

IgG4-related Disease: Current Principles and Approaches in Diagnosis and Treatment

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Abstract

IgG4-related disease (IgG4-RD) has evolved from a series of organ-specific clusters into a recognized systemic fibroinflammatory disorder defined by a unique B-T cell axis. This review provides a comprehensive analysis of current diagnostic and therapeutic paradigms, emphasizing the pathogenic roles of CD4⁺ cytotoxic T lymphocytes and follicular helper T cells in driving storiform fibrosis. Despite the utility of the 2019 ACR/EULAR classification criteria, diagnostic challenges persist; notably, serum IgG4 remains a fallible biomarker, with a significant amount of patients maintaining normal concentrations during active disease. While glucocorticoids are the traditional first-line treatment, their long-term toxicity and high relapse rates have catalyzed a shift toward targeted B-cell depletion. Emerging evidence suggests that early intervention with biological agents can arrest and even reverse established fibrotic lesions, highlighting the dynamic nature of the immune-fibroblast interface. However, the current reliance on

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retrospective data and the lack of sensitive biomarkers for diagnosis and monitoring disease activity remain significant hurdles. This review underscores the necessity for precision-driven management and large-scale randomized trials to optimize long-term outcomes and minimize organ damage in this complex multi-organ condition.

Keywords: IgG4-related Disease, retroperitoneal fibrosis, biomarker, DMARDs

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized, immune-mediated fibroinflammatory condition that can involve nearly any organ system, often presenting as tumefactive lesions that mimic malignancies [1,2]. Although some manifestations were described earlier, the disease was only recognized as a unified systemic entity in 2003, following the identification of extrapancreatic involvement in patients with autoimmune pancreatitis [1,3,4]. The condition is characterized by a distinct histopathological triad: a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis [5]. While elevated serum IgG4 concentrations are common - observed in approximately 50% to 90% of patients during the acute phase - they are not universal, and the diagnosis relies heavily on the correlation of clinical, radiological, and pathological findings [2,6].

Demographic data indicate that IgG4-RD predominantly affects middle-aged and elderly individuals, with a noted predilection for males [1,2]. However, the sex distribution can vary depending on the specific organ involved; for instance, certain head and neck manifestations such as Mikulicz syndrome show a more even distribution or even a slight female predominance [7]. Because IgG4-RD is a relatively new clinical entity, comprehensive epidemiological data regarding its global prevalence and incidence remain limited and are currently an area of active investigation [8].

The diagnostic process is frequently complicated by the "protean" nature of the disease, which serves as a major mimicker of infections, sarcoidosis, and various cancers [3]. A significant challenge for clinicians is the lack of a single, highly specific biomarker, as elevated serum IgG4 levels can be found in other inflammatory and neoplastic conditions [6,8]. From a therapeutic perspective, while most patients show a prompt initial response to glucocorticoids, the disease is often characterized by a relapsing and

remitting course. Furthermore, the degree of tissue fibrosis at the time of diagnosis is a critical determinant of treatment efficacy, as advanced storiform fibrosis may be irreversible and lead to permanent organ dysfunction or failure [2].

The aim of this review is to elucidate the complex pathophysiological mechanisms underlying the B-T cell axis and fibrotic pathways in IgG4-RD. Furthermore, we present current approaches in diagnosis and treatment, while clarifying the specific challenges and "red flags" that rheumatologists and other specialists face when managing these patients. Finally, this manuscript seeks to underline existing knowledge gaps and offer future perspectives on personalized therapeutic strategies, including the role of B-cell depletion and other targeted biologic interventions.

2. Materials and Methods

In accordance with the principles of high-quality narrative reviews outlined by Gasparyan et al. [9], we conducted a structured and comprehensive literature search to synthesize current evidence on the pathophysiology, diagnostic frameworks, and evolving therapeutic strategies for IgG4-RD.

2.1. Databases and Sources Consulted

To ensure a multi-disciplinary perspective (encompassing rheumatology, gastroenterology, pathology, and radiology), we systematically searched the following electronic databases: PubMed/MEDLINE, Scopus, and Web of Science. These platforms were selected to capture high-impact clinical trials, observational cohorts, and consensus statements. Additionally, Google Scholar was utilized to identify grey literature, conference proceedings from major international symposia on IgG4-RD, and recent preprints. The reference lists of key studies and previous systematic reviews were manually screened to ensure no seminal works were omitted.

2.2. Search Terms and Boolean Strategy

The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The Boolean logic was tailored to each database's syntax to maximize sensitivity and specificity. The primary string used was: ("IgG4-related disease" OR "IgG4-RD" OR "immunoglobulin G4-related disease" OR "systemic IgG4-related plasmacytic syndrome") AND ("diagnosis" OR "diagnostic criteria" OR "classification criteria" OR "biomarkers" OR "pathology" OR "histopathology" OR "imaging") AND ("treatment" OR "management" OR "glucocorticoids" OR "rituximab" OR "B-cell depletion" OR "targeted therapy"). The search was iterative, allowing

for the inclusion of specific organ-related manifestations (e.g., "autoimmune pancreatitis", "Mikulicz's disease", "Reidels's thyroiditis") when relevant to the systemic overview.

2.3. Inclusion and Exclusion Criteria

Articles were considered eligible if they addressed the clinical spectrum, diagnostic challenges, or therapeutic outcomes of IgG4-RD. We prioritized: original research articles (prospective and retrospective), international consensus guidelines, diagnostic and classification criteria, high-quality reviews and meta-analyses, case series providing novel insights into rare manifestations or refractory cases. We excluded studies focusing on isolated IgG4-elevation without clinical features of the disease, technical laboratory reports without clinical validation, editorials, letters, and abstracts lacking sufficient methodology, articles published in languages other than English (to ensure consistency in terminology and peer-review standards).

2.4. Study Selection Flow

To capture the most contemporary advancements, particularly the shift toward steroid-sparing agents and biological therapies, we focused the search on publications from January 2010 to April 2026. This timeframe aligns with the modern recognition of IgG4-RD as a unified systemic entity. Findings were summarized thematically.

3. Pathophysiological Insights: The B-T Cell Axis and Fibrotic Pathways

CD4⁺ cytotoxic T lymphocytes (CTLs) have emerged as a dominant and pathogenic immune cell population in the tissue infiltrates of IgG4-RD [10]. These cells are characterized by an effector memory phenotype and the expression of cytotoxic molecules such as granzyme A, perforin, and RNA-binding protein (TIA1) [11]. Phenotypically, they are often identified by the surface marker SLAMF7 and frequently lack the costimulatory molecule CD28, a feature common in chronic antigen-driven T-cell responses [12].

The pathogenic role of CD4⁺ CTLs extends beyond direct cytotoxicity; they are major producers of pro-fibrotic and pro-inflammatory cytokines, including transforming growth factor-beta 1 (TGF- β 1), interleukin-1 beta (IL-1 β), and interferon-gamma (IFN- γ) [10,13]. Evidence suggests that these CTLs are reactivated within affected tissues by B cells and plasmablasts acting as antigen-presenting cells [14,15]. This interaction is

supported by the clinical observation that B-cell depletion therapy leads to a significant decline in circulating CD4+ CTL counts [10,12]. Furthermore, these cells may contribute to organ dysfunction by inducing the apoptotic death of host cells, such as ductal epithelial cells, which present the same antigenic peptides [14].

The dynamics between B cells and specialized T-cell subsets are central to the production of IgG4 and the formation of inflammatory lesions. A hallmark of the disease is the oligoclonal expansion of circulating plasmablasts (CD19+CD20-CD27+CD38bright), which serves as a more reliable biomarker for disease activity than serum IgG4 levels [12,16]. In the tissues, B cells often aggregate into tertiary lymphoid structures (TLS), where they undergo differentiation and somatic hypermutation [17,18].

T follicular helper (Tfh) cells, specifically the Tfh2 subset, are critical drivers of this process. Activated Tfh2 cells are significantly increased in the peripheral blood and tissues of IgG4-RD patients, and they produce IL-4 and IL-10, cytokines essential for B-cell class-switching to IgG4 [17,19]. Recent studies have also highlighted the role of peripheral helper T (Tph) cells (PD-1hiCXCR5-). Tph cells produce high levels of CXCL13, which facilitates the recruitment of both B cells and Tfh cells to extranodal sites, thereby promoting the formation of ectopic germinal centers and persistent fibroinflammation [18,19]. Beyond antibody production, B cells contribute directly to tissue remodeling by secreting pro-fibrotic factors such as platelet-derived growth factor B (PDGF-B) and lysyl oxidase-like 2 (LOXL2) [20].

Storiform fibrosis is a distinctive histopathological feature of IgG4-RD, characterized by a radial, "woven mat" or cartwheel-like arrangement of collagen fibers and spindle-shaped myofibroblasts [21,22]. This fibrotic process is driven by a complex interplay between innate and adaptive immune cells. TGF- β 1, primarily secreted by CD4+ CTLs and alternatively activated (M2) macrophages, is considered the master regulator of fibroblast-to-myofibroblast differentiation [10,20]. M2 macrophages are found in high concentrations in lesions and further promote fibrosis through the production of CCL18 and IL-33 [19].

Innate immune triggers are also implicated in initiating the fibrotic cascade. In murine models, the process begins with the activation of conventional dendritic cells (cDCs) via Toll-like receptor 3, which recruit CXCR3+ T cells. These T cells then facilitate the migration of plasmacytoid dendritic cells

(pDCs) that produce high levels of IFN- α and IL-33, establishing a positive feedback loop of chronic inflammation and fibrosis [13,23]. Unlike the fibrosis seen in conditions like systemic sclerosis, the fibrotic lesions in IgG4-RD are remarkably reversible upon treatment with glucocorticoids or B-cell depletion, highlighting the dynamic nature of the immune-fibroblast axis in this disease [10].

While these studies provide strong insights, a major limitation is the absence of a natural IgG4 equivalent in murine models, which makes it difficult to definitively determine whether the IgG4 molecule itself has a pathogenic or protective role [11,24]. Many current hypotheses regarding cytokine pathways are derived from observational human studies, necessitating further mechanistic validation [15]. Figure 1 summarizes the complex pathophysiological mechanisms in IgG4-RD.

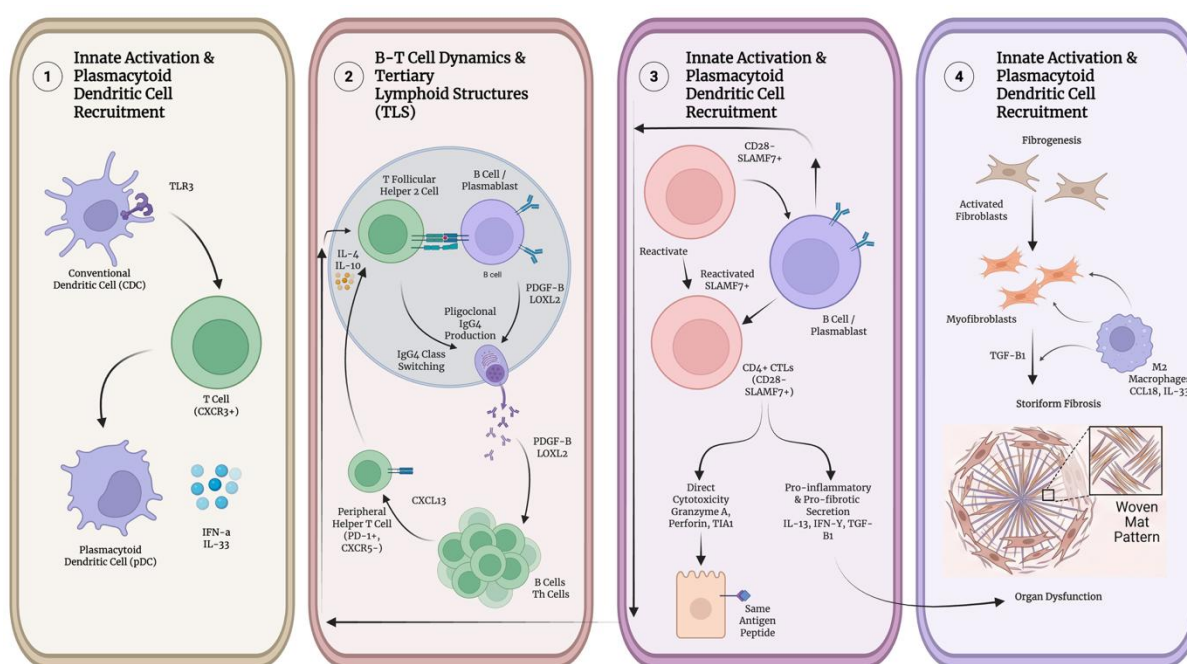


Figure 1. Multi-faceted Pathophysiology of IgG4-Related Disease.

4. Diagnostic Challenges: Integrating Clinical, Histopathological and Imaging Features

Diagnosis of IgG4-RD is challenging due to heterogeneous organ involvement and overlap with malignancy or other inflammatory disorders. A multimodal approach integrating clinical assessment, laboratory testing, imaging, and histopathology is essential for disease assessment and diagnosis.

4.1 Diagnostic Mimics: The "Great Mimicker"

IgG4-RD is frequently referred to as a "great mimicker" due to its ability to involve nearly any organ and its clinical overlap with a wide array of neoplastic, infectious, and other immune-mediated conditions [8,25]. The disease presents with remarkable clinical heterogeneity, which has been categorized into four distinct phenotypes: pancreato-hepato-biliary disease, retroperitoneal fibrosis and/or aortitis, head and neck-limited disease, and classic Mikulicz syndrome with systemic involvement [25,26]. This diversity necessitates a broad differential diagnosis; for instance, the pancreato-biliary phenotype must be distinguished from malignancies and type 2 autoimmune pancreatitis, while head and neck manifestations often overlap with Sjögren's syndrome and granulomatosis with polyangiitis [27].

A critical diagnostic challenge is the lack of a single, highly sensitive or specific biomarker. Serum IgG4 levels are elevated in 55-97% of patients but are normal in up to 40% of biopsy-proven cases and can be raised in healthy individuals or those with unrelated conditions like allergies and malignancies [8,25,28]. To address these challenges, the 2019 ACR/EULAR classification criteria utilize a three-step process that includes rigorous exclusion criteria - such as the presence of fever, specific autoantibodies (e.g., ANCA), or rapid radiological progression - to prevent misdiagnosis of mimickers [28,29]. While these criteria provide a robust framework for research, their complexity reflects the persistent challenge of diagnosing a condition that currently relies heavily on the exclusion of other diseases [8].

4.2 Histopathological Hallmarks and Limitations

Histopathology remains the cornerstone of IgG4-RD diagnosis, characterized by a "cardinal triad": a dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. The 2020 Revised Comprehensive Diagnostic (RCD) criteria and the 2012 international consensus statement emphasize that a confident diagnosis typically requires at least two of these major features in addition to an increased number of IgG4+ plasma cells (typically >10 cells/hpf) and an IgG4+/IgG+ ratio exceeding 40% [5,30].

However, histopathological diagnosis faces significant limitations. There is considerable organ-specific variability; for example, storiform fibrosis and obliterative phlebitis are frequently inconspicuous or entirely absent in the lymph nodes, minor salivary glands, and lacrimal glands, complicating the pathological confirmation in these sites [5,31]. Furthermore, the increasing reliance on small needle biopsies rather than surgical resections often

results in insufficient tissue to identify the characteristic architectural features, leading to sampling errors [29,31]. Pathologists must also be cautious as IgG4+ plasma cell infiltration is not pathognomonic and can be observed in various inflammatory and neoplastic conditions, making strict adherence to morphological criteria essential.

4.3 Role of Imaging in Disease Diagnosis and Assessment

Imaging plays a strategic role in the initial identification of "tumefactive" or mass-forming lesions and is vital for staging the disease by identifying clinically silent organ involvement [27]. While most radiological findings are non-specific, certain features are highly suggestive, such as the "sausage-shaped" pancreas with a surrounding edematous halo in autoimmune pancreatitis or the periaortitis typically affecting the infrarenal aorta [25,29].

Functional imaging, particularly 18F-FDG PET/CT, has emerged as a valuable tool for assessing disease activity and predicting outcomes, especially in retroperitoneal fibrosis [32,33]. Studies have shown that persistent FDG uptake during follow-up is a strong predictor of clinical relapse, allowing for better risk stratification and potentially guiding the duration of maintenance therapy. Additionally, advanced MRI techniques, such as Diffusion-Weighted Imaging (DWI), offer a radiation-free method to differentiate active, cellular fibroinflammation from inactive, treated fibrosis, as evidenced by significantly higher signal intensities in untreated patients [34]. Despite these strengths, the lack of standardization in PET analysis and the non-specificity of FDG uptake—which can occur in both inflammation and malignancy - remain significant limitations that necessitate correlation with clinical and pathological data [25,32].

While the 2019 ACR/EULAR and 2020 RCD criteria have significantly improved diagnostic consistency, they remain "classification" rather than "diagnostic" tools, and their application in routine clinical practice is sometimes limited by the difficulty of obtaining representative biopsies in deep-seated organs [29,30]. The diagnosis of IgG4-RD continues to be an iterative process of clinicopathological correlation where no single finding is definitive.

5. The Biomarker Challenge: Beyond Serum IgG4 Levels

5.1 Limitations of Serum IgG4

Serum IgG4 is the most commonly utilized biomarker in IgG4-RD, reflecting the proliferation of IgG4-secreting plasmablasts and plasma cells [35,36].

Nevertheless, although it has historically aided in disease identification, serum IgG4 is now recognized as neither a dependable standalone diagnostic marker nor a consistent measure of disease activity [37].

Elevated serum IgG4 levels (>135 mg/dL) are seen in a substantial proportion of patients and can aid diagnosis when interpreted within the appropriate clinical context [38]. However, its diagnostic utility is limited by suboptimal sensitivity and specificity. Notably, around 30–40% of patients with biopsy-confirmed IgG4-RD have normal serum IgG4 levels [39], representing a significant seronegative subgroup for whom reliance on this marker may result in underdiagnosis. Conversely, elevated IgG4 levels are not specific to IgG4-RD and can be seen in a range of other conditions, including malignancies (such as pancreatic cancer and lymphoma), chronic infections, and other autoimmune disorders [40]. This limits its specificity and underscores the importance of interpreting IgG4 levels within a comprehensive clinical and histopathological context.

From a prognostic standpoint, serum IgG4 concentrations exhibit significant limitations, as approximately 10% to 48% of patients maintain normal levels despite biopsy-proven active disease [41]. Although markedly elevated baseline levels often correlate with multi-organ involvement and a higher risk of relapse [40], serum IgG4 fails to reliably reflect disease activity in patients with normal baseline values, showing no significant correlation with the IgG4-RD Responder Index in this subgroup [41]. Furthermore, clinical flares can occur in roughly 10% of patients even when serum IgG4 concentrations remain low or stable, underscoring that normal laboratory findings do not definitively preclude disease progression or the need for therapeutic adjustment [40].

Clinically, serum IgG4 retains value as a supportive diagnostic marker within composite criteria [29], as a baseline measure during initial evaluation, and as a non-specific adjunct in longitudinal monitoring. However, serum IgG4 cannot be used in isolation for diagnosis, disease stratification, or therapeutic decision-making. The high prevalence of seronegative disease and its frequent discordance with disease activity underscore the need for more reliable biomarkers [42].

5.2 Novel and Emerging Biomarkers

Owing to the recognized limitations of serum IgG4 as a standalone biomarker, contemporary research has increasingly pivoted toward parameters that may more precisely reflect the underlying immunopathology of IgG4-RD [43].

Circulating plasmablasts represent a notable candidate for clinical monitoring; preliminary evidence suggests that their concentrations may correlate more closely with disease activity than serum IgG4, particularly in patients with multi-organ involvement [44]. Their rapid decline following effective immunosuppression, especially B-cell depletion therapy, underscores their potential utility in both diagnostic adjudication and longitudinal surveillance [45]. Specific T-cell subsets, particularly Tfh2 and Tph cells, further delineate the pivotal role of the B-T cell axis in the pathogenesis of IgG4-RD [46]. The expansion of these populations appears to parallel IgG4 class switching and plasmablast differentiation, positioning them as mechanistic indicators of the inflammatory cascade rather than purely descriptive markers.

Furthermore, soluble markers of immune activation, including the soluble interleukin-2 receptor (sIL-2R) and cytokines such as IL-4 and IL-21, offer supplementary insights into systemic T-cell activation [47]. While these markers may assist in identifying patients at an increased risk of relapse, their clinical specificity and predictive value require further validation. In addition to inflammatory parameters, markers associated with fibrogenesis - such as CCL18, periostin, and various indicators of extracellular matrix turnover - may facilitate the differentiation between active inflammatory and established fibrotic stages [48,49]. Identifying these signatures is critical for recognizing patients at risk of irreversible organ dysfunction.

Despite the diagnostic potential of these emerging parameters, several challenges remain. The majority of these biomarkers are currently restricted to the investigational domain, characterized by a lack of standardized assays and insufficient validation within large-scale, prospective cohorts. Consequently, they do not yet possess the clinical robustness required to replace serum IgG4 in routine practice, serving instead as complementary tools in a multi-modal diagnostic approach.

6. Evolution of Treatment: Moving Toward Steroid-Sparing Strategies

6.1 Glucocorticoid Protocols and Relapse

Glucocorticoids remain the cornerstone of initial therapy for IgG4-related disease (IgG4-RD), inducing rapid clinical and radiologic remission in most patients [50]. Standard induction regimens typically use moderate-to-high doses, followed by gradual tapering over several months [51]. Despite high initial response rates, relapse is common, affecting approximately 40–60%

of patients, particularly during dose tapering or after treatment discontinuation [52]. Risk factors for relapse include multi-organ involvement, high baseline disease activity, and delayed initiation of therapy [53].

Long-term glucocorticoid use is associated with significant morbidity, including osteoporosis, diabetes mellitus, hypertension, weight gain, and an increased risk of infection [54]. These limitations highlight the need for steroid-sparing strategies and more targeted therapeutic approaches.

6.2 The Role of Conventional DMARDs

Conventional disease-modifying antirheumatic drugs (DMARDs), including azathioprine, mycophenolate mofetil, and methotrexate, are commonly used in clinical practice as maintenance therapy or steroid-sparing agents [55–57]. These agents are intended to reduce relapse risk and limit glucocorticoid exposure. However, the evidence supporting their use is largely observational, with limited data from randomized controlled trials. Reported efficacy is variable, and there is no consensus on the optimal choice of agent, dosing strategy, or duration of therapy.

In addition, DMARDs appear less effective than targeted B-cell therapies in preventing relapse, especially in patients with severe or multi-organ disease. As a result, their role is being reconsidered in the era of precision immunotherapy [27]. Conventional disease-modifying antirheumatic drugs (DMARDs) are increasingly being repositioned as third-line or adjunctive therapies in the biologic era of IgG4-RD management, given their comparatively limited efficacy in relapse prevention when contrasted with B-cell-targeted agents such as rituximab and inebilizumab [55,56].

6.3 Novel and Emerging Targeted Therapies (B-cell Depletion and Intracellular Signaling Inhibitors)

B-cell-targeted therapy has emerged as a highly effective treatment strategy, reflecting the central role of the B–T cell axis in IgG4-RD pathogenesis [58,59] (Table 1). Rituximab, an anti-CD20 monoclonal antibody, has shown high efficacy in inducing remission and lowering relapse rates, including in patients who are refractory to glucocorticoids [60]. Clinical responses are frequently accompanied by rapid depletion of circulating plasmablasts and improvement in organ involvement. Inebilizumab, an anti-CD19 monoclonal antibody, has demonstrated promising results in the MITIGATE trial, significantly reducing relapse rates in both inflammatory and fibrotic disease manifestations [61]. Unlike rituximab, CD19-targeted therapy may affect a broader spectrum of B-

lineage cells, including plasmablasts [62]. Other B-cell-targeted agents, including obexelimab, are currently under investigation and may further expand therapeutic options [63].

Advances in understanding cytokine signaling pathways have further prompted the exploration of targeted immunomodulatory therapies [58]. IL-4 and IL-13 blockade (e.g., dupilumab) targets Th2-driven immune responses and IgG4 class switching [64]. Early data indicate potential glucocorticoid-sparing benefits, particularly in patients with pronounced allergic or Th2-dominant features [59]. Janus kinase (JAK) inhibitors represent a promising therapeutic class, targeting intracellular signaling pathways involved in cytokine-mediated inflammation [65]. Preliminary studies suggest potential efficacy, although robust clinical trial data are currently limited and their use is considered still experimental.

Table 1. Emerging and Targeted Therapies in IgG4-Related Disease.

Therapy	Target/Mechanism of Action	Key Clinical Role in IgG4-RD	Evidence/Notes	References
Rituximab	Anti-CD20 monoclonal antibody → B-cell depletion	Induction of remission; effective in glucocorticoid-refractory and relapsing disease	Rapid reduction in plasmablasts; strong real-world and observational evidence; current standard biologic therapy	[60]
Inebilizumab	Anti-CD19 monoclonal antibody → broader B-lineage depletion (including plasmablasts)	Reduction of relapse risk in inflammatory and fibrotic disease	Demonstrated efficacy in MITIGATE trial; potentially broader depletion than CD20 targeting	[61]
Obexelimab	CD19-directed B-cell modulation (FcγRIIB-mediated inhibitory signaling)	Investigational therapy aiming to suppress B-cell activation without full depletion	Early-phase evidence; potential for immune modulation with reduced immunosuppression	[62,63]
Dupilumab	Blockade of IL-4 and IL-13 signaling; targets Th2-driven	Potential glucocorticoid-sparing	Early-phase data suggest clinical benefit through	[59,64]

	immune responses and inhibits IgG4 class switching	maintenance therapy, particularly for patients with allergic or Th2-dominant clinical features	targeted immunomodulation of the Th2 pathway	
JAK inhibitors	Inhibition of JAK-STAT intracellular cytokine signaling	Experimental option for refractory disease or associated fibrosis	Limited early clinical data; potential broad anti-inflammatory effects but still investigational	[65]

CD, cluster of differentiation; FcγRIIB, Fc gamma receptor IIB; IgG4, immunoglobulin G4; IgG4-RD, immunoglobulin G4-related disease; IL, interleukin; JAK, Janus kinase; MITIGATE, Monoclonal Antibody against CD19 for the Treatment of IgG4-Related Disease; RI, responder index; STAT, signal transducer and activator of transcription; Th2, T helper type 2.

7. Strengths and Limitations

This review offers a multi-dimensional synthesis of IgG4-related disease, bridging the gap between molecular pathophysiology - specifically the B-T cell axis and the mechanisms of storiform fibrosis - and the practical challenges of clinical diagnosis and long-term therapeutic management. A primary strength of this work is the application of a structured, iterative search methodology, covering a 16-year period (2010–2026) that encompasses the most transformative era in the recognition and classification of this entity. By integrating the latest ACR/EULAR classification criteria and evaluating emerging steroid-sparing biological agents, this review provides a contemporary framework for clinicians navigating the complexities of multi-organ involvement. Furthermore, the detailed analysis of the CD4+ CTL and Tfh2 dynamics provides a robust immunobiological context for understanding why B-cell depletion has emerged as a cornerstone of modern therapy.

Despite these strengths, several methodological and inherent limitations must be acknowledged. First, a significant limitation of our methodology is the restriction of the search to English-language publications. Given that a substantial body of seminal work and large-scale cohort data on IgG4-RD originates from Japan and other East Asian countries, the exclusion of non-English literature may introduce a geographic and publication bias, potentially omitting localized clinical insights or alternative management

protocols. Secondly, although the search was systematic in its execution, this remains a narrative review. The inherent heterogeneity of the available literature - which consists predominantly of retrospective cohort studies, case series, and expert consensus rather than large-scale randomized controlled trials (RCTs) - precluded the performance of a formal meta-analysis or a universal quality appraisal of all cited sources.

The clinical evidence is further constrained by the relative rarity and phenotypic diversity of IgG4-RD. Many diagnostic and prognostic conclusions are drawn from small patient populations, which may limit their generalizability across different ethnic groups and environmental exposures. This is particularly relevant given that certain manifestations, such as IgG4-related dacryoadenitis and sialadenitis, may follow different clinical trajectories compared to retroperitoneal fibrosis or autoimmune pancreatitis. Additionally, as noted in our pathophysiological discussion, the current lack of a natural murine model for IgG4 remains a fundamental barrier to definitively establishing the pathogenic versus protective role of the IgG4 molecule itself. Finally, most data are derived from tertiary referral centers, which inherently introduces a selection bias toward more severe, symptomatic, or refractory cases, potentially overestimating the frequency of complications and the necessity for aggressive initial immunosuppression.

8. Conclusions

IgG4-related disease has evolved from a collection of isolated organ-specific conditions into a well-defined systemic entity with a unique immunopathological signature. The transition in our understanding of its pathophysiology - shifting from a purely IgG4-centric view to the recognition of the pathogenic B-T cell axis - has been transformative. The identification of CD4⁺ cytotoxic T lymphocytes and Tfh2 cells as central drivers of both inflammation and storiform fibrosis not only explains the disease's multi-organ nature but also provides a robust rationale for the clinical success of B-cell depletion therapies.

From a diagnostic perspective, the 2019 ACR/EULAR classification criteria represent a major milestone, emphasizing that while serum IgG4 remains a valuable clinical clue, it is neither a standalone diagnostic tool nor a flawless marker of disease activity. The fact that significant clinical relapses can occur despite normal IgG4 levels underscores the urgent need for more sensitive and specific biomarkers, such as circulating plasmablasts or specific cytokine profiles, to guide long-term monitoring.

Looking forward, the management of IgG4-RD is entering an era of precision medicine. While glucocorticoids remain the effective first-line response, their substantial toxicity profile necessitates the early integration of steroid-sparing strategies. The remarkable reversibility of even advanced fibrotic lesions upon B-cell depletion offers hope for preventing permanent organ damage. However, addressing the current evidence gaps - specifically the lack of large-scale randomized controlled trials and the limited understanding of the long-term outcomes in diverse ethnic cohorts - remains essential. Ultimately, a multi-disciplinary approach remains the cornerstone of achieving sustained remission and improving the quality of life for patients with this complex fibroinflammatory disorder.

Declarations

Author Contributions

Conceptualization: S.D & V.T; Methodology: S.D.; Formal analysis: S.D, V.T., G.K., M.I. & Z.K; Investigation: S.D & V.T; Writing—original draft: S.D, V.T., G.K., M.I. & Z.K; Writing—review & editing: S.D, V.T., G.K., M.I. & Z.K

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Institutional Review Board Statement

Not applicable.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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IgG4-свързана болест: Съвременни принципи и подходи в диагностиката и лечението

Резюме

IgG4-свързаната болест (IgG4-RD) еволюира от поредица от органно-специфични състояния в признато системно фиброинфламаторно заболяване, дефинирано от уникална В-Т клетъчна ос. Настоящият обзор предоставя всеобхватен анализ на съвременните диагностични и терапевтични парадигми, като акцентира върху патогенетичната роля на CD4+ цитотоксичните Т-лимфоцити и фоликуларните хелперни Т-клетки при индуцирането на сториформна фиброза. Въпреки приложимостта на класификационните критерии на ACR/EULAR от 2019 г., диагностичните предизвикателства персистират; по-специално, серумният IgG4 остава ненадежден биомаркер, тъй като значителна част от пациентите поддържат нормални концентрации по време на активно заболяване. Макар глюкокортикоидите да са традиционното лечение на първа линия, тяхната дългосрочна токсичност и високата честота на рецидивите катализират прехода към таргетна В-клетъчна деплеция. Новите доказателства сочат, че ранната интервенция с биологични средства може да спре и дори да доведе до обратимост на вече установените фиброзни лезии, подчертавайки динамичния характер на имуно-фибробластното взаимодействие. Въпреки това, настоящото разчитане на ретроспективни данни и липсата на чувствителни биомаркери за диагностика и проследяване на активността на заболяването остават значителни препятствия. Този обзор подчертава необходимостта от прецизно управление и мащабни рандомизирани проучвания за оптимизиране на дългосрочните резултати и минимизиране на органните увреждания при това комплексно мултиорганно състояние.

Ключови думи: IgG4-свързана болест, ретроперитонеална фиброза, биомаркер, БПАРС