referral center. The study protocol for retrospective data analysis was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Clinical Research Ethics Committee (approval no: AEŞH-BADEK2-2026-150, date: 10.02.2026), and all procedures were performed in accordance with the principles of the Declaration of Helsinki. Written informed consent for the biopsy procedure was obtained from all participants before tissue sampling.

Consecutive adult patients who underwent USGSB for suspected inflammatory arthritis between January 2025 and February 2026 were included. Eligible participants were required to be at least 18 years of age and to have clinical evidence of persistent synovitis warranting tissue sampling. Indications for biopsy included undifferentiated inflammatory arthritis, seronegative arthritis with ongoing synovitis, atypical clinical presentation with monoarticular or oligoarticular involvement, treatment-refractory synovitis, or persistent diagnostic uncertainty despite standard clinical, laboratory, and imaging evaluation.

Patients were excluded from the diagnostic analysis if final clinical attribution was unavailable or clinical data were insufficient for interpretation. Importantly, specimens with insufficient synovial tissue were not excluded from the overall feasibility and safety analyses. These cases were retained in the total biopsy cohort and were reported separately as histologically inadequate for Krenn scoring and as unclassifiable or insufficient for pathotype assignment. This approach allowed procedural adequacy, safety, and diagnostic attribution to be treated as distinct outcomes.

Ultrasound-guided Synovial Biopsy Procedure

Synovial biopsies were performed using ultrasound-guided minimally invasive needle biopsy in accordance with EULAR reporting recommendations and standardized procedural literature.[5,11] All procedures were carried out by an experienced rheumatologist trained in musculoskeletal ultrasonography. Musculoskeletal ultrasonography was performed using a high-resolution ultrasound system equipped with a linear-array transducer. Gray-scale (GS) and power Doppler (PD) imaging were used to evaluate synovial hypertrophy, joint effusion, and Doppler activity in clinically involved joints. Synovial hypertrophy, effusion, and PD activity were graded on 0-3 semiquantitative scales, with higher scores indicating greater structural or inflammatory activity. Biopsy specimens were preferentially obtained from joints demonstrating at least grade 2 GS synovial hypertrophy.

After sterile preparation and local anesthesia with 1% lidocaine, synovial tissue samples were obtained using a 14-18G semi-automatic core biopsy needle under continuous real-time ultrasound guidance. Multiple tissue fragments were obtained from different areas of the synovium to reduce sampling variability. A minimum of 6-8 tissue cores per joint were targeted as the procedural standard; additional cores were obtained at the operator's discretion when tissue appeared macroscopically scant. Biopsies were performed on both large and small joints, depending on clinical involvement. No routine peri-procedural antibiotic prophylaxis was administered. Patients were observed for immediate complications and followed clinically for adverse events.

Procedural adequacy was defined separately from pathotype assignment. Histological adequacy required the presence of identifiable synovial lining and/or sublining tissue. Pathotype adequacy required both sufficient synovial tissue and interpretable immunohistochemical staining. Complications were categorized as major (infection, hemarthrosis requiring intervention, neurovascular injury, hospitalization, or any event requiring invasive treatment) or minor (self-limited pain, bruising, vasovagal symptoms, transient sensory symptoms, or transient swelling).

Histopathological Assessment

Synovial tissue specimens were fixed in 10% neutral-buffered formalin and embedded in paraffin. Serial sections (3-4 µm) were stained with hematoxylin and eosin for routine histopathological evaluation.[6]

Histological assessment focused on synovial lining layer hyperplasia, density and distribution of inflammatory infiltrates, stromal activation and fibrosis, and vascular proliferation or endothelial activation. Inflammatory activity was quantified using the Krenn synovitis score, which evaluates three domains: enlargement of the synovial lining cell layer, density of resident stromal cells, and intensity of inflammatory infiltrates.[6] Each domain was scored from 0 to 3, yielding a total score from 0 to 9. Synovitis was classified as absent/minimal (0-1), low-grade (2-4), or high-grade (5-9). Krenn scoring was performed only on specimens that met the histological adequacy criteria for synovial tissue.

Immunohistochemical Analysis

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded sections using standardized protocols. The predefined panel included CD3 for T lymphocytes, CD20 for B lymphocytes, CD138 for plasma cells, CD68 for macrophages, and CD31 for vascular/endothelial structures. CD34 and CD38 were excluded from the final quantitative analysis to maintain consistency among the methods, results, and figures.

For each marker, staining patterns and cellular distribution were evaluated by experienced observers, and relative abundance was assessed using a semiquantitative approach. Staining was recorded as present or absent and graded on a 0-3 scale when applicable (0=absent or background-level staining; 1=mild/focal staining; 2=moderate/multifocal staining; 3=dense/diffuse staining or organized aggregates). Scoring was performed separately for lining and sublining compartments when tissue orientation permitted. Immunophenotypic features were integrated with routine histopathological findings to support dominant pathotype assignment and to describe the synovial inflammatory microenvironment.

Antigen retrieval and staining were performed according to the manufacturer's recommendations. Appropriate positive and negative controls were included in each staining run. Immunostaining was evaluated by observers blinded to clinical data. To improve interobserver standardization, representative sections were reviewed in a calibration session before final classification, and ambiguous or borderline cases were re-reviewed jointly by rheumatology and pathology investigators. Discrepant interpretations were resolved by consensus.

Synovial Pathotype Classification

Based on integrated histological and immunohistochemical findings, synovial tissue samples were categorized into predefined pathotypes according to previously described classification frameworks.[7-9] The lympho-myeloid pathotype was defined by dense B-cell aggregates, lymphoid organization (ectopic lymphoid-like structures), or prominent infiltration by CD20-positive B-cells and CD138-positive plasma cells. The diffuse-myeloid pathotype was characterized by dominant diffuse CD68-positive macrophage infiltration with limited lymphoid organization and absent or low CD20/CD138 staining. The pauci-immune/fibroid pathotype was characterized by marked stromal fibrosis, low inflammatory cell density, and minimal immune cell marker expression. A separate mixed category was not used for quantitative reporting. Samples with overlapping features with no clearly dominant pattern, limited tissue or IHC quality, or inadequate histological evidence of synovial tissue were classified as unclassifiable or insufficient for pathotype analysis.

EULAR Reporting Standards and Quality Control

The study adhered to the EULAR points to consider for minimal reporting requirements in synovial tissue research. Key methodological aspects were systematically documented, including ultrasound guidance, rationale for joint selection, number of tissue fragments targeted, fixation and processing procedures, scoring systems, and immunohistochemical markers. To minimize interobserver variability, representative sections were reviewed jointly by rheumatologists and pathologists experienced in synovial tissue evaluation, and discrepant cases were resolved by consensus.[5]

Patient-reported Outcome Measures and Pain-related Assessments

Validated patient-reported outcome measures and pain-related assessments were analyzed descriptively to capture patient-centered disease impact. Functional status was evaluated using the Health Assessment Questionnaire (HAQ), which ranges from 0 to 3, with higher scores indicating greater functional impairment.[12] Neuropathic pain-related symptom burden was assessed using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale, which ranges from 0 to 24.[13] Central sensitization-related symptom burden was evaluated using the Central Sensitization Inventory-9 (CSI-9) short form.[14,15] Patient global assessment, physician global assessment, and fatigue severity were recorded using 0-100 mm visual analogue scales, with higher scores reflecting greater perceived disease activity or symptom burden.[16] These measures were not used for formal pathotype-related inference.

Diagnostic Contribution and Management-relevant Outcomes

Diagnostic contribution was operationally defined as biopsy-supported diagnostic reclassification or the identification of a clinically actionable alternative etiology beyond routine clinical, laboratory, and imaging assessments. Management-relevant biopsy contribution was considered present when tissue-based evaluation supported infection-directed investigation or treatment, reduced the likelihood of inappropriate immunosuppressive escalation, or refined the differential diagnosis toward degenerative, crystal-related, systemic inflammatory, or structural synovial disease. The term "biopsy contribution" was used to indicate support for the final diagnostic interpretation after multidisciplinary integration; it was not used to imply that all diagnoses were established by histology alone. Longitudinal treatment-response prediction was not analyzed because medication-response data were not systematically collected.

Statistical Analysis

Normality of continuous variables was assessed visually and, where appropriate, using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation for approximately normally distributed variables and as median with interquartile range (IQR) for skewed variables; categorical variables were presented as number and percentage. Krenn synovitis scores were summarized for histologically adequate specimens only. LANSS and CSI-9 scores were analyzed as continuous variables and summarized descriptively. Because of the modest sample size, uneven distribution of pathotypes, and 9 unclassifiable or insufficient cases, formal inferential comparisons between synovial pathotypes and clinical variables were not performed. Relationships between pathotype, serological findings, inflammatory markers, ultrasonographic activity, and PROMs were interpreted descriptively and as hypothesis-generating. Statistical analyses were performed using SPSS version 25.0 (IBM Corp.).

Results

Baseline Characteristics of the Study Population

A total of 53 patients undergoing USGSB were included in the biopsy cohort. The mean age was 47.7±13.6 years. Women constituted the majority of the study population, with 34 women (64.2%) and 19 men (35.8%). The mean body mass index was 28.0±6.8 kg/m^2. Baseline demographic and clinical characteristics are summarized in Table 1.

Comorbidity Profile and Analytical Denominators

Comorbid conditions were frequently observed among the study participants. Hypertension was the most prevalent comorbidity (14/53, 26.4%), followed by diabetes mellitus (9/53, 17.0%), thyroid disorders (6/53, 11.3%), and chronic lung disease (4/53, 7.5%). No patient had a documented history of malignancy at the time of synovial biopsy. Final diagnostic attribution was available for 51 of 53 patients. Histologically adequate synovial tissue for Krenn scoring was available in 50 of 53 specimens; the remaining 3 specimens did not meet adequacy criteria. Definitive pathotype classification could be assigned in 44 of 53 cases after the integration of histology and IHC. Thus, final diagnosis, Krenn scoring, procedural adequacy, and pathotype classification were analyzed using their respective denominators.

Final Diagnostic Distribution and Biopsy-supported Diagnostic Contribution

Following synovial biopsy, a wide spectrum of final diagnoses was identified (Figure 1). Final diagnoses were available for 51 patients, while final diagnostic attribution was missing for two patients, who were excluded from the diagnostic distribution analysis. Overall, inflammatory arthritis remained the predominant diagnostic category, identified in 39 of 51 patients (76.5%). Within this group, rheumatoid arthritis (RA) was the most frequent diagnosis (25/51, 49.0%), and two additional patients were classified as having RA with overlap features

Table 1. Baseline characteristics of the study population

Characteristics	Mean ± SD or n (%)
Age, years	47.7±13.6
Female sex	34 (64.2)
Male sex	19 (35.8)
Body mass index, kg/m^2	28.0±6.8
Hypertension	14 (26.4)
Diabetes mellitus	9 (17.0)
Thyroid disorders	6 (11.3)
Chronic lung disease	4 (7.5)
History of malignancy	0 (0)

SD: Standard deviation

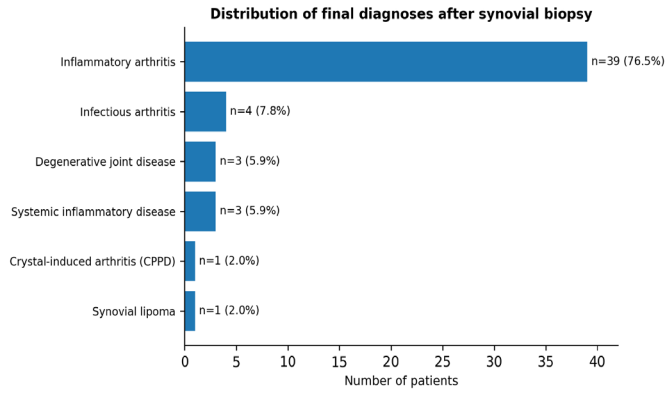

Figure 1. Distribution of final diagnoses following ultrasound-guided synovial biopsy. Final diagnostic attribution was available for 51 patients. Inflammatory arthritis constituted the predominant diagnostic category. Alternative etiologies included infectious arthritis, degenerative joint disease, systemic inflammatory diseases, crystal-induced arthritis, and synovial lipoma

(RA with antisynthetase syndrome, n=1; RA with suspected immunoglobulin G4-related disease, n=1). Other inflammatory arthritis diagnoses included spondyloarthritis (5/51, 9.8%), psoriatic arthritis (3/51, 5.9%), juvenile idiopathic arthritis (2/51, 3.9%), and undifferentiated/inflammatory arthritis (2/51, 3.9%).

A biopsy-supported diagnostic contribution was identified in 12 of 51 patients (23.5%). These cases included infectious arthritis in 4/51 patients (7.8%; septic arthritis, n=1; tuberculous arthritis, n=1; fungal arthritis, n=2), degenerative joint disease in 3/51 patients (5.9%), systemic inflammatory diseases in 3/51 patients (5.9%; Behçet disease, familial Mediterranean fever, and connective tissue disease; each n=1), crystal-induced arthritis in 1/51 patient (2.0%), and synovial lipoma in 1/51 patient (2.0%). In these patients, tissue-based evaluation contributed to the final diagnostic interpretation after integration with clinical, laboratory, imaging, and microbiological data. The alternative diagnoses, biopsy-supported diagnostic contributions, and management-relevant implications are summarized in Table 2. Therefore, the findings should be interpreted as diagnostic and management-relevant observations rather than evidence of longitudinal treatment-response benefit.

Laboratory, Serological, and Patient-reported Measures

Laboratory and serological findings are summarized in Table 3. The mean white blood cell count was 8.77±2.30 ×10^9/L, hemoglobin level was 12.78±2.49 g/dL, and platelet count was 321.69±102.36 ×10^9/L. The median erythrocyte sedimentation rate and C-reactive protein levels were 17.0 mm/h (IQR 9.75-24.25) and 7.5 mg/L (IQR 1.97-17.27), respectively. Rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies were positive in 18/53 (34.0%) and 17/53 (32.1%) patients, respectively, while antinuclear antibodies were detected in 15/53 (28.3%) patients.

Patient-reported outcome measures and pain-related assessments are summarized descriptively in Table 4. These variables were retained to describe the clinical burden of the cohort but were not used to draw formal pathotype-related conclusions. The HAQ score indicated mild-to-moderate functional impairment. LANSS, CSI-9, global assessment, and fatigue scores suggested a substantial symptom burden in the available dataset.

Ultrasonographic Findings and Biopsy Sites

Ultrasonographic findings are summarized in Table 5. The mean GS synovitis score was 2.04±0.62, indicating moderate to severe synovial hypertrophy in most patients selected for biopsy. The mean joint effusion score was 1.89±0.78, and the mean PD score was 1.08±0.92, reflecting heterogeneous inflammatory activity across the cohort.

Synovial biopsies were performed across a broad range of joints, reflecting heterogeneous clinical involvement patterns (Figure 2). The knee was the most commonly sampled joint (27/53, 50.9%), followed by the wrist (12/53, 22.6%), ankle (5/53, 9.4%), elbow (3/53, 5.7%), small joints (3/53, 5.7%), shoulder (2/53, 3.8%), and hip (1/53, 1.9%).

Histopathological and Immunohistochemical Findings

Histopathological evaluation demonstrated variable degrees of synovial inflammatory activity (Table 6).

Table 2. Alternative diagnoses and biopsy-supported diagnostic contribution

Final diagnostic category	n/51 (%)	How biopsy contributed to the diagnostic work-up	Management-relevant implication
Infectious arthritis: septic arthritis, tuberculous arthritis, fungal arthritis	4 (7.8)	Tissue-based evaluation supported an infectious differential and prompted or complemented infection-directed microbiological work-up after integration with clinical data	Supported antimicrobial or infection-directed management and reduced the risk of inappropriate immunosuppressive escalation
Degenerative joint disease	3 (5.9)	Histological and clinical-radiological integration favored a non-primary inflammatory explanation for synovitis-like symptoms	Reduced the risk of over-classifying degenerative presentations as active inflammatory arthritis
Systemic inflammatory diseases: Behcet disease, familial Mediterranean fever, connective tissue disease	3 (5.9)	Biopsy findings did not establish these diagnoses alone but contributed to exclusion/refinement of competing etiologies in a multidisciplinary diagnostic assessment	Supported extension of the differential diagnosis beyond primary inflammatory arthritis
Crystal-induced arthritis (gout, CPPD, etc.)	1 (2.0)	Tissue-based evaluation contributed to recognition of a crystal-associated inflammatory process in the final integrated diagnosis	Supported crystal-focused management rather than escalation for seronegative inflammatory arthritis alone
Synovial lipoma	1 (2.0)	Tissue morphology supported a structural/non-inflammatory synovial lesion	Redirected the diagnostic interpretation toward a structural synovial disorder
Total biopsy-supported alternative etiology or diagnostic reclassification	12 (23.5)	Contribution was defined as support for final diagnostic interpretation after integration with clinical, laboratory, imaging, and microbiological data	Indicates diagnostic refinement, not longitudinal treatment-response benefit

The term biopsy-supported indicates contribution to the final diagnostic interpretation; it does not imply that all diagnoses were established by histology alone
CPPD: Calcium pyrophosphate deposition disease

Table 3. Laboratory and serological characteristics of the study population

Hematological and inflammatory parameters	Mean ± SD or median (IQR)
White blood cell count ($\times 10^9$/L)	8.77±2.30
Hemoglobin (g/dL)	12.78±2.49
Platelet count ($\times 10^9$/L)	321.69±102.36
Erythrocyte sedimentation rate (mm/h)	17.0 (9.75-24.25)
C-reactive protein (mg/L)	7.5 (1.97-17.27)
Rheumatoid factor positivity	18 (34.0)
RF titer	35.0 (15.5-59.8)
Anti-CCP positivity	17 (32.1)
Anti-CCP titer	144.0 (89.2-214.2)
Antinuclear antibody positivity	15 (28.3)

CCP: Cyclic citrullinated peptide, IQR: Interquartile range, RF: Rheumatoid factor, SD: Standard deviation

Krenn scoring was performed only on histologically adequate specimens (n=50). The mean synovial lining layer thickness score was 1.92±0.71, the mean sublining stromal cellularity score was 1.84±0.68, and the mean inflammatory infiltrate density score was 2.01±0.74. The mean total Krenn synovitis score was 5.77±1.86. High-grade synovitis (score ≥5) was observed in 34/50 assessable specimens (68.0%), while 16/50 (32.0%) showed low-grade synovitis. Three specimens did not meet histological adequacy criteria for Krenn scoring.

Krenn scoring was performed only in histologically adequate specimens (n=50). Three specimens lacked adequate synovial tissue and were therefore not included in Krenn-grade percentage calculations.

Immunohistochemical analysis demonstrated prominent macrophage and T-cell infiltration. CD68-positive macrophages were detected in 48/53 cases (90.6%) and represented the dominant immune cell population. CD3-positive T lymphocytes were observed in 42/53 patients (79.2%), frequently located in the sublining and perivascular regions. CD20-positive B-cell infiltration was present in 26/53 patients (49.1%), and CD138-positive plasma cells were identified in 21/53 patients (39.6%). CD31 positivity, reflecting vascular/endothelial structures, was observed in 37/53 patients (69.8%). CD34 and CD38 were not included in the final quantitative marker analysis.

Table 4. Patient-reported outcomes and pain-related assessments

Parameter	Mean ± SD
HAQ	0.92±0.74
LANSS total score (0-24)	14.6±4.5
CSI-9 score	19.48±0.44
VAS patient global assessment (0-100)	64.34±21.10
VAS physician global assessment (0-100)	52.64±21.50
VAS fatigue (0-100)	65.28±26.65

Higher scores indicate greater disability or symptom burden. These outcomes were analyzed descriptively
CSI-9: Central Sensitization Inventory-9, HAQ: Health Assessment Questionnaire, LANSS: Leeds assessment of neuropathic symptoms and signs, SD: Standard deviation, VAS: Visual analogue scale

Table 5. Ultrasonographic findings of the study population

Ultrasonographic parameter	Mean ± SD
Gray-scale synovitis score (0-3)	2.04±0.62
Joint effusion score (0-3)	1.89±0.78
Power Doppler score (0-3)	1.08±0.92

SD: Standard deviation

Table 6. Histopathological characteristics of synovial biopsies

Histopathological parameter	Mean ± SD or n/N (%)
Synovial lining layer thickness (0-3), mean ± SD	1.92±0.71
Sublining stromal cellularity (0-3), mean ± SD	1.84±0.68
Inflammatory infiltrate density (0-3), mean ± SD	2.01±0.74
Total Krenn synovitis score (0-9), mean ± SD	5.77±1.86
High-grade synovitis (score ≥5), n/N (%)	34/50 (68.0)
Low-grade synovitis (score 2-4), n/N (%)	16/50 (32.0)
Not assessable for Krenn scoring	3/53 (5.7)

SD: Standard deviation

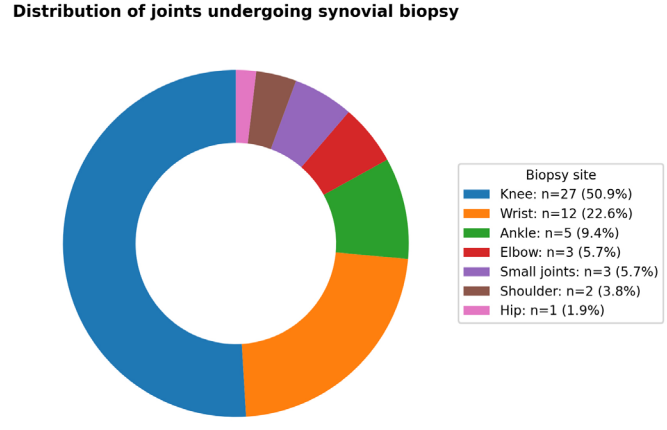

Figure 2. Distribution of joints undergoing synovial biopsy. Values are reported as patient-level biopsy sites in the total biopsy cohort (n=53)

Diagnostic and Procedural Contribution

Safety outcomes were assessed retrospectively from procedure and follow-up records. Very mild or delayed symptoms may have been under-recorded because of the retrospective design. Procedural adequacy, feasibility, and safety outcomes are summarized in Table 7. No major procedure-related complication, bleeding event, infection, neurovascular injury, hospitalization, or repeat biopsy due to an adverse event was documented.

Synovial Pathotype Distribution

Based on combined histological and immunophenotypic features, 44/53 cases (83.0%) were classifiable into predefined synovial pathotypes (Table 8). Percentages were reported using the total biopsy cohort (n=53) as the primary denominator, and the classifiable denominator (n=44) was also provided to aid interpretation. The lympho-myeloid pathotype was the most frequent, identified in 25/53 patients (47.2%; 25/44, 56.8% of classifiable cases), followed by diffuse-myeloid synovitis in 10/53 patients (18.9%; 10/44, 22.7%), and pauci-immune/fibroid synovitis in 9/53 patients (17.0%; 9/44, 20.5%). Nine cases (17.0%) were unclassifiable or insufficient: three specimens did not meet histological criteria for adequate synovial tissue, and 6 had limited tissue or IHC quality or overlapping non-dominant features.

The primary denominator for percentages is the total biopsy cohort (n=53); percentages among classifiable cases use n=44. Unclassifiable or insufficient cases were excluded from definitive pathotype-specific interpretation.

Table 7. Procedural adequacy, feasibility, and safety outcomes		
Indicator	**n/N(%)**	**Interpretation**
Final diagnostic attribution available	51/53 (96.2)	Most patients had a final diagnostic classification after biopsy-based evaluation
Alternative etiology or diagnostic reclassification	12/51 (23.5)	Biopsy-supported evaluation provided added diagnostic value beyond routine assessment
Specimens not meeting histological criteria for adequate synovial tissue	3/53 (5.7)	Retained in feasibility/safety analyses and included within the unclassifiable/insufficient pathotype category
Targeted tissue fragments per procedure	Minimum 6-8 cores	Adequacy-oriented sampling protocol was used to reduce sampling error
Definitive pathotype classification	44/53 (83.0)	Sufficient tissue and IHC quality were obtained for definitive pathotype assignment in most cases
Any recorded minor adverse event	18/53 (34.0)	All recorded events were minor and self-limited; no event required hospitalization or invasive intervention
Self-limited post-biopsy pain	17/53 (32.1)	Most frequent minor event; managed conservatively
Vasovagal reaction/transient sensory symptom	1/53 (1.9) / 1/53 (1.9)	Transient events; event counts are not necessarily additive at patient level
Bleeding-related complication	0/53 (0)	No ecchymosis, hemarthrosis, or bleeding event requiring medical intervention was documented
Infection, thrombophlebitis/DVT, or neurovascular/tendon injury	0/53 (0)	No skin/joint infection, thrombophlebitis, deep venous thrombosis, neurovascular injury, or tendon/ligament/muscle injury was documented
Major procedure-related complications	0/53 (0)	No infection, hemarthrosis requiring intervention, neurovascular injury, hospitalization, or invasive treatment was documented
Repeat biopsy because of a procedure-related adverse event	0/53 (0)	No repeat biopsy attributable to a procedural adverse event was documented in the available records
DVT: Deep venous thrombosis, IHC: Immunohistochemistry		

Table 8. Synovial pathotype distribution and operational criteria			
Pathotype	**n (%)**	**Operational criteria used for classification**	**Interpretive comment**
Lympho-myeloid	25/53 (47.2); 25/44 (56.8 of classifiable cases)	Dense B-cell aggregates, lymphoid organization/ectopic lymphoid-like structures, or prominent CD20-positive B cells and CD138-positive plasma cells	Adaptive immune-rich inflammatory pattern
Diffuse-myeloid	10/53 (18.9); 10/44 (22.7 of classifiable cases)	Dominant diffuse CD68-positive macrophage infiltration with limited lymphoid organization and low/absent CD20 or CD138 staining	Macrophage/innate immune-dominant pattern
Pauci-immune/fibroid	9/53 (17.0); 9/44 (20.5 of classifiable cases)	Marked stromal fibrosis, low inflammatory-cell density, and minimal immune-cell marker expression	Low-inflammatory or remodeling-dominant pattern
Unclassifiable/insufficient	9/53 (17.0)	Three specimens did not meet histological criteria for adequate synovial tissue; six had limited tissue/IHC quality or overlapping features without a clearly dominant pattern	Excluded from definitive pathotype-specific interpretation A separate mixed category was not used for quantitative reporting

Pathotype-stratified immunophenotypic analysis demonstrated distinct cellular compositions among synovial tissue subtypes. Lympho-myeloid synovitis showed higher expression of B-cell and plasma-cell markers, including CD20 and CD138, whereas diffuse-myeloid synovitis was characterized by predominant infiltration of CD68-positive macrophages. Pauci-immune/fibroid synovitis exhibited low expression of immune cell markers. Because of small subgroup sizes and the unavailability of definitive pathotype assignment in 9 cases, formal inferential comparisons were not performed; these findings are presented descriptively and as hypothesis-generating. The revised heatmap includes only markers specified in the final IHC panel (Figure 3).

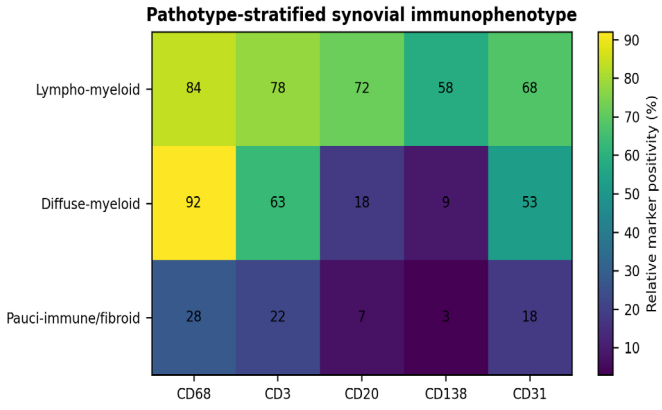

Figure 3. Synovial tissue immunophenotyping and pathotype-specific immune signatures. Values represent descriptive relative marker positivity (%) and are used to visualize pathotype-specific immune-cell patterns. CD38 was removed from the heatmap to maintain consistency with the final immunohistochemical panel. Formal statistical comparisons were not performed

Collectively, these findings demonstrate substantial heterogeneity in clinical characteristics, ultrasonographic activity, serological profiles, and synovial tissue immunophenotypes among patients undergoing synovial biopsy. However, because the study was cross-sectional and did not include longitudinal treatment-response data, tissue-based findings should be interpreted as supporting diagnostic refinement and biological characterization rather than proving biopsy-guided treatment selection.

Discussion

In this single-center real-world cohort, USGSB provided clinically useful diagnostic refinement and synovial tissue-level characterization in patients evaluated for suspected inflammatory arthritis. The principal finding was that biopsy-supported evaluation contributed to the final diagnostic interpretation for approximately one-quarter of patients for whom final diagnoses were available. This contribution was most evident in cases ultimately attributed to infectious, degenerative, crystal-related, systemic inflammatory, or structural synovial diseases. The study demonstrated substantial heterogeneity in synovial inflammation within routine tertiary rheumatology practice, identifying macrophage-dominant, lympho-myeloid, and pauci-immune/fibroid patterns.

The novelty of the present study lies less in describing synovial pathotypes themselves, which have been reported previously, and more in showing how tissue sampling functions in a routine care population characterized by diagnostic uncertainty, seronegativity, atypical presentations, and monoarticular or oligoarticular involvement. In such scenarios, synovial biopsy should be considered a complementary diagnostic tool rather than a replacement for clinical reasoning. Our data suggest that its greatest immediate value lies in refining the differential diagnosis and providing tissue-level information that cannot be fully captured by peripheral blood biomarkers, imaging, or clinical scoring systems alone.

The observed distribution of immune-cell markers is consistent with previous work showing that synovial inflammation is biologically heterogeneous.[7,17,18] CD68-positive macrophages were the most frequent cellular component, whereas CD3-positive T-cells, CD20-positive B-cells, and CD138-positive plasma cells showed variable involvement. These patterns support the concept that inflammatory arthritis encompasses distinct tissue microenvironments rather than a single uniform pathological process. Nevertheless, the present study was not designed to test treatment-response prediction, and the findings should not be interpreted as evidence for biopsy-guided therapeutic selection.

The lympho-myeloid pathotype was the most common classifiable pattern in our cohort. This pattern has been associated in previous studies with adaptive immune activation, B-cell aggregates, plasma-cell infiltration, and ectopic lymphoid-like organization.[7,17,18] Diffuse-myeloid synovitis, in contrast, reflects macrophage-rich innate immune activation, whereas pauci-immune/fibroid synovitis reflects low-inflammatory or remodeling-dominant tissue features.[7,19] Our findings demonstrate that these patterns are identifiable using conventional histology and IHC in a real-world setting, although their clinical implications require prospective validation.

Serological findings further highlight the limitations of relying solely on peripheral markers. A substantial proportion of patients were seronegative for rheumatoid factor and anti-CCP antibodies, which is expected in undifferentiated, atypical, or early inflammatory arthritis populations.[20] Prior studies have shown that synovial immune phenotypes may diverge from circulating autoantibody status, with lymphoid or plasma-cell-rich infiltrates detectable even in seronegative individuals.[7,19] Thus, tissue-level assessment may add information when serology is non-informative, particularly in selected patients with persistent diagnostic uncertainty.

Patient-reported measures showed a meaningful symptom burden, including functional impairment, fatigue, and pain-related symptoms. These variables were analyzed descriptively and were not used to infer pathotype-specific associations. Their inclusion emphasizes that clinical disease expression is multidimensional: pain, fatigue, disability, synovial inflammation, and imaging activity may not always move in parallel.[21,22] Future studies with larger cohorts should evaluate whether tissue phenotypes relate to pain mechanisms or patient-reported outcomes after controlling for inflammatory activity and comorbidity.

A clinically important aspect of synovial biopsy is its contribution to the differential diagnosis of infectious and non-inflammatory joint disorders. Chronic monoarthritis and oligoarthritis can be diagnostically challenging, particularly when systemic inflammatory markers are modest or synovial fluid studies are inconclusive. Previous studies have demonstrated that synovial tissue examination may support recognition of granulomatous inflammation, crystal-associated disease, amyloid deposition, occult infection, or structural synovial lesions.[23-26] In our cohort, tissue-based evaluation contributed to the work-up of septic, tuberculous, and fungal arthritis cases after integration with clinical and microbiological data. This finding is clinically relevant because delayed recognition of infection may expose patients to inappropriate immunosuppression, whereas early tissue-based investigation may redirect management.

The safety profile observed in this cohort was acceptable. No major procedure-related complications, bleeding events requiring intervention, joint or skin infections, neurovascular injuries, hospitalizations, or repeat biopsies due to adverse events were documented. Minor self-limited events, mostly transient post-biopsy pain, were relatively common but were managed conservatively. Because safety outcomes were assessed retrospectively, very mild or delayed symptoms may have been under-recorded. Nonetheless, the findings are in keeping with previous reports that USGSB is feasible and generally well tolerated when performed by trained operators.[2,4,11,27,28]

Study Limitations

Several limitations should be acknowledged. First, the study was retrospective and single-center, with a moderate sample size, thereby limiting generalizability. Second, the final diagnostic attribution was unavailable for two patients, and three specimens were histologically inadequate for Krenn scoring. Third, although 44 cases were classifiable by pathotype, subgroup sizes were small, and formal inferential comparisons were intentionally avoided. Fourth, detailed medication changes and longitudinal treatment-response outcomes were not systematically collected, precluding any conclusions about the prediction of therapeutic response. Fifth, molecular analyses, such as transcriptomics, spatial profiling, and single-cell technologies, were not performed. Finally, because the diagnostic contribution was defined pragmatically after multidisciplinary integration, biopsy should be interpreted as supporting, rather than independently establishing, all final diagnoses.

Future multicenter prospective studies should integrate standardized synovial histology, IHC, high-dimensional molecular profiling, predefined diagnostic endpoints, and longitudinal treatment-response outcomes. Such designs will be necessary to determine whether biopsy-based phenotyping can move beyond diagnostic refinement toward validated therapeutic stratification in inflammatory arthritis.

Conclusion

The findings of this study have practical implications for tertiary rheumatology care. First, USGSB can provide objective tissue-level characterization of synovial inflammation in selected patients with persistent diagnostic uncertainty. Second, biopsy-supported evaluation may refine the differential diagnosis in seronegative, undifferentiated, monoarticular, oligoarticular, atypical, or treatment-refractory arthritis. Third, integration of synovial pathology with ultrasonographic, serological, microbiological, and clinical data offers a multidimensional diagnostic framework. However, its role in treatment selection remains investigational and should not be overstated without prospective outcome-driven validation.

Taken together, our results support the selective incorporation of ultrasound-guided synovial biopsy into tertiary rheumatology practice as a feasible and biologically informative procedure when diagnostic uncertainty persists after standard evaluation. The present findings should be viewed as real-world evidence for diagnostic refinement and immunophenotypic characterization, whereas biopsy-based personalized treatment strategies require prospective validation.

Ethics

Ethics Committee Approval: The study protocol for retrospective data analysis was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Clinical Research Ethics Committee (approval no: AEŞH-BADEK2-2026-150, date: 10.02.2026), and all procedures were performed in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consent for the biopsy procedure was obtained from all participants before tissue sampling.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Ç.Y., H.A., H.Ü., G.E.T.K., Concept: G.Ç.Y., H.A., Design: G.Ç.Y., H.A., M.P., C.Ö., E.B.D., Data Collection and Processing: G.Ç.Y., H.A., E.B.D., M.İ.B., Analysis or Interpretation: H.A., A.S., S.C.S., E.G.A.G., E.B.D., Literature Search: G.Ç.Y., Writing: G.Ç.Y., H.A., M.P., C.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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