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Clinical characteristics of treatment-resistant spondyloarthritis patients treated with multiple biologic pathways

Çoklu biyolojik yolakların kullanıldığı tedavi dirençli spondiloartrit hastalarının klinik özellikleri

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Abstract

Objective: With increasing use of biologics targeting multiple pathways in treatment-resistant spondyloarthritis (SpA), understanding patient characteristics has become crucial. This study aims to assess the clinical and demographic characteristics of patients with SpA treated with anti-tumour necrosis factor (TNF) and interleukin (IL)-17/23 inhibitors.

Methods: We retrospectively reviewed 90 SpA patients treated at Gazi University Faculty of Medicine, Rheumatology Clinic between 2018 and 2022 who had received both anti-TNF and IL-17/23 inhibitors. Clinical data, treatment lines, and responses were evaluated using ankylosing spondylitis disease activity scores.

Results: 51% of patients were female, with a mean disease duration of 10.9 years. Of the patients, 76% had axial SpA and 24% had peripheral SpA. Remission rate with IL-17 inhibitors was 79% when used as second-line therapy, but decreased to 35% when used as fourth-line therapy (p=0.044). Patients with comorbid fibromyalgia showed a significantly lower response to treatment.

Conclusion: Our findings indicate that IL-17 inhibitors are more effective when used earlier in the treatment course. Fibromyalgia negatively impacts treatment outcomes, highlighting the importance of differentiating centralized pain from inflammatory disease. Early initiation of IL-17 and careful evaluation for fibromyalgia are recommended.

Keywords: Spondyloarthritis, IL-17 inhibitors, TNF inhibitors, fibromyalgia, biologic DMARDs, treatment resistance

Özet

Amaç: Tedaviye dirençli spondiloartrit (SpA) hastalarında, çoklu biyolojik yolakları hedefleyen tedavi seçeneklerinin artmasıyla birlikte, bu hastaların klinik özelliklerini değerlendirmek önem kazanmıştır. Bu çalışmanın amacı, hem anti-tümör nekrozis faktör (TNF) hem de interlökin (İL)-17/23 inhibitörleriyle tedavi edilen SpA hastalarının demografik, klinik ve tedavi yanıtlarını değerlendirmektir.

Yöntem: Gazi Üniversitesi Tıp Fakültesi, Romatoloji Kliniği'nde, 2018-2022 yılları arasında hem anti-TNF hem de İL-17/23 inhibitörleri kullanmış 90 SpA hastasının verileri retrospektif olarak incelendi. Hastaların klinik verileri, biyolojik tedavi sıraları ve tedavi yanıtları ankilozan spondilit hastalık aktivite skorlarıyla değerlendirildi.

Bulgular: Hastaların %51'i kadın, ortalama hastalık süresi 10.9 yıldı. Hastaların %76'sı aksiyel SpA, %24'ü periferik SpA tanısı aldı. İL-17 inhibitörleri ikinci basamakta kullanıldığında %79 remisyon oranı gözlendi, bu oran dördüncü basamakta %35'e düştü (p=0,044). Fibromiyalji eşlik eden hastalarda biyolojik tedavilere yanıt oranı belirgin olarak düşüktü.

Sonuç: Çalışmamız, İL-17 inhibitörlerinin özellikle erken basamakta daha etkili olduğunu ve fibromiyaljinin tedavi yanıtını olumsuz etkileyebileceğini göstermektedir. Tedavi planlamasında fibromiyalji ayırıcı tanısının dikkatle yapılması ve İL-17 tedavisinin geciktirilmemesi önerilmektedir.

Anahtar Kelimeler: Spondiloartrit, İL-17 inhibitörleri, TNF inhibitörleri, fibromiyalji, biyolojik DMARD'lar, tedavi direnci

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Introduction

Spondyloarthritis (SpA) comprises a group of related but phenotypically distinct inflammatory diseases.[1] SpA is classified into two main categories: axial SpA (AxSpA) and peripheral SpA (pSpA).[1] In patients with AxSpA who do not respond to first-line treatment with non-steroidal anti-inflammatory drugs (NSAIDs), or in those with pSpA who fail conventional disease-modifying antirheumatic drug (DMARD) therapy, a transition to biologic DMARDs is recommended, with tumour necrosis factor inhibitors (TNFi) as the preferred initial option.[2] However, approximately 40% of AxSpA patients have inadequate responses to TNFi treatments.[1]

Treatment failure with biologic DMARDs can be identified through persistent symptoms or physical examination findings, elevated C-reactive protein (CRP) levels, or the presence of inflammatory lesions on magnetic resonance imaging (MRI).[3] Additionally, indices such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) are commonly used to assess disease activity and clinical response in AxSpA.[4]

Numerous studies have demonstrated the roles of interleukin-23 (IL-23) and IL-17 in SpA pathogenesis, suggesting that targeting the IL-17/IL-23 cytokine pathway could be an effective therapeutic strategy.[1] Secukinumab and ixekizumab, developed as anti-IL-17A monoclonal antibodies, have demonstrated efficacy in the treatment of ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis in clinical trials.[1,5] Ustekinumab, which targets the IL-23 pathway by blocking the p40 subunit shared by IL-12 and IL-23, has proven efficacy in psoriasis and psoriatic arthritis (PsA) and is approved for their treatment.[2,6]

While tumor necrosis factor inhibitors were previously the only approved biologic DMARDs for AxSpA, the development of the first two IL-17 inhibitors, secukinumab and ixekizumab, has expanded therapeutic options, especially for patients unresponsive to TNFi therapy.[7]

In light of these points, the present study aims to comprehensively evaluate the demographic characteristics, clinical findings, treatment histories, comorbidities, acute-phase reactant levels, imaging features, and disease activity scores of patients with SpA treated with biologic therapies targeting different pathways. Furthermore, this study seeks to compare patients who responded to, and those who did not respond to, treatments targeting two distinct pathways-TNFi and IL-17/23 inhibitors.

Materials and Methods

Patient Selection

This single-centre retrospective study reviewed the data of 539 patients aged 18 years or older who were diagnosed with SpA and received biologic DMARD therapy at the Rheumatology Clinic of Gazi University Faculty of Medicine, Department of Internal Medicine, between January 2018 and October 2022.

The inclusion criteria were patients aged 18 years or older who were followed up at the Gazi University Rheumatology Clinic for SpA, had been treated with both anti-TNF agents and IL-17 and/or IL-23 inhibitors, and had received biologic DMARD therapy for at least 12 weeks. Patients with incomplete medical records and those under 18 years of age were excluded from the study. A total of 90 patients who met these inclusion criteria were enrolled in the study.

Data Collection

The following parameters were retrospectively collected: age, sex, diagnosis, date of diagnosis, disease duration, comorbidities, height, weight, body mass index (BMI), exercise history, family history, orthopedic surgery history, presence of concomitant fibromyalgia, history of prior rheumatologic treatments before biologic DMARDs, erythrocyte sedimentation rate (ESR), and CRP values prior to each biologic DMARD initiation, as well as BASDAI, ASDAS-ESR, and ASDAS-CRP scores. Reasons for switching biologic agents (primary or secondary non-response, adverse events, patient or physician preference, or change in administration route) were also recorded.

BMI was calculated as weight divided by height squared (kg/m^2). Patients who had received biologic DMARDs for at least 12 weeks and whose ASDAS-CRP and/or ASDAS-ESR scores were ≥ 2.1 during follow-up were considered to have active disease. Remission was defined as ASDAS <1.3, while scores between 1.3 and 2.1 were classified as low disease activity. These cases were classified as treatment failures, and subsequent changes in therapy were recorded. For each biologic DMARD initiated, ESR, CRP, BASDAI, ASDAS-ESR, and ASDAS-CRP scores were documented.

Statistical Analysis and Ethical Considerations

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 22. Categorical variables (qualitative) were expressed as frequencies, and numerical variables (quantitative) were expressed as means ± standard deviations for normally distributed data or medians (interquartile range) for non-normally distributed data. The normality of the distribution was assessed using the Kolmogorov-Smirnov test. Parametric or nonparametric tests were applied as appropriate. For subgroup analyses, the chi-square test was used for categorical variables, and the Bonferroni-adjusted Mann-Whitney U test was employed for numerical variables. A p-value of <0.05 was considered statistically significant.

This study, titled "Clinical characteristics of treatment-resistant SpA patients treated with multiple biologic pathways",

was approved by the Clinical Research Ethics Committee of Gazi University on December 5, 2022, with decision number 883.

Results

Axial SpA, Peripheral SpA, and Sequential Biologic Outcomes

A total of 90 patients with SpA who had received both anti-TNF agents and IL-17 or IL-23 pathway inhibitors were included in the study. Of these patients, 46 (51%) were female. The mean age at diagnosis was 35.0±12.0 years, while the mean age at the last follow-up visit was 46.2±12.3 years. The mean disease duration was 10.9±7.4 years. Among the included patients, 54 (60%) had AS, 19 (21.1%) had PsA, 14 (15.6%) had non-radiographic axSpA, and 3 (3.3%) had enteropathic arthritis. Comorbidities included psoriasis (38 patients, 42.2%), hypertension (19 patients, 21.1%), diabetes mellitus (12 patients, 13.3%), and familial Mediterranean fever (9 patients, 10%). Among patients with psoriasis, only 19 met the CASPAR criteria for psoriatic arthritis, while the remaining patients had psoriasis without articular involvement or paradoxical psoriasis that developed during TNF inhibitor therapy.

Of the 90 patients, 68 (76%) had axSpA, while 22 (24%) had peripheral SpA. Table 1 presents the demographic, clinical, and radiological features and pre-biologic DMARD treatments of patients with axial and peripheral SpA. The median time from diagnosis to the initiation of biologic DMARD therapy was 34 months (12-95 months) for axSpA patients and 42 months (17-96 months) for peripheral SpA patients (p=0.906). The biologic agents used at each treatment step for patients with axSpA and pSpA are summarised in Table 2.

Among the 90 patients who received two lines of biologic DMARDs, 23 (25.6%) achieved remission after second-line therapy. The median disease duration was shorter in patients who achieved remission (median 6 years; range 4-9) than in those who did not (median 12 years; range 6-15) (p=0.009). The median time from diagnosis to initiation of biologic DMARD therapy was similar between patients who achieved remission (31.0 months, range 14.5-81.0 months) and those who did not (40.0 months, range 12.0-115.0 months; p=0.610).

For third-line biologic DMARDs, the median duration of use was 10.1 months (range, 4.0-21.5 months). Of the 67 patients who received a third-line therapy, 21 (31.3%) achieved remission. Among these patients, the median time from diagnosis to biologic DMARD initiation was 28.5 months (12.0-121.5) for those in remission, compared to 48.0 months (11.5-115.0) for those not in remission (p=0.857).

Among the 46 patients who did not achieve remission and who proceeded to fourth-line biologic DMARD therapy, 18 (39.1%) were treated with IL-17 inhibitors (13 with secukinumab and 5 with ixekizumab), 5 (10.9%) with IL-12/23 inhibitors, and 23 (50.0%) with TNFi. The median duration of fourth-line therapy was 6.3 months (3.9-10.5 months). Remission was achieved in 16 patients (34.8%) following fourth-line treatment.

In the fifth line, 30 patients who did not achieve remission received biologic DMARDs, including IL-17 inhibitors (10 patients, 33.3%), IL-12/23 inhibitors (5 patients, 16.7%), and TNFi (15 patients, 50%). Among these, remission was achieved in 15 patients (50%). In the sixth line, 15 patients received biologic DMARDs: IL-17 inhibitors (n=6; 40%), IL-12/23 inhibitors (n=1; 6.7%), and TNFi (n=8; 53.3%). Remission was achieved in eight patients (53.3%) after sixth-line therapy.

Among the 81 patients treated with IL-17 inhibitors, 49 (60.5%) achieved remission. Of these, five patients (6.1%) initiated secukinumab as first-line therapy. As second-line therapy, 24 patients (29.6%) received IL-17 inhibitors, and 19 patients (79%) achieved remission. In the third line, 20 patients (24.7%) received IL-17 inhibitors, of whom 13 (65%) achieved remission. Comparison of remission rates between second- and fourth-line IL-17 inhibitor use showed a higher rate in the second-line group (p=0.044). Detailed comparisons between patients who achieved remission and those who did not while receiving IL-17 inhibitors are shown in Table 3.

Among the 25 patients treated with IL-23 inhibitors, 7 (28%) achieved remission. Of these, one patient received IL-23 inhibitors as second-line therapy, two as third-line therapy, and four in later lines.

Overall, 27 patients (30%) achieved remission on TNFi. Of these, 18 patients achieved remission in later lines (fourth line and beyond), 6 in the third line, and 3 in the second line. Transitions between biologic classes were also recorded to describe treatment sequencing. As shown in Table 4, the most frequent transition occurred from TNF inhibitors to IL-17 inhibitors, followed by transitions from TNF inhibitors to IL-12/23 inhibitors. Reverse transitions and movements between other classes were observed less frequently.

Discussion

The concept of treatment-resistant SpA was acknowledged as an emerging clinical entity, emphasizing its relevance to our study design and future research directions.

Table 1. Demographic and clinical parameters of patients				
	All patients (n=90)	**Axial SpA (n=68)**	**Peripheral SpA (n=22)**	**p***
Age at diagnosis, mean ± SD	35.0±12.0	33.1±11.5	40.8±11.7	0.056
Age at last visit, mean ± SD	46.2±12.3	45.0±12.6	49.7±10.8	0.178
Sex, female, n (%)	46 (51.1)	29 (42.6)	17 (77.3)	0.005
Disease duration, year, mean ± SD	10.9±7.4	11.6±7.8	8.9±5.7	0.356
BMI (kg/m^2), mean ± SD	27.5±6.2	26.9±5.6	29.2±6.7	0.496
Diagnosis, n (%)				
Ankylosing spondilitis	54 (60.0)	54 (79.4)	-	-
Nr-axSpA	14 (15.6)	14 (20.6)	-	-
Psoriatic arthritis	19 (21.1)	-	19 (86.4)	-
Enteropathic SpA	3 (3.3)	-	3 (13.6)	-
History of orthopedic surgery, n (%)	8 (8.9)	7 (10.3)	1 (4.5)	0.405
Fibromyalgia, n (%)	23 (25.6)	19 (27.9)	4 (18.2)	0.362
Exercise, n (%)	24 (26.7)	16 (23.5)	8 (36.4)	0.237
Family history of SpA	23 (25.6)	19 (27.9)	4 (18.2)	0.362
X-ray finding of sakroiliitis (right) n (%)				
Normal-grade 2	49 (54.4)	27 (39.7)	22 (100)	**<0.001**
Grade 3-4	41 (45.6)	41 (60.3)	0 (0)	**<0.001**
X-ray finding of sacroiliitis (left) n (%)				
Normal-grade 2	51 (56.7)	29 (42.6)	22 (100)	**<0.001**
Grade 3-4	39 (43.3)	39 (57.3)	0 (0)	**<0.001**
MRI before biologic treatment, n (%)	n=40			
Ankylosis n (%)	3 (7.5)	3 (8.3)	0 (0)	-
Sclerosis n (%)	11 (27.5)	11 (27.5)	0 (0)	-
Bone marrow edema n (%)	29 (72.5)	29 (72.5)	0 (0)	-
Sacroiliitis n (%)	31 (77.5)	31 (77.5)	0 (0)	-
MRI after biologic treatment, n (%)	n=21			
Ankylosis	2 (9.5)	2 (9.5)	0 (0)	-
Sklerosis	13 (61.9)	13 (61.9)	0 (0)	-
Bone marrow edema	12 (57.1)	12 (57.1)	0 (0))	-
Sacroileitis	12 (57.1)	12 (57.1)	0 (0)	-
Kyphosis, n (%)	29 (32.2)	23 (33.8)	6 (27.3)	0.568
Scoliosis, n (%)	18 (20.0)	14 (20.6)	4 (18.2)	0.806
Syndesmophyte, n (%)	15 (16.7)	14 (20.6)	1 (4.5)	0.079
HLA-B27, n (%)	58 (64.4)	50 (73.5)	8 (36.4)	**0.036**
Enthesitis, n (%)	56 (62.2)	42 (61.8)	14 (63.6)	0.875
Dactylitis, n (%)	18 (20.0)	8 (11.8)	10 (45.5)	**0.001**
Anterior uveitis, n (%)	18 (20.0)	18 (26.5)	0 (0)	**0.007**
Peripheral arthritis, n (%)	60 (66.7)	38 (55.9)	22 (100)	**<0.001**
Kidney findings, n (%)	6 (6.7)	5 (7.4)	1 (4.5)	0.646
Aortic regurgitation, n (%)	6 (6.7)	5 (7.4)	1 (4.5)	0.646
Corticosteroid, n (%)	63 (70.0)	43 (63.2)	20 (90.9)	**0.014**
NSAID, n (%)	82 (91.1)	65 (95.6)	17 (77.3)	**0.029**
Conventional DMARD, n (%)	84 (93.3)	62 (91.2)	22 (100)	0.146
Sulfasalazin, n (%)	70 (77.8)	56 (82.4)	14 (63.6)	0.066
Methotrexate, n (%)	58 (64.4)	39 (57.4)	19 (86.4)	**0.013**
Leflunomide, n (%)	36 (40.0)	19 (27.9)	17 (77.3)	**<0.001**

Comparison results of axial and peripheral spondyloarthritis are provided. BMI: Body mass index, DMARDs: Disease-modifying anti-rheumatic drugs, HLA-B27: Human leukocyte antigen-B27, MRI: Magnetic resonance imaging, nr-axSpA: Non-radiographic axial spondyloarthritis, NSAIDs: Non-steroidal anti-inflammatory drugs, SD: Standard deviation

Table 2. The biologic agents used at each treatment step for axial and peripheral SpA patients					
	Axial SPA	**Peripheral SPA**		**Axial SPA**	**Peripheral SPA**
First line biological DMARD	n=68	n=22	**Fourth line biological DMARD**	n=36	n=10
Adalimumab	29 (42.7)	14 (63.7)	Secukinumab	13 (36.1)	-
Infliximab	12 (17.7)	2 (9.1)	Sertolizumab	9 (25.0)	3 (30.0)
Etanercept	11 (16.2)	2 (9.1)	Golimumab	4 (11.1)	-
Certolizumab	8 (11.8)	2 (9.1)	Infliximab	3 (8.3)	-
Golimumab	4 (5.9)	1 (4.5)	Adalimumab	2 (5.6)	-
Secukinumab	4 (5.9)	1 (4.5)	Etanercept	2 (5.6)	-
Second line biological DMARD	n=68	n=22	Ixekizumab	2 (5.6)	3 (30.0)
Adalimumab	12 (17.6)	2 (9.1)	Ustekinumab	1 (2.7)	4 (40.0)
Etanercept	21 (30.9)	5 (22.8)	**Fifth line biological DMARD**	n=26	n=4
Secukinumab	16 (23.5)	6 (27.3)	Secukinumab	10 (38.5)	-
Certolizumab	7 (10.3)	1 (4.5)	Infliximab	4 (15.4)	-
Golimumab	5 (7.4)	-	Ustekinumab	3 (11.5)	2 (50.0)
Infliximab	5 (7.4)	4 (18.2)	Adalimumab	3 (11.5)	-
Ustekinumab	2 (2.9)	1 (4.5)	Etanercept	3 (11.5)	1 (25.0)
Ixekizumab	-	2 (9.1)	Certolizumab	2 (7.7)	-
Vedolizumab	-	1 (4.5)	Golimumab	1 (3.9)	1 (25.0)
Third line biological DMARD	n=51	n=16	**Sixth line biological DMARD**	n=13	n=2
Secukinumab	17 (33.3)	3 (18.7)	Secukinumab	4 (30.7)	1 (50.0)
Adalimumab	9 (17.6)	3 (18.7)	Adalimumab	2 (15.4)	
Ustekinumab	8 (15.7)	4 (25.0)	Golimumab	2 (15.4)	
Etanercept	6 (11.8)	1 (6.3)	Etanercept	1 (7.7)	
Certolizumab	5 (9.8)	3 (18.7)	Infliximab	1 (7.7)	1 (50.0)
Golimumab	2 (3.9)	-	Ixekizumab	1 (7.7)	
Infliximab	4 (7.9)	1 (6.3)	Certolizumab	1 (7.7)	
Ixekizumab	-	1 (6.3)	Ustekinumab	1 (7.7)	
DMARD: Disease modifying anti-rheumatic drug, SpA: Spondyloarthritis					

Among the 81 patients treated with IL-17 inhibitors, 49 (60.5%) achieved remission, demonstrating the efficacy of IL-17 pathway inhibition in the management of SpA. However, response rates declined with each successive treatment line; remission was significantly higher in the second-line group (79%) than in the fourth-line group (34.8%; p=0.044), underscoring the advantage of earlier IL-17 use. In contrast, patients with coexisting fibromyalgia showed persistently poor treatment responses, regardless of biologic choice, reinforcing the challenge of distinguishing true inflammatory disease activity from centralised pain sensitisation. This highlights the critical need for precision in treatment decisions, as delayed IL-17 initiation and fibromyalgia both emerged as key factors associated with poor remission outcomes.

The introduction of biologic DMARDs in the treatment of SpA has transformed disease management. For patients unresponsive to NSAIDs and conventional DMARDs, treatment guidelines now include options such as anti-TNF agents, IL-17 inhibitors, IL-23 inhibitors, and Janus kinase (JAK) inhibitors. Despite expanding therapeutic options, treatment-resistant patients continue to present a significant management challenge in our clinical practice. With the development of new treatment options for SpA, there has been growing interest in exploring the causes of treatment resistance and optimising treatment strategies. In this study, we examined the characteristics of SpA patients who received biologic therapies targeting multiple pathways and evaluated changes in their treatment regimens.[8]

In our study, patients who achieved remission with a second-line biologic DMARD had a median disease duration of 6 years, compared to 12 years in those who did not achieve remission. Previous studies have shown that patients with shorter disease durations respond more effectively to anti-TNF therapy. For instance, a study involving 1,281 patients divided into groups receiving etanercept, sulfasalazine, or placebo demonstrated that patients with a disease duration of less than 2 years experienced greater improvement in BASFI scores than those with longer disease durations.[9] These findings emphasise the importance of initiating biologic DMARD therapy promptly, particularly in patients with longer disease durations.

Table 3. Comparison results of patients absence and presence of remission with IL-17 inhibitor therapy			
	Absence of remission (n=32)	**Presence of remission (n=49)**	**p**
Age at las visit, mean ± SD	47.7±12.1	45.9±12.6	0.526
Sex, female, n (%)	14 (43.8)	26 (53.1)	0.413
Disease duration, year, median (IQR)	12.0 (7.0-16.0)	8.5 (4.3-14.8)	0.380
Duration between diagnosis and biologic DMARD, month, median (IQR)	35.0 (9.8-106.5)	38.5 (12.8-83.3)	0.807
BMI (kg/m^2), mean ± SD	28.2±5.7	27.8±6.8	0.825
Diagnosis, n (%)			
Ankylosing spondilitis	22 (68.8)	28 (57.1)	0.293
Nr-axSpA	4 (12.5)	10 (20.4)	0.357
Psoriatic arthritis	6 (18.8)	11 (22.4)	0.689
History of orthopedic surgery, n (%)	4 (12.5)	3 (6.1)	0.318
Fibromyalgia, n (%)	13 (40.6)	9 (18.4)	**0.028**
Exercise, n (%)		13 (26,5)	0.878
Family history of SpA	10 (31.3)	12 (24.5)	0.504
X-ray finding of sakroileitis (right), n (%)			
Normal-grade 2	15 (46.9)	28 (57.1)	0.365
Grade 3-4	17 (53.1)	21 (42.9)	0.365
X-ray finding of sakroiliac joint (left), n (%)			
Normal-grade 2	14 (43.8)	30 (61.2)	0.123
Grade 3-4	18 (56.2)	19 (38.8)	0.123
MRI before biologic treatment, n (%)			
Ankylosis, n (%)	2 (6.3)	1 (2.0)	0.485
Sclerosis, n (%)	7 (21.9)	4 (8.2)	0.200
Bone marrow edema, n (%)	13 (40.6)	14 (28.6)	0.880
Sacroiliitis, n (%)	13 (40.6)	16 (32.7)	0.573
Kyphosis, n (%)	13 (40.6)	11 (22.4)	0.080
Scoliosis, n (%)	5 (15.6)	11 (22.4)	0.451
Syndesmophyte, n (%)	8 (25.0)	5 (10.2)	0.076
HLA-B27, n (%)	23 (71.9)	30 (65.2)	0.535
Enthesitis, n (%)	19 (59.4)	32 (65.3)	0.589
Dactylitis, n (%)	3 (9.4)	12 (24.5)	0.087
Anterior uveitis, n (%)	7 (21.9)	9 (18.4)	0.698
Peripheral arthritis, n (%)	21 (65.6)	31 (63.3)	0.829
Kidney findings, n (%)	3 (9.4)	2 (4.1)	0.333
Aortic regurgitation, n (%)	3 (9.4)	3 (6.1)	0.585
Corticosteroid, n (%)	20 (62.5)	34 (69.4)	0.520
NSAID, n (%)	30 (93.8)	47 (95.9)	0.660
Conventional DMARD, n (%)	28 (87.5)	47 (95.9)	0.157
Sulfasalazin, n (%)	23 (71.9)	40 (81.6)	0.302
Methotrexate, n (%)	22 (68.8)	31 (63.3)	0.612
Leflunomide, n (%)	11 (34.4)	20 (40.8)	0.546
Before first line biologic treatment, median (IQR)	n=32	n=49	
ASDAS-CRP	3.7 (3.1-4.4)	3.8 (3.4-4.3)	1.000
ASDAS-ESR	3.6 (3.1-4.9)	3.9 (3.3-4.3)	0.450
BASDAI	7.9 (5.3-8.3)	6.4 (5.7-6.8)	0.522
Erythrocyte sedimentation rate	27.0 (14.0-41.0)	31.5 (18.0-43.5)	0.766
C-reactive protein	11.0 (7.1-18.7)	15.3 (4.5-27.0)	0.371

Table 3. Continued			
	Absence of remission (n=32)	**Presence of remission (n=49)**	**p**
Before second line biologic treatment, median (IQR)	n=32	n=49	
ASDAS-CRP	3.9 (3.5-4.5)	3.8 (3.2-4.3)	0.929
ASDAS-ESR	3.6 (3.2-4.6)	3.7 (3.1-4.3)	0.737
BASDAI	7.0 (6.6-8.2)	6.0 (5.5-6.4)	**<0.001**
Erythrocyte sedimentation rate	22.0 (10.0-37.0)	29.0 (12.0-52.0)	0.306
C-reactive protein	8.1 (3.0-18.2)	10.1 (3.5-20.8)	0.424
Before third line biologic treatment, median (IQR)	n=32	n=30	
ASDAS-CRP	3.8 (3.2-4.9)	3.9 (3.4-4.2)	1.000
ASDAS-ESR	3.7 (2.9-4.8)	3.9 (3.5-4.1)	0.722
BASDAI	6.2 (5.4-7.0)	6.2 (5.9-7.0)	0.874
Erythrocyte sedimentation rate	24.0 (12.8-33.5)	30.0 (14.0-40.0)	0.480
C-reactive protein	12.0 (3.0-27.0)	9.1 (2.7-20.8)	0.478

ASDAS-CRP: Ankylosing spondylitis disease activity score-C-reactive protein, ASDAS-ESR: Ankylosing spondylitis disease activity score-erythrocyte sedimentation rate, BASDAI: Bath ankylosing spondylitis disease activity index, BMI: Body mass index, CRP: C-reactive protein, DMARDs: Disease-modifying anti-rheumatic drugs, HLA-B27: Human leukocyte antigen-B27, IQR: Interquartile range, MRI: Magnetic resonance imaging, nr-axSpA: Non-radiographic axial spondyloarthritis, NSAIDs: Non-steroidal anti-inflammatory drugs, SD: Standard deviation

Table 4. Distribution of biologic DMARDs in patients with absence and presence of remission with IL-17 inhibitor therapy			
	Absence of remission (n=32)	**Presence of remission (n=49)**	**p**
1st DMARD			
Adalimumab	11 (34.4)	27 (55.1)	0.068
Infliximab	5 (15.6)	8 (16.3)	0.933
Etanercept	7 (21.9)	4 (8.2)	0.078
Certolizumab	3 (9.4)	6 (12.2)	0.688
Golimumab	1 (3.1)	4 (8.2)	0.357
Secukinumab	5 (15.6)	0 (0)	**0.004**
2nd DMARD			
Adalimumab	8 (25.0)	4 (8.2)	**0.037**
Etanercept	8 (25.0)	16 (32.7)	0.461
Secukinumab	5 (15.6)	17 (34.1)	0.059
Certolizumab	5 (15.6)	3 (6.1)	0.161
Golimumab	2 (6.3)	3 (6.1)	0.981
Infliximab	3 (9.4)	3 (6.1)	0.585
Ustekinumab	1(3.1)	1 (2.0)	0.759
Ixekizumab	0 (0)	2 (4.1)	0.247
3rd DMARD	n=32	n=30	
Secukinumab	7 (24.1)	13 (43.3)	0.119
Adalimumab	7 (24.1)	5 (16.7)	0.476
Ustekinumab	10 (21.7)	2 (9.5)	0.226
Etanercept	5 (17.2)	2 (6.7)	0.209
Certolizumab	3 (10.3)	2 (6.7)	0.612
Golimumab	1 (3.4)	0 (0)	-
Infliximab	1 (3.4)	3 (10.0)	0.317
Ustekinumab	4 (13.8)	5 (16.7)	0.759
Ixekizumab	1 (3.4)	0 (0)	-

DMARD: Disease modifying anti-rheumatic drug, IL: Interleukin

In a study evaluating patients with axSpA, secukinumab was used as a first-line therapy in 8% of cases, as a second-line therapy in 15% of cases, and as a third-line or later therapy in 77% of cases.[10] Similarly, in a study involving patients with psoriatic arthritis, secukinumab was used as first-, second-, third-, and fourth-line or beyond treatments in 15%, 17%, 21%, and 47% of patients, respectively.[11] Our findings align with these data, showing that among 81 patients treated with IL-17 inhibitors, 6% used them as first-line therapy, 30% as second-line, 25% as third-line, and 39% as fourth-line or beyond. This dataset shows similar treatment patterns and physician preferences in the management of SpA patients globally.

In addition to individual treatment responses, class-to-class transitions provided further insight into therapeutic sequencing (Table 5). Most patients underwent at least one switch between biologic classes during follow-up, reflecting the complexity of managing treatment-resistant disease. The predominance of transitions from TNFi to IL-17 inhibitors highlights a common pathway of escalation in patients with inadequate TNFi response, whereas reverse transitions and transitions to IL-12/23 inhibitors were less frequent. These patterns underscore the clinical relevance of sequencing decisions and emphasise the need to define optimal transition strategies for refractory SpA more precisely.

When comparing patients who achieved remission with IL-17 inhibitors to patients who did not, we found that fibromyalgia was present in 18.4% of patients in remission, compared with 40.6% of patients not in remission. A meta-analysis revealed that approximately one in six patients with axSpA has fibromyalgia.[12] Similarly, another study reported that 11-34% of SpA patients had coexisting fibromyalgia.[8] In our study, fibromyalgia was present in 25.6% of the included patients. Fibromyalgia is frequently observed in patients with SpA and can complicate the assessment of disease activity and treatment response. Symptoms of fibromyalgia may overlap with those of inflammation, potentially leading to the misclassification of patients as treatment-resistant and to premature, unnecessary changes in therapy.[8,12]

A study of 196 patients demonstrated that fibromyalgia in patients with SpA could impact disease activity and anti-TNF treatment retention rates.[13] In this study, patients with fibromyalgia had higher BASDAI scores than patients without fibromyalgia. Additionally, the average duration of the first anti-TNF therapy was 1.7±2.4 years in patients with fibromyalgia, compared with 3.5±4.0 years in those without the condition. Patients with fibromyalgia were also significantly affected. The study concluded that fibromyalgia is associated with higher disease activity scores, poorer functional indices, shorter treatment retention, and more frequent therapy changes.[13] These findings emphasise the challenge of distinguishing true inflammatory burden from fibromyalgia-driven symptom amplification potentially leading to misguided treatment decisions. Because patients with fibromyalgia tend to have lower response rates to biologic therapies, clinicians must carefully assess whether persistent symptoms stem from active SpA or from centralised pain sensitisation, to avoid unnecessary escalation of therapy.

Our findings and existing literature underscore the importance of assessing fibromyalgia in SpA patients who are candidates for biologic DMARDs, particularly before initiating therapy changes. Addressing fibromyalgia in these patients may improve overall outcomes; however, attributing all symptoms to fibromyalgia and focusing solely on its treatment may delay appropriate care and allow the underlying inflammatory disease to progress. Larger studies are needed to better understand how to manage treatment plans in SpA patients with coexisting fibromyalgia.

A study evaluating treatment retention rates for secukinumab and anti-TNF therapies in SpA patients found that secukinumab retention rates at one year were comparable to those of adalimumab when used as a first- or second-line biologic DMARD, but were significantly lower for secukinumab when used as a third-line or later therapy.[14] Another study showed that biologic therapies used as third-line or later treatments were associated with a higher risk of discontinuation compared to those used as second-line therapies.[15]

In our study, 79% of patients using IL-17 inhibitors in the second line achieved remission, compared to 65% in the third line and 53% in the fourth line or beyond (Supplementary Graph 1). Response rates to IL-17 inhibitors were significantly

Table 5. Class-to-class transitions between biologic treatment pathways in spondyloarthritis patients

From → to*	TNFi	IL-17i	IL-12-23i	Other
TNFi	-	65	24	1
IL-17i	28	-	1	0
IL-12/23i	8	11	-	0
Other	1	0	0	-

*: Transitions represent the number of patients who switched from one biologic class to another at any point during follow-up. IL: Interleukin, TNFi: Tumour necrosis factor inhibitor

higher in the second-line group than in the fourth-line and later groups. However, even in later lines of therapy, more than 50% of patients achieved remission with IL-17 inhibitors, suggesting they remain a viable option in advanced treatment stages. These findings highlight the importance of early use of IL-17 inhibitors; however, even in late stages, IL-17 inhibitors show promising results, according to these data.

Study Limitations

Our study has several limitations. The small sample size, single-centre design, absence of a control group, limited number of JAK inhibitor-treated patients, and retrospective data collection are significant constraints. Additionally, the lack of data on initial dosages and subsequent dose adjustments for biologic DMARDs is another limitation.

The concept of patients resistant to multiple biological pathways, which has emerged with the growing number of biological treatment options for SpA, is relatively new. Future studies are needed to define this concept and investigate clinical and pathogenetic predispositions.

Conclusion

As disease duration increases, treatment response declines, reinforcing the importance of starting biologic DMARD therapy as early as possible. However, significant uncertainties persist regarding treatment-resistant patients. The exact mechanisms underlying their lack of response to biologic DMARDs are not yet fully understood, with potential contributors including genetic factors, immune system dysregulation, and central sensitisation. A deeper understanding of these mechanisms is crucial for developing more targeted and effective treatment strategies for patients with refractory conditions.

Prospective studies with larger patient cohorts and control groups of SpA patients who achieve remission with a single biologic pathway are needed to optimise treatment changes and to better understand the reasons for treatment resistance in these patients.

Ethics

Ethics Committee Approval: This study, titled "Clinical characteristics of treatment-resistant SpA patients treated with multiple biologic pathways", was approved by the Clinical Research Ethics Committee of Gazi University on December 5, 2022, with decision number 883.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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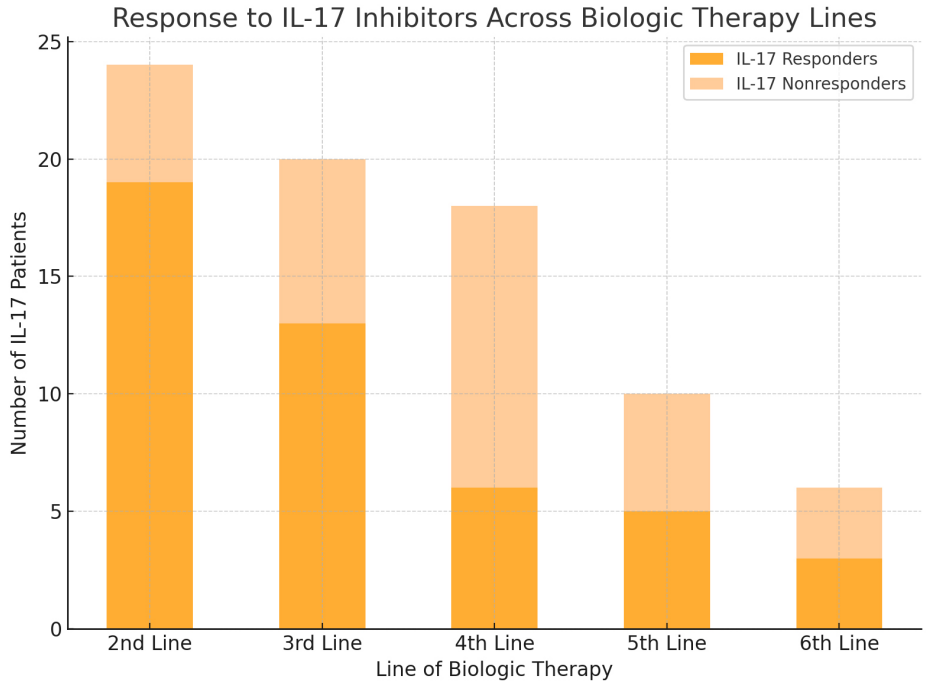

Supplementary Graph 1. Response to IL-17 inhibitors across biologic therapy lines
IL: Interleukin