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IgG4-Related Disease: Fibrofire to B-Cell Breakthroughs

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ABSTRACT

IgG4-related disease (IgG4-RD) is a systemic immune-mediated disorder that may involve multiple organs and typically presents with inflammatory tissue enlargement and variable fibrotic changes. Since its recognition in the early 2000s, IgG4-RD has been increasingly recognized as a systemic condition encompassing a wide range of clinical manifestations. The latter often mimicking malignancy, infection or other autoimmune diseases contribute to persistent underdiagnosis and delayed treatment. Yet, early recognition is crucial, as timely immunosuppressive therapy can induce remission and prevent irreversible fibrotic sequelae. This narrative review synthesizes current knowledge on the epidemiology, immunopathogenesis, clinical spectrum, diagnostic criteria, differential diagnoses and therapeutic strategies of IgG4-RD, with particular emphasis on evolving targeted therapies that are reshaping disease management and prognosis.

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Introduction

IgG4-related disease (IgG4-RD) represents one of the most intriguing immunological entities of modern medicine. Defined as a systemic fibro-inflammatory disorder, it is characterized by dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells, storiform fibrosis and in many cases obliterative phlebitis, with the capacity to affect virtually any organ system [1,2]. Owing to its tumefactive presentation and indolent course, IgG4-RD frequently mimics malignant, infectious or other inflammatory conditions, often leading to unnecessary surgical procedures or prolonged diagnostic delays [3,4].

Despite increasing clinical awareness, IgG4-RD remains substantially underrecognized, largely due to its remarkable clinical heterogeneity and the historical compartmentalization of organ-specific inflammatory diseases [5]. The unifying recognition that autoimmune pancreatitis, Mikulicz disease, retroperitoneal fibrosis and inflammatory pseudotumors share a common immunopathological substrate has profoundly reshaped diagnostic paradigms and redefined these entities within a single systemic disease spectrum [1,6].

This review aims to provide an integrated and contemporary overview of IgG4-RD, highlighting its systemic nature, immunological foundations and evolving therapeutic implications.

Epidemiology

IgG4-RD was first conceptualized in the early 2000s following seminal observations in Japan that linked autoimmune pancreatitis (AIP) with markedly elevated serum IgG4 concentrations and distinctive histopathological features characterized by lymphoplasmacytic infiltration rich in IgG4-positive plasma cells [1,7]. These findings challenged conventional organ-specific disease paradigms and led to the recognition of IgG4-RD as a systemic fibro-inflammatory disorder capable of affecting virtually any organ system [3,8]. Subsequent clinicopathological correlations demonstrated that conditions previously regarded as unrelated (such as retroperitoneal fibrosis, sclerosing cholangitis and Mikulicz disease) shared a common immunopathological signature, thereby consolidating the concept of IgG4-RD as a single disease spectrum [9].

Epidemiological data remain relatively limited and are largely derived from population-based studies conducted in East Asia, particularly Japan and South Korea, where diagnostic awareness and structured registries are more established. Available estimates suggest an annual incidence ranging from approximately 0.28 to 1.08 per 100,000 inhabitants, with prevalence likely underestimated due to subclinical disease, diagnostic delays and frequent misclassification as malignancy or other inflammatory disorders [10,11]. The disease predominantly manifests in older adults, with a peak age at diagnosis between the sixth and seventh decades of life. Importantly, symptom onset often precedes formal diagnosis by several years, reflecting the smoldering nature of IgG4-RD and its tendency to present with nonspecific mass-

forming lesions rather than overt systemic inflammation [12].

A pronounced male predominance is consistently reported across most large cohorts, with male-to-female ratios ranging from approximately 2:1 to 3.5:1, particularly in pancreatic, retroperitoneal and renal manifestations [13,14]. However, this sex disparity appears to attenuate or even disappear in certain phenotypic subsets, notably IgG4-related sialadenitis and dacryoadenitis, where the sex distribution approaches parity [12,15]. Intriguingly, women with IgG4-RD tend to present at a younger age and frequently exhibit more symptomatic disease, including higher rates of sicca symptoms, constitutional complaints and multi-organ involvement [16]. These observations suggest the existence of sex-specific immunological or hormonal modifiers influencing disease expression [17].

Immunopathogenesis

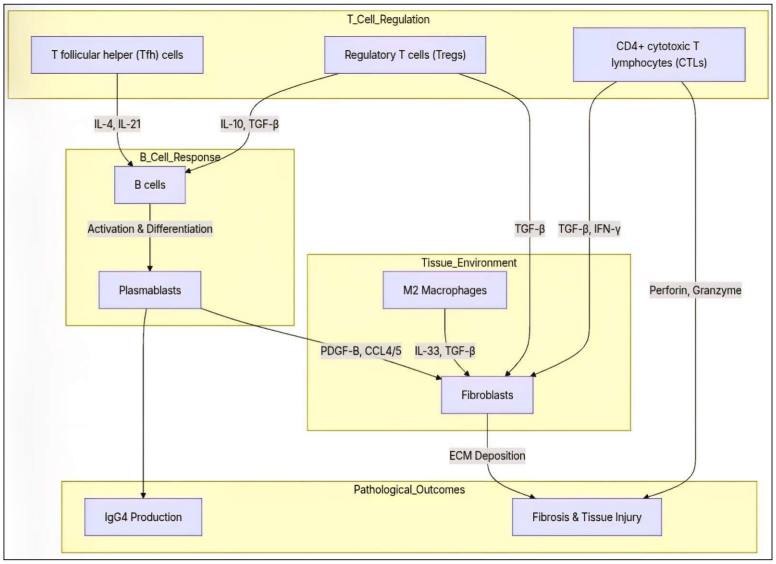

Figure 1: The interactions between key immune cells leading to high IgG4 production and fibrosis

The pathogenesis of IgG4-RD reflects a complex interplay between innate and adaptive immunity (Figure 1), culminating in persistent inflammation and progressive fibrosis across multiple organ systems [18].

Innate Immunity

Although historically underappreciated, innate immune cells contribute significantly to IgG4-RD initiation and amplification [19]

- Monocytes, macrophages and plasmacytoid dendritic cells (pDCs) are activated by tissue damage-associated signals and microbial ligands through pattern recognition receptors such as toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs).
- These cells produce B cell activating factor (BAFF), A proliferation-inducing ligand (APRIL), IL-33, and type I interferons, which drive B-cell survival, plasmablast expansion and a Th2-favoring milieu.
- Macrophages of the M2 phenotype accumulate in lesions and secrete IL-33 and TGF-β, fostering fibroblast activation and extracellular matrix deposition.

Innate immune cells thereby establish a pro-fibrotic and B-cell supportive environment even before adaptive responses dominate.

Adaptive Immunity: T and B Cell Interactions

The adaptive immune system orchestrates the hallmark features of IgG4-RD through aberrant T and B cell activation.

B Cells and Plasmablasts

B cells in IgG4-RD show abnormal activation and expansion, producing large numbers of IgG4-secreting plasmablasts that both correlate with disease activity and infiltrate affected tissues. Plasmablasts express high levels of fibrogenic mediators such as platelet-derived growth factor, isoform B (PDGF-B), C-C motif chemokine ligand 4 (CCL4), C-C motif chemokine ligand 5 (CCL5) and C-C motif chemokine ligand 11 (CCL11), directly stimulating fibroblasts and extracellular matrix production.

Some B-cell subsets may themselves produce collagenous proteins, suggesting a direct fibrogenic role beyond antibody secretion [20].

T Cell Subsets

IgG4-RD is characterized by distinctive T-cell involvement that diverges from classical autoimmune patterns:

- $CD4^+$ cytotoxic T lymphocytes (CTLs): Abundant in lesions, these cells release perforin, granzyme A/B and pro-fibrotic cytokines (TGF-β, IL-1β, IFN-γ…). They may contribute both to tissue injury and fibrosis.
- T follicular helper (Tfh) cells, especially Tfh2 subsets, drive germinal center formation and assist B cells in isotype switching toward IgG4 production via IL-21 and IL-4.
- Regulatory T cells (Tregs) produce high amounts of IL-10 and TGF-β, further polarizing the immune environment toward immunoregulation and fibrogenesis.
- Additional subsets such as T follicular regulatory cells (Tfr) can modulate germinal center dynamics and promote IgG4 class switching [21].

These T-cell populations create a non-classical adaptive response characterized by Th2-skewing and regulatory dominance rather than an outright Th1 or Th17 autoimmune profile.

Cytokine Milieu and Fibrogenesis

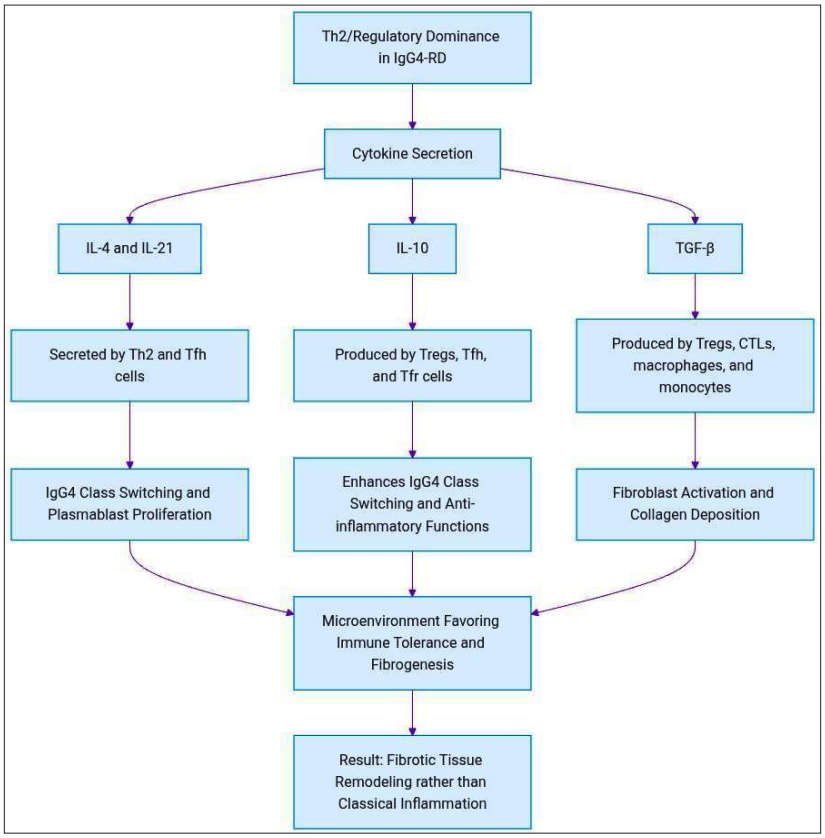

Figure 2: Key Cytokines in IgG4-RD [22]

Perspectives

Advances in immunopathology and translational science over the past few years are rapidly reshaping our understanding of IgG4-RD. Although the core features of B-cell expansion, plasmablast proliferation and a Th2/regulatory skew have long been recognized, recent work emphasizes high-resolution immune profiling, multi-omics integration, novel biomarkers and precision therapeutic strategies that may transform both mechanistic insight and clinical care.

High-resolution analyses of immune cell subsets have underscored the central role of Tfh and Treg networks in driving IgG4 class switching and plasmablast differentiation, with these cells now considered potential biomarkers and therapeutic targets. Studies also highlight the presence of tertiary lymphoid structures and diverse Tfh subpopulations within affected tissues, suggesting localized immune activation may sustain disease chronicity and relate to organ-specific phenotypes. These insights support a move beyond simple Th2/Treg models toward complex adaptive immune circuit mapping as a means to stratify patients based on immunological signatures and therapeutic risk profiles [23].

Multi-omics and systems biology approaches combining transcriptomics, proteomics and cellular phenotyping are emerging as powerful tools to uncover molecular drivers of heterogeneity in IgG4-RD. Such integrative strategies promise to identify novel biomarkers of early disease activity and flare risk that outperform traditional metrics like serum IgG4 levels. By linking gene expression patterns with immune cell states and cytokine networks, researchers aim to construct predictive models for disease classification, progression and treatment response [24].

On the therapeutic front, the landscape is rapidly evolving from broad glucocorticoid-based immunosuppression to mechanism-based interventions. Although steroids remain effective for induction of remission, their long-term use is limited by side effects and relapse risk. Biologic therapies targeting B-cell compartments (especially CD19-directed agents like inebilizumab) represent a major breakthrough, having demonstrated robust reductions in IgG4-RD flares and glucocorticoid dependence in large clinical trials. Complementary approaches and targeted inhibition of signaling pathways involved in B-cell activation and T-B cell interactions, are in development and may offer further precision in managing disease subtypes [25].

Advances in digital pathology and artificial intelligence are enhancing diagnosis and disease monitoring by integrating histological, radiologic and molecular features into unified platforms. This may facilitate earlier detection of IgG4-RD and more accurate differentiation from mimics such as malignancy or other autoimmune disorders. Despite these gains, several key challenges remain. The triggering antigens and upstream drivers of IgG4-RD are not yet fully defined, and how environmental factors or host genetics interact with immune regulatory circuits to initiate and sustain disease is an active area of research. Moreover, most current immunophenotypic signatures require validation in larger, diverse cohorts and need to be correlated with long-term outcomes. Integrating multi-omics with longitudinal clinical data in international consortia will be essential to refine personalized treatment algorithms and to identify patients most likely to benefit from specific targeted therapies [24,26].

Clinical Spectrum

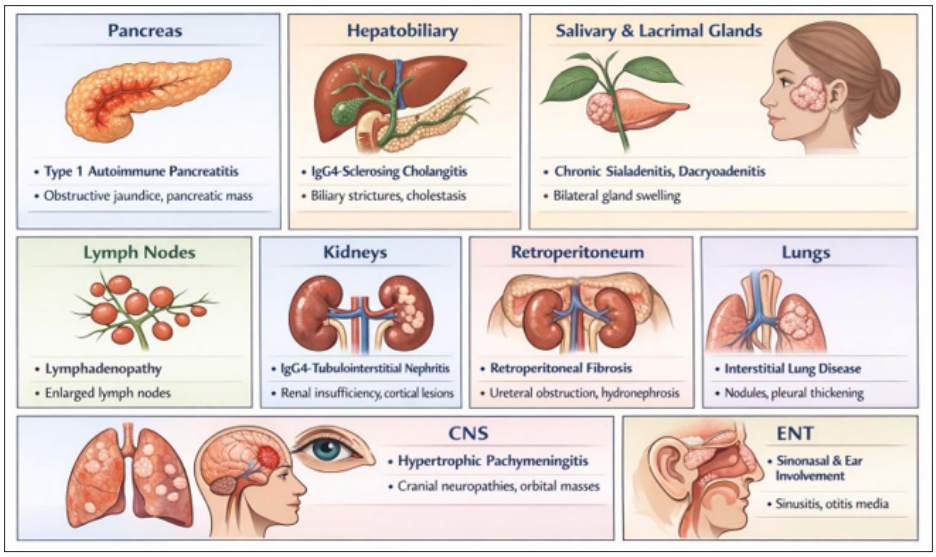

Figure 3: Major Organ Involvement in IgG4-RD

Among IgG4-RD diverse manifestations, pancreatic involvement remains the most emblematic presentation. Type 1 AIP represents the prototypical form. It often presents with obstructive jaundice, pancreatic enlargement and imaging features that closely mimic pancreatic adenocarcinoma, thereby posing significant diagnostic challenges. Histologically, this entity exemplifies the cardinal features of IgG4-RD, including dense lymphoplasmacytic infiltrates enriched in IgG4-positive plasma cells and storiform fibrosis [27].

Hepatobiliary involvement is another major disease domain, most notably IgG4-related sclerosing cholangitis (IgG4-SC). This condition frequently presents with biliary strictures that are radiologically and clinically indistinguishable from cholangiocarcinoma or primary sclerosing cholangitis at initial evaluation. The coexistence of AIP, elevated serum IgG4 concentrations and a prompt response to glucocorticoid therapy are often critical clues to diagnosis, underscoring the importance of clinical integration beyond imaging alone [28].

Exocrine gland involvement is common and classically affects the salivary and lacrimal glands, manifesting as chronic sialadenitis and dacryoadenitis. These lesions are typically bilateral, painless and slowly progressive, a constellation historically described as Mikulicz disease. Unlike Sjögren's disease, glandular dysfunction is often mild, autoantibodies are absent and tissue fibrosis rather than epithelial destruction predominates. Regional or generalized lymphadenopathy is frequently observed and may precede or accompany other organ involvement, occasionally leading to suspicion of lymphoproliferative disorders [3,29].

Renal involvement in IgG4-RD demonstrates considerable heterogeneity. IgG4-related tubulointerstitial nephritis is the most frequent manifestation and may present with renal insufficiency, imaging abnormalities such as multiple low-density cortical lesions or hypocomplementemia. Additionally, retroperitoneal fibrosis can lead to ureteral obstruction and secondary hydronephrosis, highlighting the potential for irreversible organ damage if diagnosis is delayed [30].

Beyond these core organs, IgG4-RD may involve the lungs, central or peripheral nervous systems without omitting otorhinolaryngological structures. Pulmonary disease mainly includes inflammatory pseudotumors, interstitial lung disease and pleural thickening. Neurological manifestations encompass hypertrophic pachymeningitis, hypophysitis and orbital disease, while sinonasal and middle ear involvement further reinforce the multisystemic reach of the condition [4,31,32,33].

Despite this striking heterogeneity, IgG4-RD lesions share unifying characteristics across organ systems such as a tumefactive enlargement, an indolent yet progressive course and a remarkable sensitivity to immunosuppressive therapy. Recognition of these shared features is essential, as timely diagnosis can prevent unnecessary surgical interventions and avert permanent fibrotic damage. Consequently, IgG4-RD should be systematically considered in patients presenting with unexplained mass-like lesions, multiorgan involvement or steroid-responsive inflammatory disease [2,34].

Diagnostic Criteria

IgG4-RD relies on a deliberate integration of clinical phenotype, serological markers, radiological patterns and histopathological confirmation. Early reliance on single-domain indicators (most notably serum IgG4 elevation) proved insufficient, prompting the development of multidimensional diagnostic frameworks over the past decade [3,35].

Over time, several classification and diagnostic criteria have been proposed for this fibro-inflammatory disease (Figure 4).

Criteria	Year	Primary Purpose	Key Features
Japanese Comprehensive Criteria	2012	Clinical diagnosis	Clinical, serological, histological domains
Revised Comprehensive Diagnostic (RCD) Criteria	2020	Clinical diagnosis	Multidomain integration, refined pathology
ACR/EULAR Criteria	2019	Research classification	Weighted scoring, high specificity
Organ-Specific Criteria	2011–2020	Organ-level diagnosis	Tailored imaging and pathology

Figure 4: Major Diagnostic and Classification Criteria for IgG4-RD

The 2020 Revised Comprehensive Diagnostic (RCD) criteria represent a critical evolution of earlier Japanese frameworks by formalizing the necessity of cross-domain concordance while refining histopathological thresholds [9,36]. These criteria emphasize that IgG4-RD should be diagnosed only when characteristic organ involvement is supported by compatible serology and/or imaging and anchored by histopathology whenever feasible.

Clinical and Radiological Domains

Characteristic organ involvement constitutes the clinical entry point for IgG4-RD. The disease typically presents with tumefactive enlargement, diffuse or focal organ swelling and an indolent clinical course. It often affects the pancreas, bile ducts, salivary and lacrimal glands, kidneys, lungs, retroperitoneum and large vessels [37]. Radiological findings frequently mirror this behavior, demonstrating homogeneous enhancement, infiltrative borders and soft-tissue encasement rather than destruction, features that often simulate malignancy or chronic infection [38].

The recognition of multiorgan involvement, whether synchronous or metachronous, substantially increases diagnostic probability and underpins the systemic nature of IgG4-RD. In this context, whole-body imaging, particularly fluorodeoxyglucose positron emission tomography/Computed tomography (FDG-PET/CT), has emerged as a valuable adjunct for disease mapping and biopsy targeting [39].

Serological Assessment

Elevated serum IgG4 concentrations (>135 mg/dL) are incorporated as a supportive diagnostic element in both the 2020 RCD criteria and earlier Japanese frameworks [9,40]. However, their diagnostic value is constrained by limited sensitivity and specificity, as up to one-third of patients with histologically confirmed IgG4-RD exhibit normal IgG4 levels, while elevated concentrations are observed in allergic disorders, chronic infections, malignancies and other autoimmune diseases. Recent investigations suggest that marked IgG4 elevation, high IgG4/IgG ratios or dynamic changes paralleling disease activity may enhance diagnostic confidence, though none are sufficiently robust to obviate tissue diagnosis [41].

Histopathology

Across all modern diagnostic frameworks, histopathology remains the gold standard for confirming IgG4-RD (Table 1). The 2020 RCD criteria require the presence of at least two of three cardinal histological features [9,42]

- Dense lymphoplasmacytic infiltration with fibrosis.
- IgG4-positive plasma cell enrichment, defined as an $IgG4^+/IgG^+$ plasma cell ratio >40% and >10 $IgG4^+$ cells per high-power field (with higher organ-specific thresholds in certain tissues).
- Characteristic storiform fibrosis and/or obliterative phlebitis.

These requirements are concordant with international pathology consensus recommendations, which emphasize that quantitative IgG4 immunostaining must be interpreted in conjunction with architectural features, rather than in isolation (Figure 5).

Table 1: Histopathological Requirements across Diagnostic Frameworks

Feature	RCD 2020	ACR/EULAR 2019	Pathology Consensus
Lymphoplasmacytic infiltrate	Required	Weighted	Required
$IgG4^+$ plasma cells	Quantitative threshold	Weighted	Context-dependent
Storiform fibrosis	Characteristic	Weighted	Highly characteristic
Obliterative phlebitis	Characteristic	Weighted	Highly specific

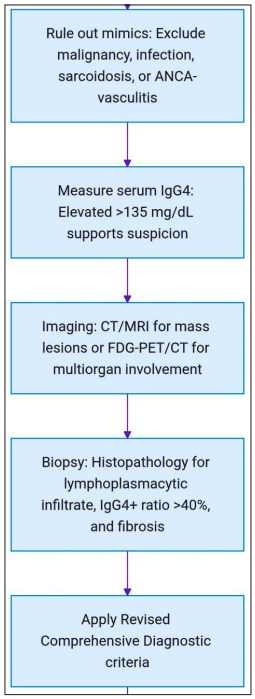

Figure 5: Diagnostic Algorithm for IgG4-RD

Additional Criteria

ACR/EULAR 2019 Classification Criteria

The 2019 ACR/EULAR classification criteria introduced a data-driven, weighted scoring system designed primarily for research classification rather than routine clinical diagnosis [43]. These criteria incorporate mandatory entry criteria, explicit exclusion items and weighted inclusion domains encompassing clinical features, serology, imaging and histopathology. While highly specific, their stringency may reduce sensitivity in early or organ-limited disease.

Organ-Specific Diagnostic Criteria

Several organ-specific diagnostic frameworks remain clinically relevant, particularly when systemic features are absent:

- AIP international consensus criteria, integrating imaging, serology, histology and steroid responsiveness [44].
- IgG4-related kidney disease criteria, emphasizing tubulointerstitial nephritis patterns and characteristic imaging findings [45].
- IgG4-related sclerosing cholangitis criteria, facilitating distinction from primary sclerosing cholangitis and cholangiocarcinoma [46].
- These organ-specific approaches often complement systemic criteria and may precede recognition of multisystem disease.

Differential Diagnosis

The differential diagnosis of IgG4-RD is exceptionally broad and of substantial clinical consequence, as erroneous attribution may result in inappropriate immunosuppression or, conversely, delay potentially life-saving oncologic or antimicrobial therapy. Malignancies constitute the most critical exclusions, particularly pancreatic ductal adenocarcinoma and cholangiocarcinoma, which frequently mirror IgG4-RD through mass-forming lesions, biliary obstruction and constitutional symptoms. Similarly, lymphomas and other lymphoproliferative disorders may present with tumefactive organ involvement and dense lymphoplasmacytic infiltrates, further compounding diagnostic ambiguity [35,47,48].

Beyond neoplastic entities, a wide array of immune-mediated and inflammatory diseases must be considered. Sarcoidosis can closely resemble IgG4-RD owing to multisystem involvement and granulomatous inflammation, while systemic vasculitides (including granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis and polyarteritis nodosa) may overlap clinically and radiographically, particularly in cases involving the retroperitoneum, kidneys or large vessels. Autoimmune conditions such as Sjögren's disease, primary sclerosing cholangitis, systemic lupus and inflammatory bowel disease-associated hepatobiliary disorders further broaden the diagnostic spectrum, especially when salivary glands, pancreas or bile ducts are involved [49].

Chronic infectious diseases represent another crucial category of mimickers. Tuberculosis, histoplasmosis, actinomycosis and other granulomatous or fibrosing infections may reproduce the mass-like appearance and chronic inflammatory histology characteristic of IgG4-RD, particularly in endemic regions. In addition, fibro-inflammatory disorders such as idiopathic retroperitoneal fibrosis, inflammatory pseudotumor, Rosai–Dorfman disease and Erdheim–Chester disease must be carefully distinguished. [49,50].

In this diagnostically complex landscape, histopathological evaluation is paramount. The identification of the characteristic triad (dense lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis) provides strong diagnostic support, particularly when complemented by immunohistochemical demonstration of increased IgG4-positive plasma cells and an elevated IgG4/IgG ratio. However, these findings are not pathognomonic and must be interpreted within a comprehensive clinicopathological framework, as increased IgG4-positive cells have been reported in malignancies, chronic infections and other inflammatory conditions [41,51].

Accordingly, definitive diagnosis relies on the integration of clinical features, imaging patterns, serologic data and meticulous histological assessment, underscoring the necessity of a multidisciplinary approach to reliably differentiate IgG4-RD from its numerous and often deceptive mimickers (Table 2).

Table 2: Differential Diagnosis of IgG4-RD

Organ	Differential diagnoses
Head and neck / Orbit	Lymphoma
	Graves' disease
	Sarcoidosis
	Granulomatosis with polyangiitis
	Idiopathic orbital inflammation
Salivary glands	Sjögren's disease
	Lymphoma
	Chronic sialadenitis
	Sarcoidosis
Pancreas / Biliary tract	Pancreatic adenocarcinoma Cholangiocarcinoma
	Primary sclerosing cholangitis
	Type 2 autoimmune pancreatitis
Lung	Primary lung carcinoma Lymphoma
	Sarcoidosis
	ANCA-associated vasculitis Endemic fungal infections
	Inflammatory pseudotumor / myofibroblastic tumor
Retroperitoneum / Mesentery / Aorta	Idiopathic retroperitoneal fibrosis
	Sarcoma
	Lymphoma
	Erdheim–Chester disease
	Large vessel vasculitis Atherosclerotic aneurysm
Kidney / Urinary tract	Chronic interstitial nephritis (non-IgG4)
	Renal cell carcinoma Amyloidosis
	Hypertrophic pachymeningitis (non-IgG4)
	Giant cell arteritis
Meninges / Pituitary	Hypophysitis (autoimmune / sarcoid)
	Langerhans cell histiocytosis
Multi-system / Others	Systemic lupus
	Eosinophilic granulomatosis with polyangiitis
	Dermatomyositis
	Multicentric Castleman disease

Therapeutic Management

The therapeutic paradigm for IgG4-RD is expressly individualized, with clinical decisions anchored in the pattern of organ involvement, the intensity of immune-mediated inflammation and the patient's intrinsic risk of relapse (Figure 6). Glucocorticoids remain the foundational first-line therapy, owing to their robust capacity to rapidly suppress inflammatory activity and induce clinical remission; typical induction regimens employ prednisolone at approximately 0.6–1.0 mg/kg/day, followed by a judicious taper over weeks to months to balance efficacy with the potential for steroid-related toxicity. However, disease relapse during dose reduction is common, underscoring the limitations of steroid monotherapy and the need for durable, steroid-sparing strategies [52].

In clinical practice, conventional immunosuppressive agents such as azathioprine, mycophenolate mofetil and methotrexate are frequently deployed as adjunctive, steroid-sparing therapies or maintenance regimens in corticosteroid-dependent or relapsing disease, despite limited prospective, controlled data defining

their optimal use [53]. By contrast, rituximab, a B-cell–depleting anti-CD20 monoclonal antibody, has emerged as a cornerstone of second-line therapy in IgG4-RD. Observational and prospective cohort studies indicate that rituximab-mediated B-cell depletion can achieve sustained remission while reducing glucocorticoid use. Protocolized B-cell depletion has been associated with low flare rates and favorable clinical responses, supporting its efficacy in multisystem disease [54].

Inebilizumab, a CD19-targeted monoclonal antibody, represents a significant advance in the treatment of IgG4-RD. It was evaluated in the multicenter, randomized, double-blind, placebo-controlled phase 3 MITIGATE trial. The study demonstrated that inebilizumab significantly reduced disease flares (10% vs 60% with placebo; hazard ratio 0.13; $P < 0.001$) and increased the likelihood of flare-free complete remission at 52 weeks. These benefits were observed with or without glucocorticoid therapy [25,55]. These findings establish CD19-directed B-cell depletion as an effective, novel therapeutic modality in IgG4-RD; inebilizumab subsequently received regulatory approval for this indication in 2025.

Both anti-CD20 and anti-CD19 therapies target B cells in IgG4-RD but differ fundamentally in scope. Rituximab depletes mature B cells (CD20+) while sparing CD20-negative plasmablasts and early precursors, achieving rapid clinical responses in 70-95% of patients but with relapses in 30-60% due to incomplete long-term control (56). Anti-CD19 therapies, by contrast, provide broader depletion across the B-cell lineage (including pro/pre-B cells, naïve/memory B cells and CD19+ plasmablast precursors) potentially yielding deeper remission and addressing rituximab-resistant clones. Anti-CD19 is thus considered as a « new gold standard » for refractory cases with promising early data in relapsing patients (57).

Beyond CD19 targeting, novel agents with alternative mechanisms are entering clinical evaluation. Bruton's tyrosine kinase (BTK) inhibitors, exemplified by rilzabrutinib, have shown promise in early phase studies by attenuating disease flares and facilitating reductions in steroid use over one year of treatment. Rilzabrutinib has been granted orphan and fast track designations, reflecting its potential to expand the therapeutic armamentarium for IgG4-RD [58].

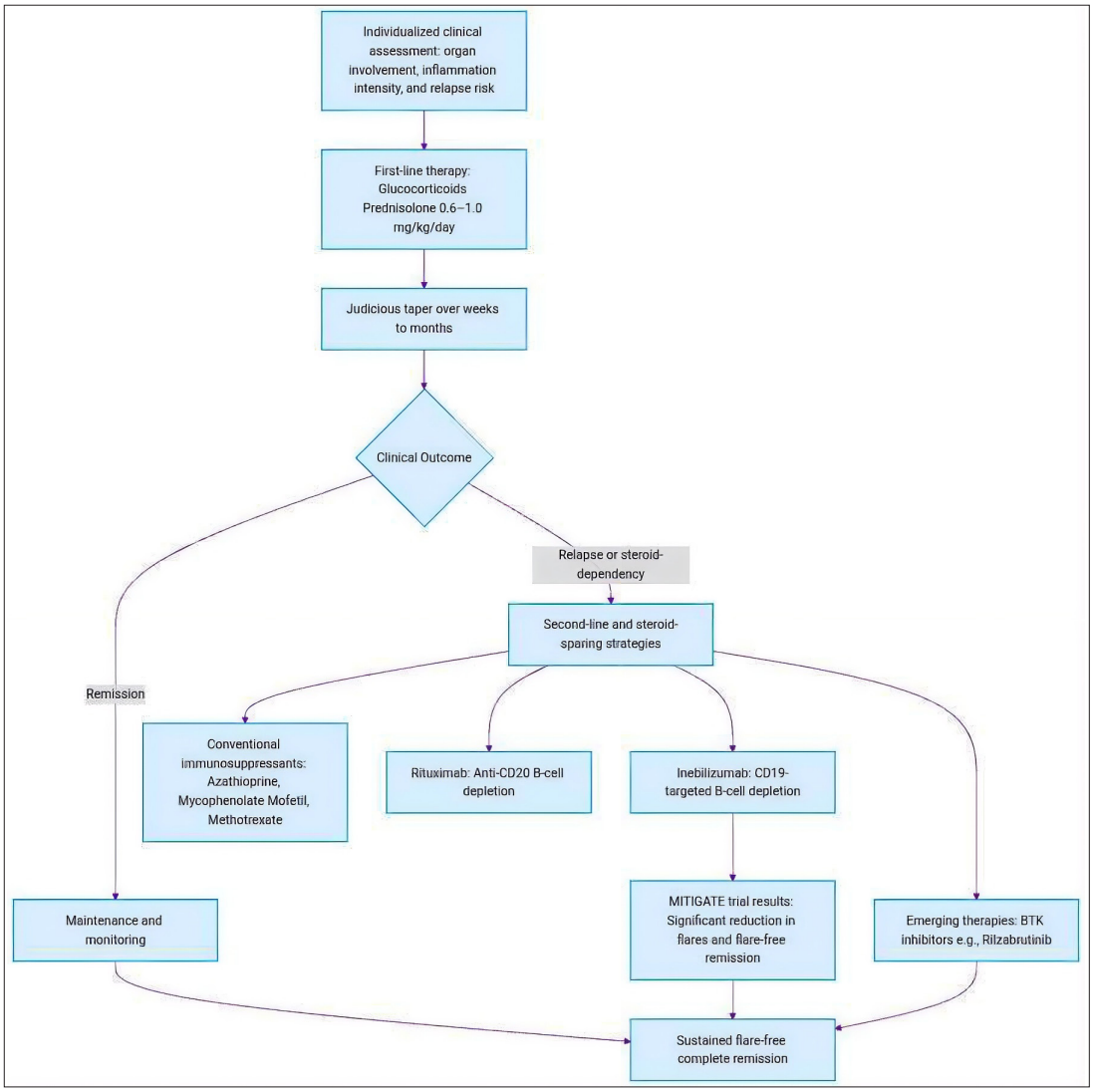

Figure 6: Therapeutic Algorithm for IgG4-RD

Prognosis

Without appropriate treatment, IgG4-RD typically follows a progressive and relapsing course in which ongoing inflammation drives cumulative fibrotic remodeling and leads to irreversible organ damage and dysfunction over time. This natural history has been documented in multiple cohort studies and long-term observations, which emphasize that untreated or under-treated IgG4-RD can result in persistent inflammation, progressive fibrosis and structural loss of function in organs [59].

Early in the disease, affected tissues often show reversible inflammatory changes, but as disease activity persists, the development of extensive fibrotic tissue significantly reduces the likelihood of therapeutic responsiveness and increases the risk of permanent organ injury. By contrast, early and sustained immunosuppressive therapy has dramatically improved clinical outcomes in IgG4-RD. Glucocorticoids are highly effective in inducing remission, with response rates reported in the majority of treated patients; remission induction often results in marked symptom resolution and can prevent progression to organ dysfunction if initiated before extensive fibrosis develops [24,59].

Combination therapy (for example, corticosteroids with immunosuppressants or targeted biologics like rituximab) has been shown to reduce relapse rates and help maintain remission, especially in patients at higher risk of recurrent disease or with multiorgan involvement. Despite effective induction of remission, relapses are common in IgG4-RD. Long-term cohort studies and meta-analyses report relapse rates in the range of approximately 20 %–40 % within two to three years after initial therapy, with many patients requiring additional courses of therapy or ongoing maintenance treatment [60,61].

These high relapse rates underscore the importance of long-term surveillance, including clinical, serological and imaging assessments, to detect disease reactivation early and adjust therapy accordingly.

Circulating plasmablasts (CD19+CD27+CD38hi) are recognized as a promising biomarker in IgG4-RD, particularly for assessing disease activity and treatment response, but their direct role in determining treatment duration or predicting relapse remains investigational and not standardized in clinical practice [62]. They are elevated during active disease and decrease significantly with glucocorticoids or rituximab, correlating better than serum IgG4 with clinical response, potentially guiding treatment tapering or discontinuation, though no recommendations specify a precise duration based solely on this marker. Their persistence or re-elevation may predict relapse even in patients with normal IgG4, correlating with residual activity after B-cell therapy, but this requires confirmation from prospective studies and is not validated in guidelines (63). Practically, they are measured via flow cytometry on blood (not routine), offering greater sensitivity than IgG4 for diagnosis and monitoring, with limited availability; recommended follow-up includes plasmablasts, IgG4 and imaging/PET-CT.

Maintenance strategies vary by patient, but often include low-dose glucocorticoids and/or immunosuppressive or B-cell-depleting agents to prolong relapse-free periods and protect organ function. Ultimately, an individualized approach to IgG4-RD management significantly improves prognosis, reduces disease-related morbidity and enhances quality of life [61,64].

Conclusion

IgG4-related disease exemplifies the convergence of immunology, pathology and clinical medicine. Once fragmented across organ-specific diagnoses, it is now recognized as a unified systemic disorder with distinctive histological and immunological features. Early diagnosis and appropriate therapy are paramount, as timely intervention can arrest inflammation before fibrosis becomes irreversible. With the advent of targeted immunotherapies, the therapeutic landscape of IgG4-RD is rapidly evolving, offering renewed hope for durable remission and improved long-term outcomes. Continued research into disease mechanisms and biomarkers will be essential to refine personalized management strategies and fully unravel the complexities of this fascinating disease.

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