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Immunological endotypes in IgG4-RD: An endotype-guided therapeutic framework

IgG4-RD'de immünolojik endotipler: Endotip-rehberli tedavi çerçevesi

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Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a systemic fibroinflammatory disorder characterized by tumefactive organ involvement, lymphoplasmacytic infiltration enriched with IgG4-positive plasma cells, storiform fibrosis, and a relapsing-remitting clinical course. Although glucocorticoids remain the cornerstone of induction therapy, relapse rates following dose tapering or discontinuation remain high, and long-term steroid exposure is associated with substantial morbidity. Increasing translational evidence suggests that IgG4-RD is not a uniform disease entity but rather a spectrum of immunologically distinct endotypes driven by heterogeneous dominant immune axes. These include a type 2 inflammatory axis [interleukin-4 (IL-4)/IL-13-dominant], B-cell and plasmablast expansion, T follicular helper cell activation, cytotoxic CD4+T-cell responses, complement-associated mechanisms, and profibrotic macrophage signaling. Recognition of these immune endotypes provides a mechanistic framework for phenotype-driven therapy. B-cell-targeted therapies (rituximab and the newly United States Food and Drug Administration-approved anti-CD19 agent inebilizumab) have demonstrated efficacy in relapsing disease, whereas IL-4/IL-13 blockade may represent a rational strategy in selected Th2-skewed patients. Emerging approaches targeting B-cell activating factor signaling, Bruton's tyrosine kinase pathways, and fibrotic mechanisms further support a shift toward precision immunotherapy. This review synthesizes current evidence on immunological endotypes in IgG4-RD and proposes a conceptual framework linking immune signatures to rational therapeutic strategies. An endotype-guided management paradigm may reduce cumulative steroid exposure and prevent relapses in this heterogeneous disease spectrum.

Keywords: IgG4-related disease, immunological endotypes, clinical phenotypes, B-cell therapy, inebilizumab, therapeutic stratification

Özet

İmmünoglobulin G4-ilişkili hastalık (IgG4-RD), tümefaktif organ tutulumu, IgG4-pozitif plazma hücrelerle zengin lenfoplazmasitik infiltrasyon, storiform fibrozis ve relapsing-remitting seyir ile karakterize sistemik fibroenflamatuvar bir hastalıktır. Glukokortikoidler indüksiyon tedavisinin temel taşı olmakla birlikte, doz azaltılması sonrasında relaps oranları yüksek kalmakta ve uzun süreli steroid maruziyeti önemli morbiditeye neden olmaktadır. Artan kanıtlar, IgG4-RD'nin tek tip bir hastalık olmaktan ziyade, heterojen immün yolaklar tarafından yönlendirilen immunolojik olarak farklı endotipler spektrumu olduğunu göstermektedir. Bunlar tip 2 enflamatuvar aksı [interlökin-4 (IL-4)/IL-13-dominant], B-hücre ve plazmablast ekspansiyonu, T foliküler yardımcı hücre aktivasyonu, sitotoksik CD4+T-hücre yanıtları, kompleman-ilişkili mekanizmalar ve profibrotik makrofaj sinyallemesini içermektedir. Bu immün endotipler tanınması, fenotip-yönelimli terapi için mekanik bir çerçeve sağlamaktadır. B-hücre-hedefli terapiler (rituksimab ve yeni Amerikan Gıda ve İlaç Dairesi-onaylı inebilizumab) nükseden hastalıkta etkinlik göstermiş, oysa IL-4/IL-13 blokajı seçilmiş Th2-eğilimli hastalarda rasyonel bir strateji olabilmektedir. B-hücre aktive edici faktör sinyallemesi, Bruton tirozin kinaz yolakları ve fibrotik mekanizmaları hedef alan yaklaşımlar, hassas immünoterapiye doğru bir kayışı desteklemektedir. Bu derleme, IgG4-RD'deki immünolojik endotipler hakkında mevcut kanıtları sistematikleştirmekte ve immün imzaları terapötik stratejilere bağlayan kavramsal bir çerçeve sunmaktadır. Endotip-rehberli yönetim paradigması, bu heterojen hastalık spektrumunda kümülatif steroid maruziyetini azaltabilir ve nüks riskini düşürebilir.

Anahtar Kelimeler: IgG4-ilişkili hastalık, immünolojik endotipler, klinik fenotipler, B-hücre terapisi, inebilizumab, terapötik stratifikasyon

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a chronic, immune-mediated fibroinflammatory disorder capable of affecting nearly any organ system.[1,2] First recognized in the context of autoimmune pancreatitis, it is now understood to represent a systemic condition characterized by tumor-like swelling of affected organs, elevated serum IgG4 levels in many patients, and a distinctive histopathologic pattern including dense lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis.[3,4] The 2019 American College of Rheumatology/European Alliance of Associations for

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Rheumatology classification criteria have improved diagnostic consistency; however, they do not fully capture the biological heterogeneity underlying disease expression.[5]

Clinical variability in IgG4-RD is striking. Some patients exhibit predominantly glandular disease frequently associated with allergic features and elevated IgE levels, whereas others develop progressive fibrotic manifestations such as retroperitoneal fibrosis or large-vessel involvement, often with minimal systemic inflammatory markers.[6,7] Relapse occurs in approximately 30-50% of patients following glucocorticoid tapering, and response durability varies considerably between individuals.[8]

These observations suggest that IgG4-RD represents a spectrum of immune activation states rather than a single linear inflammatory pathway. The concept of "endotype"—defined as a subtype characterized by a distinct pathobiological mechanism—provides a mechanistically grounded framework for understanding such heterogeneity.[9] Applying immunological endotyping to IgG4-RD may refine disease stratification, improve relapse prediction, and align therapeutic strategies with dominant immune axes.

1. Immunopathogenesis of IgG4-RD: A Network Disorder

IgG4-RD is increasingly recognized as a coordinated immune network disorder rather than a single-axis inflammatory condition. Multiple interacting immune axes—including B-cell expansion, T-cell polarization, germinal center dynamics, cytotoxic effector responses, and macrophage-driven fibrosis—converge to produce a shared histopathologic phenotype. The relative dominance of these pathways may vary across patients and over time, contributing to clinical heterogeneity.

1.1. The B-cell and Plasmablast Axis

One of the most reproducible immunological findings in IgG4-RD is the expansion of circulating plasmablasts (CD19+CD20-CD27+CD38+), which demonstrate oligoclonal B-cell receptor repertoires and correlate strongly with disease activity.[4,5,10] Importantly, plasmablast levels frequently rise prior to clinical relapse, suggesting a dynamic role in disease propagation and potential utility as a predictive biomarker.[4,5]

Elevated levels of B-cell activating factor (BAFF) have been reported in many patients and may support B-cell survival, differentiation, and persistence of autoreactive clones.[11] The therapeutic efficacy of rituximab underscores the centrality of B-cells in disease pathogenesis.[8] However, because plasmablasts lack CD20 expression, incomplete depletion of the broader B-cell lineage may allow residual pathogenic clones to persist or re-emerge during B-cell repopulation, potentially explaining relapse patterns observed after therapy.[8,9]

Rather than representing an isolated B-cell disorder, this axis appears to be tightly coupled to T follicular helper (Tfh)-dependent germinal center activity.

1.2. The Type 2 Inflammatory Axis

IgG4 class-switch recombination is strongly influenced by interleukin-4 (IL-4) and IL-10, cytokines characteristic of type 2 immune polarization.[12,13] A substantial proportion of patients exhibit elevated serum IgE levels and peripheral eosinophilia, and allergic comorbidities such as asthma or chronic rhinosinusitis are reported in up to one-third of cases.[6]

Tfh type 2 (Tfh2) cells produce IL-4 and promote germinal center reactions, facilitating IgG4 production.[12,13] IL-13, closely related to IL-4, has been implicated in glandular inflammation and fibrotic remodeling.[13] While T helper type 2 (Th2) skewing is prominent in many patients, it does not fully account for all clinical phenotypes, indicating that additional dominant immune axes operate in parallel.

1.3. Tfh-cells and Tertiary Lymphoid Structures

Affected tissues frequently demonstrate tertiary lymphoid structures, reflecting *in situ* germinal center formation and sustained local antigen-driven immune activation.[12,13] IL-4+basic leucine zipper activating transcription factor-like transcription factor+Tfh cells have been directly linked to IgG4 class-switch recombination *in vivo*.[13] These findings reinforce the importance of T-cell-B-cell interactions in disease propagation.

Such compartmentalized immune activation may explain why systemic inflammatory markers are sometimes modest despite active tissue disease.

1.4. Cytotoxic CD4+T-cells

Recent immunophenotyping studies have identified an expanded population of signaling lymphocyte activation molecular family 7+CD4+cytotoxic T lymphocytes enriched in IgG4-RD.[14,15] These cells express granzyme B and perforin and are present within affected tissues.[14,15] Their presence challenges the notion that IgG4-RD is exclusively a Th2-dominant condition.

CD4+cytotoxic T-cells (CTLs) may directly mediate tissue injury and contribute to fibroinflammatory remodeling, potentially linking immune activation to structural damage.[15]

1.5. The Profibrotic Macrophage-transforming Growth Factor-β (TGF-β) Axis

Fibrosis is a defining feature of IgG4-RD. M2-polarized macrophages are abundant in affected tissues and produce TGF-β, a central mediator of extracellular matrix deposition and fibroblast activation.[16,17] IL-13 may further amplify profibrotic signaling.[13]

As inflammation transitions toward structural remodeling, the reversibility of disease may diminish. This inflammation-to-fibrosis continuum underscores the importance of early immune modulation.

1.6. Complement-associated Mechanisms

A subset of patients demonstrates hypocomplementemia, particularly in the context of renal involvement such as tubulointerstitial nephritis.[18] While IgG4 itself poorly activates complement, co-dominance of other IgG subclasses—particularly IgG1—may contribute to immune complex-mediated injury in selected cases.[18]

2. Dominant Immune Axis-defined Endotypes in IgG4-RD

The immunological heterogeneity described above does not occur randomly; rather, dominant immune axes appear to cluster into biologically coherent patterns. These patterns—defined by shared cytokine profiles, cellular drivers, biomarker signatures, and clinical correlates—can be conceptualized as immunological endotypes. Although overlap exists, identifying the prevailing immune axis in an individual patient may provide mechanistic clarity and therapeutic direction. The concept of "endotype," originally developed in asthma research to describe biologically defined disease subtypes, provides a useful framework for this stratification approach.[19]

2.1. Type 2/Th2-dominant Endotype

This endotype reflects a dominant type 2 immune axis characterized by IL-4/IL-13 signaling, elevated serum IgE, peripheral eosinophilia, and expansion of Tfh2 cells.[12,13,20]

Clinically, patients often present with head and neck involvement, including lacrimal and salivary gland enlargement, and frequently exhibit allergic comorbidities.[6] Enhanced IgE responses and Th2 activation have been consistently documented in this subgroup.[20] Mechanistically, this group represents a coherent immunobiological cluster in which type 2 cytokine signaling drives both IgG4 production and local tissue inflammation. While glucocorticoids remain effective for induction, relapse propensity may persist if the dominant Th2 axis is not selectively addressed.

2.2. Plasmablast-high/B-cell-driven Endotype

This endotype reflects a dominant B-cell/plasmablast axis, characterized by elevated circulating CD19+CD20- plasmablasts, oligoclonal B-cell expansion, and increased serum IgG4 levels.[4,5,10]

Clinically, these patients often demonstrate multiorgan involvement and a higher frequency of relapse.[6] Plasmablast levels frequently rise before clinical flare, reinforcing their role as both effector cells and biomarkers.[4,5]

This endotype provides the strongest mechanistic rationale for B-cell-targeted therapy. Rituximab has demonstrated substantial efficacy in relapsing and multiorgan disease.[8,9] However, incomplete depletion of CD20-negative plasmablasts may permit relapse during B-cell repopulation.[9] The centrality of B-cell-Tfh interaction in IgG4-RD has been emphasized in comprehensive immunologic reviews.[21,22]

2.3. Tfh-dominant Germinal Center Endotype

This endotype reflects a dominant Tfh-driven germinal center axis, characterized by expansion of Tfh-cells and formation of tertiary lymphoid structures that sustain local immune activation.[12,13]

The presence of tertiary lymphoid structures in affected organs supports the concept of compartmentalized immune activation.[21] Patients frequently present with glandular enlargement and dense local infiltration of IgG4-positive plasma cells.

From a therapeutic perspective, interventions targeting Tfh-driven pathways—such as IL-4 blockade or costimulatory inhibition—may be mechanistically justified; however, prospective validation remains limited.

2.4. CTL-associated Endotype

This endotype reflects a dominant CTL axis, characterized by expansion of CD4+ cytotoxic T lymphocytes capable of mediating direct tissue injury and contributing to fibroinflammatory remodeling.[14,15,23]

Clinically, this endotype may correlate with progressive fibrosis and more aggressive structural damage. The identification of expanded circulating cytotoxic CD4+T-cells further supports a distinct immunopathogenic axis beyond Th2 polarization.[23]

Currently, no established targeted therapy specifically addresses this cytotoxic pathway, highlighting an unmet therapeutic need.

2.5. Fibrotic-dominant Endotype

This endotype reflects a dominant fibrotic (TGF-β-driven) immune axis associated with macrophage activation and progressive extracellular matrix deposition.[16,17,22]

Clinically, retroperitoneal fibrosis, periaortitis, and late-stage organ remodeling predominate. Inflammatory markers may be low, reflecting the transition from immune activation to structural remodeling. The interplay between immune activation and fibrosis has been emphasized in recent immunopathogenic models.[22]

Early intervention appears critical, as established fibrosis may only partially respond to immunosuppression.

2.6. Hypocomplementemic/Immune Complex Endotype

This endotype reflects a complement-mediated immune axis, characterized by reduced complement levels, particularly in the context of renal involvement such as tubulointerstitial nephritis.[18,24]

This endotype reflects a complement-mediated immune axis, characterized by reduced complement levels, particularly in the context of renal involvement such as tubulointerstitial nephritis.[12] Consistent with the complement-associated mechanisms described above, hypocomplementemia may identify a subgroup of patients in whom immune complex-mediated pathways contribute more prominently to tissue injury. These findings support the mechanistic diversity within IgG4-RD and suggest that complement-associated pathways may be relevant in selected clinical phenotypes.

Integrative Perspective

Taken together, these findings provide an integrative perspective on the proposed endotypes. Importantly, these endotypes should not be considered mutually exclusive or static categories. Rather, they represent overlapping and potentially dynamic immune states that may coexist within individual patients and evolve over the disease course.

Importantly, these endotypes are not mutually exclusive and may evolve over time. A patient may initially exhibit a Th2-dominant inflammatory phenotype and later transition toward fibrotic predominance. Similarly, relapse following B-cell depletion may reflect persistence or emergence of non-B-cell-driven immune axes.

Understanding the relative dominance of these immune axes provides the conceptual basis for immunophenotype-guided management in IgG4-RD. In this context, endotypes should be viewed as dynamic immune dominance states rather than fixed diagnostic categories (Table 1). Building upon these immunological endotypes, a proposed endotype-guided management algorithm integrating immune profiling, endotype identification, therapeutic selection, and longitudinal reassessment is presented in Figure 1.

2.7. Clinical Phenotypes and Their Immunological Basis

Recent work emphasizes that IgG4-RD can also be classified into four distinct clinical phenotypes based on organ distribution, with each phenotype showing different dominant immune cell subsets:[25]

Group 1 (retroperitoneal fibrosis/aortitis): Often associated with a more aggressive, fibrotic course and linked to the CTL

Table 1. IgG4-RD immunological endotypes, clinical phenotypes, and therapeutic implications immunological

Endotype	Dominant immune axis	Key biomarkers	Associated clinical phenotype	Rational targeted therapy	Evidence level
Plasmablast-high/B-cell-driven	Plasmablasts, B-cells, Tfh	High circulating plasmablasts, oligoclonal B-cells, high serum IgG4	Multi-organ involvement, high relapse risk, Mikulicz disease with systemic features	Anti-CD19 (Inebilizumab), anti-CD20 (rituximab), BTK inhibitors	High (FDA-approved inebilizumab)
Type 2/allergic/ Th2-dominant	Tfh2, Th2 cells, IL-4, IL-13	High serum IgE, eosinophilia, allergic comorbidities	Head & neck involvement (Mikulicz), glandular enlargement, allergic features	IL-4/IL-13 blockade (dupilumab), glucocorticoids	Moderate (case series)
CTL-associated	CD4+CTLs, CX3CR1+ CTLs	SLAMF7+ CTLs, Granzyme B, Perforin	Retroperitoneal fibrosis, aortitis, aggressive fibrosis, large vessel involvement	Unmet need (investigational agents)	Low (emerging data)
Tfh-dominant germinal center	IL-4+Tfh cells, tertiary lymphoid structures	Elevated Tfh cells, local germinal centers	Glandular enlargement, dense local IgG4+ infiltrate	IL-4 blockade, costimulatory inhibition	Moderate (limited prospective data)
Fibrotic-dominant	M2 macrophages, TGF-β, IL-13	Low inflammatory markers, advanced fibrosis on imaging	Late-stage disease, retroperitoneal fibrosis, organ remodeling	Antifibrotic agents (investigational), early immunomodulation	Moderate (mechanistic rationale)
Hypocomplementemic/ immune comple	Immune complexes (IgG1), complement activation	Low C3/C4, IgG1 antibodies	Renal disease, tubulointerstitial nephritis	Broader immunosuppression, complement pathway inhibition	Low (selected cases)

BTK: Bruton's tyrosine kinase, CTL: Cytotoxic T-cell, FDA: United States Food and Drug Administration, Ig: Immunoglobulin, IL-4: Interleukin-4, SLAMF7: Signaling lymphocyte activation molecular family 7, TGF-β: Transforming growth factor-β, Tfh2: T follicular helper type 2, Th2: T helper type 2

endotype (CX3CR1+CTLs). This phenotype typically shows lower inflammatory markers but exhibits significant structural damage, particularly in large vessels and retroperitoneal tissues.

Group 2 (Mikulicz's disease & systemic involvement): Characterized by lacrimal and salivary gland swelling and frequently aligns with the type 2/Tfh2-dominant endotype. These patients often have elevated IgE and eosinophilia, with a more favorable prognosis when treated appropriately.

Group 3 (pancreato-hepato-biliary disease): A common presentation that can show features of multiple endotypes, often with a mix of inflammatory and fibrotic components affecting the pancreas, bile ducts, and liver.

Group 4 (head & neck-limited disease): Often shows prominent allergic features, consistent with the type 2 endotype, with predominantly glandular involvement and a generally favorable prognosis.

Furthermore, phenotypes associated with malignancy or allergy show distinct immunopathology. The malignancy phenotype is characterized by an increase in CXCR5+CD2- double negative T-cells compared to the allergy phenotype, along with a decrease in naive CD8+T-cells, highlighting the disease's immunological complexity.[25]

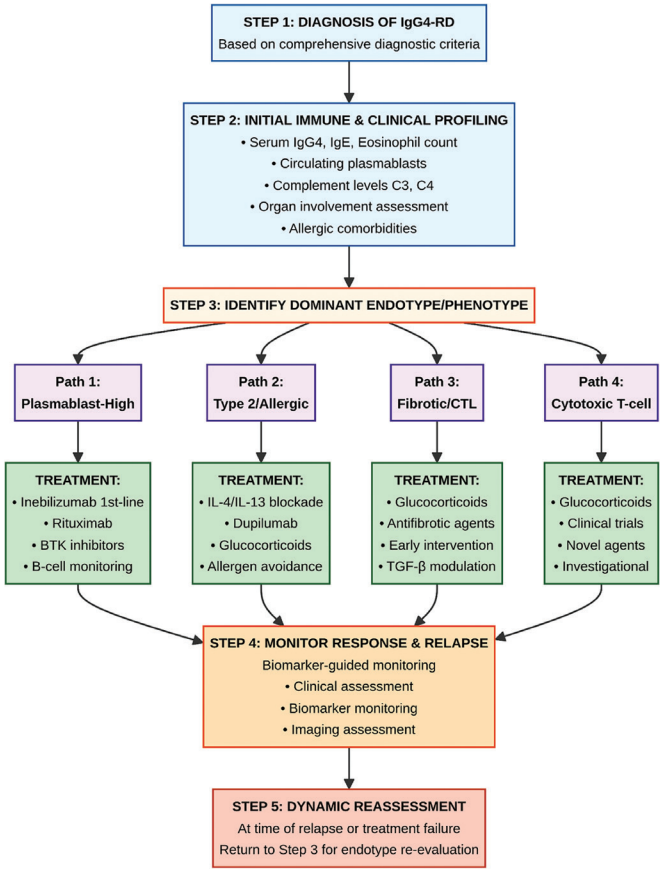

Figure 1. Proposed endotype-guided management algorithm for IgG4-RD
BTK: Bruton's tyrosine kinase, CTL: Cytotoxic T-cell, IgG4-RD: Immunoglobulin G4-related disease, IL-4: Interleukin-4, TGF: Transforming growth factor-β

3. Linking Endotypes to Treatment Strategies

The identification of immunological endotypes in IgG4-RD provides an opportunity to align therapeutic selection with dominant immune axes. While most current treatments were not originally developed within an endotype-stratified framework, accumulating clinical experience suggests that response heterogeneity may reflect underlying immune dominance patterns.[22,26,27] A simplified biomarker-to-endotype-to-therapy decision framework is presented in Figure 2.

3.1. Glucocorticoids: Broad Suppression without Endotype Specificity

Glucocorticoids remain the universal induction therapy across phenotypes.[6,21] Their pleiotropic immunosuppressive effects attenuate cytokine production, B-cell activation, and inflammatory cell trafficking. However, this broad suppression does not discriminate between mechanistic endotypes and may transiently obscure underlying immune heterogeneity.

Although effective for initial disease control, glucocorticoids do not selectively modify dominant immune axes. Consequently, relapse following tapering may reflect persistence of the primary pathogenic axis rather than inadequate dosing.[6] From an endotype perspective, glucocorticoids serve as a non-specific reset rather than a targeted intervention.

3.2. B-cell-targeted Therapy in Plasmablast-driven Endotypes

Among available therapies, B-cell-directed strategies most clearly align with a defined immunological endotype. Rituximab has demonstrated high response rates in relapsing and multiorgan disease, particularly in patients with elevated plasmablast levels.[8,9,28] Clinical improvement frequently parallels reduction in circulating plasmablasts.[4,5,10]

However, CD20-targeted depletion does not directly eliminate CD20-negative plasmablasts,[5] which may partially explain relapse during B-cell repopulation.[9] Anti-CD19 agents, such as inebilizumab, extend depletion across a broader B-cell lineage spectrum, including plasmablast populations, and may provide deeper and more sustained remission in B-cell-dominant disease.[29] The United States Food and Drug Administration (FDA) approval of inebilizumab (UPLIZNA®) in April 2025 represents a significant milestone, as it is the first CD19-targeted therapy specifically approved for IgG4-RD. The pivotal MITIGATE Phase 3 trial demonstrated that inebilizumab significantly reduced the risk of disease flares and increased the likelihood of remission, establishing it as an effective steroid-sparing option.[29]

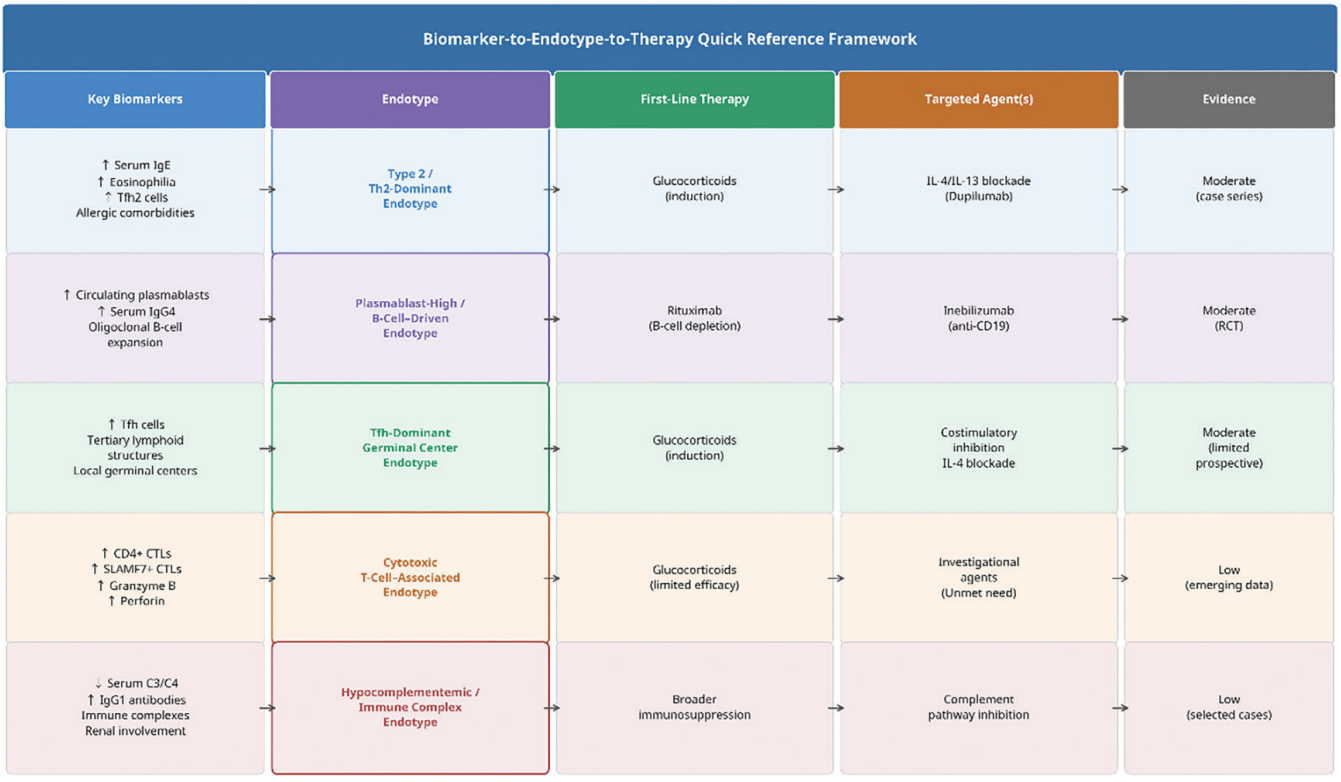

Figure 2. Biomarker-to-endotype-to-therapy quick reference framework
CTL: Cytotoxic T-cell, Ig: Immunoglobulin, IL-4: Interleukin-4, RCT: Randomised controlled trial, SLAMF7: Signaling lymphocyte activation molecular family 7, Tfh: T follicular helper

In plasmablast-high endotypes, maintenance strategies guided by peripheral B-cell monitoring represent a biologically coherent approach. Re-treatment triggered by B-cell repopulation rather than fixed intervals may reduce overtreatment while limiting relapse risk.[9,30]

In addition, therapeutic approaches targeting B-cell receptor signaling, including Bruton's tyrosine kinase (BTK) inhibitors, as well as modulation of BAFF-mediated survival pathways, further support refinement of B-cell-axis targeting in selected phenotypes.[26,31]

3.3. Targeting the Type 2 Axis in Th2-dominant Disease

In patients exhibiting a Th2-skewed immune profile—characterized by elevated IgE, eosinophilia, and Tfh2 expansion[12,20]—targeting IL-4 and IL-13 signaling represents a mechanistically rational strategy. Dupilumab, an IL-4Rα antagonist, blocks both IL-4 and IL-13 pathways and has demonstrated steroid-sparing potential in small case series and observational reports.[20,32]

Although prospective controlled trials are limited, the biological plausibility of type 2 axis inhibition in selected patients is compelling. Endotype-driven selection may prove critical, as type 2 blockade is unlikely to benefit patients whose disease is primarily B-cell-dominant or fibrotic.[22]

3.4. Addressing Cytotoxic and Fibrotic Pathways: Emerging Directions

Therapeutic targeting of cytotoxic CD4+T-cell-associated endotypes.[14,15,23] or fibrotic-dominant disease characterized by TGF-β-mediated remodeling[16,17,22] remains an unmet need. Agents modulating B-cell receptor signaling (BTK inhibitors),[31] BAFF-mediated survival pathways,[26] and costimulatory interactions may expand the therapeutic landscape. BTK inhibitors such as rilzabrutinib and zanubrutinib are currently in clinical development, with rilzabrutinib receiving orphan drug designation in August 2025, highlighting the promise of this therapeutic class.[33]

Additionally, interventions aimed at interrupting TGF-β-driven fibrotic remodeling warrant further investigation.[29]

Importantly, precision therapy in IgG4-RD requires prospective validation in endotype-stratified clinical trials.[27] Without immunophenotypic selection, therapeutic signals may be diluted by biological heterogeneity.

Mechanistic alignment between the dominant immune axis

and the therapeutic target represents the central premise of precision management in IgG4-RD.

4. Precision Medicine Framework

4.1. Relapse-oriented Management and Dynamic Endotype Reassessment

Relapse represents a central challenge in IgG4-RD, occurring in approximately 30-50% of patients following glucocorticoid tapering.[6] Importantly, relapse is not merely a clinical event but often reflects reactivation of dominant immune axes. In B-cell-driven disease, rising plasmablast levels and peripheral B-cell repopulation frequently precede clinical flare,[4,5,9] supporting a biologically measurable preclinical phase of disease reactivation.

Longitudinal immune profiling studies have further demonstrated that dynamic changes in circulating immune subsets may anticipate relapse and reflect shifting immune dominance states.[27,34]

In plasmablast-dominant endotypes, maintenance strategies guided by B-cell kinetics may represent a mechanistically aligned approach. Re-dosing rituximab when peripheral CD19+B-cells exceed predefined thresholds (e.g., >10 cells/μL) has been associated with lower relapse rates compared with fixed-interval retreatment.[9,28,30,35] Such biomarker-guided maintenance shifts management from empiric scheduling toward immune-informed timing and may reduce cumulative immunosuppressive exposure.

Equally important is the recognition that immune dominance may evolve over time. Patients who relapse despite adequate B-cell depletion may no longer exhibit a primarily B-cell-driven phenotype. Instead, CTL-associated pathways[14,23] or fibrotic-dominant remodeling circuits driven by TGF-β signaling[16,17,22] may emerge. These observations support the concept that endotypes represent dynamic immune states rather than static classifications.[27,34]

In this context, reassessment of the prevailing immune endotype is essential, as therapeutic strategies effective in one phase of disease may not remain optimal in another. Thus, precision management in IgG4-RD requires not only baseline endotype identification but also longitudinal immune profiling to capture dynamic shifts in pathobiology and guide adaptive therapeutic sequencing.[26,27,35]

5. Toward Precision Medicine in IgG4-RD

Translating immunological endotyping into clinical practice requires a structured yet flexible framework. While comprehensive immune profiling may not be universally available, a pragmatic approach can be implemented using accessible clinical and laboratory parameters aligned with dominant immune axes.[26,27,36-39]

A practical endotype-guided strategy may incorporate the following elements:

1. Assessment of organ threat: Initial evaluation should distinguish urgent, organ-threatening manifestations (e.g., vascular involvement, obstructive disease, renal dysfunction) from non-urgent inflammatory phenotypes.[21,24] This step determines the immediacy of intervention but does not substitute for immunological stratification.

2. Measurement of immune biomarkers: Whenever feasible, quantification of circulating plasmablasts, serum IgG4, IgE levels, peripheral eosinophil counts, and complement levels may provide insight into dominant immune axes. Elevated plasmablasts may suggest B-cell-driven disease,[4,5,10] whereas high IgE and eosinophilia may indicate a Th2-skewed phenotype.[12,20] Hypocomplementemia may point toward immune complex-associated mechanisms.[18] Integration of biomarker-driven monitoring into routine care is increasingly advocated in precision-oriented models.[34,37,39]

3. Evaluation of allergic comorbidity and fibrotic burden: The presence of allergic disease supports type 2 immune dominance,[20] whereas imaging evidence of advanced fibrosis may indicate a transition toward structural remodeling mediated by TGF-β-driven pathways.[16,17,22] The timing of immunomodulation relative to fibrotic progression may critically influence reversibility.[40] Recognizing this inflammatory-fibrotic continuum is essential for therapeutic alignment.

4. Selection of therapy aligned with the dominant immune axis: Rather than applying uniform treatment strategies, therapy selection may be informed by prevailing dominant immune axes, with B-cell-targeted approaches in plasmablast-high disease,[8,9,28] type 2 pathway inhibition in Th2-dominant phenotypes,[20,32] or investigational strategies in cytotoxic or fibrotic-dominant states.[14,23,31] Contemporary stratification models emphasize that mechanistic alignment, rather than organ-based classification alone, should guide therapeutic sequencing.[26,27,38]

Relapse prevention should incorporate longitudinal biomarker monitoring, particularly plasmablast counts and B-cell repopulation kinetics in B-cell-driven disease.[4,9,34,35,37]

Importantly, precision management in IgG4-RD is not a single decision point but a dynamic process requiring periodic reassessment of immune dominance and adaptive therapeutic adjustment (Figure 1).[27,38,39]

6. Future Directions

Advancing precision medicine in IgG4-RD requires a shift from empiric treatment paradigms toward biologically stratified investigation. Future research should prioritize prospective clinical trials incorporating immunological endotype stratification

at baseline, rather than enrolling biologically heterogeneous populations under a single diagnostic label.[26,27,38,41]

Standardization of immune profiling techniques—particularly flow cytometry-based plasmablast quantification—may facilitate integration of biomarker-driven monitoring into routine practice.[4,10,34,37,39] Validation of relapse-predictive biomarkers, including plasmablast kinetics and complement dynamics, remains a critical unmet need.[6,18,35]

Equally important is the investigation of therapeutic strategies targeting cytotoxic and fibrotic pathways, especially in patients with advanced structural remodeling. Expansion of cytotoxic CD4+T-cell populations[14,23] and the role of TGF-β-mediated remodeling[16,17,22,40] suggest that antifibrotic interventions and therapies modulating macrophage polarization or TGF-β signaling warrant systematic evaluation. Emerging B-cell-receptor-modulating strategies and BTK inhibition further expand mechanistic therapeutic exploration.[29,31]

Ultimately, a deeper understanding of the dynamic interplay between immune activation and fibrotic progression may redefine treatment timing, sequencing, and long-term disease modification strategies in IgG4-RD.[27,36,38,41]

Conclusion

IgG4-RD should be understood as a biologically heterogeneous condition composed of overlapping but distinct immunological endotypes rather than a single-pathway inflammatory disorder. Recognition of dominant immune signatures—including B-cell and plasmablast expansion, type 2 cytokine polarization, Tfh-mediated germinal center activity, cytotoxic CD4+T-cell involvement, complement-associated mechanisms, and profibrotic macrophage signaling—provides a mechanistic framework that explains clinical variability and differential therapeutic responses.

Integrating immunological profiling into routine assessment may refine risk stratification, improve relapse prediction, and align treatment strategies with prevailing dominant immune axes. Moving beyond empiric steroid-centered management toward mechanism-informed therapy has the potential to reduce cumulative toxicity while enhancing durability of remission.

As immunophenotyping tools become more accessible and endotype-stratified trials emerge, precision-based management may redefine the clinical approach to IgG4-RD in the coming decade. The recent FDA approval of inebilizumab validates the B-cell axis as a critical therapeutic target and signals a new era of targeted, steroid-sparing treatments. Future advances will likely depend on integrating clinical phenotyping with scalable immunoprofiling strategies and validated diseasemodification endpoints.

Footnotes

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Declaration on the Use of Artificial Intelligence (AI): During the preparation of this manuscript, the author employed artificial intelligence tools for the following specific purposes: 1. Proof reading and grammatical verification. 2. Reference management and bibliographic formatting. 3. Turkish-English translation and technical terminology verification. 4. Refinement of table and figure legends. 5. Academic writing style assessment and improvement. The entirety of the scientific content, argumentation, and conclusions presented in this manuscript were generated and validated by the author. Artificial intelligence tools were employed exclusively for technical editing and formatting purposes and were not utilized in scientific decision-making or substantive content generation. The author accept complete responsibility for all material presented in this publication.

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