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IgG4-related disease: A descriptive review of an emerging fibroinflammatory disorder

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Abstract
Background: IgG4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory disorder characterized by lymphoplasmacytic infiltration, tumefactive lesions, IgG4-positive plasma cells, and progressive fibrosis affecting multiple organs. Its heterogeneous presentation frequently overlaps with malignancy, infection, vasculitis, and other autoimmune disorders.
Objectives: This review summarizes contemporary evidence on the epidemiology, immunopathogenesis, clinical manifestations, diagnosis, treatment, and prognosis of IgG4-RD.
Methods: A descriptive review of English-language literature published from January 2019 through June 2026 was conducted using PubMed/MEDLINE, Web of Science, and Google Scholar. Relevant original studies, observational studies, reviews, meta-analyses, consensus statements, guidelines, and classification criteria were considered and narratively synthesized.
Results: IgG4-RD involves complex interactions among B cells, plasmablasts, T-cell subsets, macrophages, cytokines, and fibroblasts, resulting in chronic inflammation and fibrosis. Commonly affected sites include the pancreas, biliary tract, salivary and lacrimal glands, kidneys, lungs, retroperitoneum, orbit, and vascular and nervous systems. Diagnosis requires integration of clinical findings, serology, imaging, and histopathology while excluding mimicking disorders. Serum IgG4 elevation is supportive but neither sensitive nor specific enough for diagnosis alone. Characteristic histopathology includes lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis, and increased IgG4-positive plasma cells. Glucocorticoids remain widely used for remission induction, while rituximab is increasingly important for relapsing, refractory, or steroid-dependent disease.
Conclusion: Early recognition of IgG4-RD is essential to prevent irreversible fibrosis and organ dysfunction. Improved understanding of its immunopathogenesis and expanding targeted therapies may enhance long-term disease control.

Keywords: IgG4 related disease, IgG4 RD, fibroinflammatory disease, storiform fibrosis, autoimmune pancreatitis, plasmablasts, obliterative phlebitis, rituximab, B-cell depletion, multisystem disease

Introduction
IgG4-related disease is a systemic immune-mediated fibroinflammatory condition that has transformed the understanding of several disorders once regarded as separate organ-specific entities. Before the concept of IgG4-related disease became widely accepted, conditions such as autoimmune pancreatitis, Mikulicz disease, Riedel thyroiditis, IgG4-related sclerosing cholangitis, inflammatory pseudotumor, and some forms of retroperitoneal fibrosis were often considered unrelated diseases. The recognition that these disorders shared common pathological, serological, and clinical features led to the modern concept of IgG4-related disease as a unified multisystem disorder [1, 2].
The disease is clinically important because it may present as organ enlargement, mass-like lesions, obstructive disease, or progressive fibrosis, frequently mimicking malignancy, infection, or other autoimmune conditions. This diagnostic mimicry is particularly relevant in pancreatic, hepatobiliary, pulmonary, renal, retroperitoneal, orbital, and lymph node disease, where delayed recognition may lead to unnecessary surgery, irreversible organ damage, or prolonged exposure to inappropriate therapy [3, 4]. Although some patients present with indolent disease, others develop severe organ-threatening manifestations such as obstructive jaundice, renal impairment, retroperitoneal fibrosis with ureteral obstruction, hypertrophic pachymeningitis, aortitis, or orbital disease threatening vision [5].
The current understanding of IgG4-related disease emphasizes that serum IgG4 elevation alone is insufficient for diagnosis. Some patients with biopsy-proven disease have normal serum IgG4 concentrations, while elevated serum IgG4 may occur in malignancy, allergic disease, infection, vasculitis, and other inflammatory disorders. Therefore, diagnosis depends on a careful synthesis of clinical findings, radiologic patterns, serology, histopathology, immunostaining, and exclusion of mimickers [6]. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria provided an important framework for research classification by combining entry criteria, exclusion criteria, and weighted inclusion domains across clinical, serologic, radiologic, and pathologic findings [7].
Management has also evolved. Glucocorticoids remain effective for initial disease control in many patients, but relapse is common, and long-term steroid exposure is associated with substantial adverse effects. B-cell depletion, particularly with rituximab, has become a major therapeutic option in relapsing, refractory, or steroid-dependent disease, and newer therapies targeting B-cell lineage pathways are reshaping the treatment landscape [8, 9]. Because IgG4-related disease often affects multiple organs and may cause

progressive fibrosis, early recognition and multidisciplinary care are essential to prevent irreversible structural damage.

This descriptive review summarizes current evidence on IgG4-related disease with emphasis on epidemiology, etiologic and immunologic mechanisms, histopathologic features, organ involvement, diagnostic approach, differential diagnosis, treatment, prognosis, limitations in current knowledge, and future research directions.

Methods

This descriptive review was conducted to synthesize current evidence on IgG4-related disease, focusing on publications from January 2019 to June 2026. The selected period was chosen to capture contemporary advances in classification, pathogenesis, diagnosis, imaging, treatment, and prognosis, while including the 2019 ACR/EULAR classification framework that remains central to modern research and clinical discussion.

A literature search was performed using PubMed/MEDLINE, Web of Science, and Google Scholar. Search terms included "IgG4-related disease," "IgG4-RD," "IgG4-related fibroinflammatory disease," "autoimmune pancreatitis," "IgG4-related sclerosing cholangitis," "IgG4-related kidney disease," "IgG4-related lung disease," "IgG4-related ophthalmic disease," "storiform fibrosis," "obliterative phlebitis," "IgG4-positive plasma cells," "plasmablasts," "B cells," "rituximab," "glucocorticoids," "classification criteria," "diagnosis," "differential diagnosis," and "treatment." Boolean operators were used to combine disease-specific and organ-specific terms.

Articles were considered eligible if they were original research studies, cohort studies, case-control studies, clinically relevant case series, narrative reviews, systematic reviews, meta-analyses, consensus statements, guidelines, or classification criteria addressing IgG4-related disease in humans. Priority was given to studies with clear clinical relevance, adequate methodological description, and relevance to diagnosis, pathogenesis, treatment, or prognosis. Articles were excluded if they were non-English publications, conference abstracts without full text, duplicate reports, animal-only studies without direct clinical relevance, editorials without substantive scientific content, or articles with insufficient methodological detail.

Data were synthesized narratively. Key themes were organized into epidemiology, etiology and risk factors, immunopathogenesis, histopathology, clinical manifestations, diagnostic evaluation, differential diagnosis, treatment and management, prognosis, discussion, limitations, and future directions. Because this was a descriptive review rather than a systematic review or meta-analysis, no PRISMA flow diagram was used.

Epidemiology

IgG4-related disease is considered uncommon, although its true epidemiologic burden remains uncertain because of underrecognition, variable organ-specific presentation, evolving diagnostic criteria, and differences in referral patterns across specialties. The disease has been reported worldwide, but much of the early epidemiologic literature came from Japan and other Asian countries, particularly through studies of autoimmune pancreatitis and IgG4-related sclerosing cholangitis. More recent reports from Europe and North America have expanded recognition of the disease across rheumatology, gastroenterology, nephrology, pulmonology, ophthalmology, neurology, pathology, and internal medicine settings [3, 4].

The condition is most often diagnosed in middle-aged and older adults, with many cohorts showing a male predominance, particularly in pancreatobiliary, renal, retroperitoneal, and aortic disease. However, sex distribution varies by organ phenotype. Head and neck manifestations, including salivary, lacrimal, and orbital involvement, may show a less pronounced male predominance than pancreatobiliary or retroperitoneal disease. Pediatric IgG4-related disease is uncommon and remains less well characterized than adult disease.

The pancreas, biliary tree, lacrimal glands, salivary glands, kidneys, retroperitoneum, lungs, lymph nodes, aorta, thyroid, meninges, and orbits are among the commonly reported sites of involvement. Many patients have multiorgan diseases at diagnosis or develop additional organ involvement over time. Because presentations may be localized, indolent, or mistaken for malignancy or other inflammatory diseases, epidemiologic estimates likely underestimate the true prevalence.

This is summarized in table 1 below;

Table 1: Epidemiological Characteristics and Descriptions

Characteristic	Description	
Global distribution	IgG4-RD has been reported worldwide, with increasing recognition across Asia, Europe, North America, South America, and Africa. Initial reports originated predominantly from Japan, where the disease was first characterized.	[3,8,13]
Estimated prevalence	The exact prevalence remains uncertain because of underdiagnosis and heterogeneous clinical presentation. Population-based studies from Japan estimate prevalence between approximately 6 and 10 cases per 100,000 population.	[3,9]
Annual incidence	Estimated annual incidence ranges from approximately 0.3 to 1.0 per 100,000 population, although true incidence is likely underestimated.	[3,9]
Age at diagnosis	Most patients are diagnosed between 50 and 70 years of age, with peak incidence occurring during the sixth decade of life.	[3,9,13]
Sex distribution	Overall male predominance is observed, particularly in pancreatobiliary, renal, retroperitoneal, and cardiovascular disease; however, head and neck involvement demonstrate a more balanced sex distribution.	[9,13]
Commonly affected organs	Pancreas, biliary tract, salivary glands, lacrimal glands, kidneys, lungs, retroperitoneum, lymph nodes, thyroid gland, aorta, meninges, pituitary gland, and orbital tissues.	[3,8,9]
Pattern of organ involvement	Disease may involve a single organ or multiple organs simultaneously, with multiorgan disease becoming increasingly common as recognition improves.	[3,9,13]
Geographic variation	Most epidemiologic data originate from East Asia, although increasing numbers of cases are being reported from Europe, North America, and other regions due to improved awareness and standardized diagnostic criteria.	[3,8,13]

Etiology and Risk Factors

The etiology of IgG4-related disease (IgG4-RD) remains incompletely elucidated despite significant advances in understanding its clinical, pathological, and immunological characteristics. Current evidence indicates that IgG4-RD is a multifactorial immune-mediated fibroinflammatory disorder that arises from a complex interplay among genetic predisposition, environmental factors, immune dysregulation, and aberrant tissue remodeling. Unlike classical autoimmune diseases in which specific autoantigens have been identified, the initiating antigenic stimulus responsible for IgG4-RD remains unknown. Consequently, the disease is believed to result from multiple interacting pathogenic mechanisms rather than a single etiologic factor. Persistent immune activation, coupled with dysregulated fibroblast function and excessive extracellular matrix deposition, is thought to drive the progressive fibroinflammatory process that characterizes the disease [8. 11].

Genetic susceptibility is considered an important contributor to disease development. Several studies have identified associations between IgG4-RD and specific human leukocyte antigen (HLA) haplotypes, particularly in Japanese and other Asian populations, suggesting that inherited variations in immune regulation may influence disease susceptibility. [8, 10] In addition to HLA genes, polymorphisms involving immune-regulatory molecules, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Fc gamma receptor (FCGR) genes, and other immune signaling pathways, have been implicated in abnormal immune tolerance and chronic inflammatory responses. [10, 12] Although these genetic associations vary among different populations, they collectively support the concept that host genetic factors predispose susceptible individuals to inappropriate immune activation following environmental or immunologic stimuli.

Environmental exposures have also been proposed as potential initiating or amplifying factors in IgG4-RD. Chronic antigenic stimulation, occupational exposures, infectious agents, and molecular mimicry have all been investigated as possible triggers; however, none has been conclusively established as the primary cause of disease. [10, 12] Experimental studies suggest that microbial antigens may induce immune activation through molecular mimicry in genetically predisposed individuals, resulting in sustained inflammatory responses and subsequent tissue fibrosis. Nevertheless, the available evidence indicates that environmental factors are more likely to function as disease modifiers or amplifiers rather than direct etiologic agents.

An increased prevalence of allergic diseases among patients with IgG4-RD has generated considerable interest in the contribution of type 2 immune responses to disease pathogenesis. Many affected individuals exhibit peripheral eosinophilia, elevated serum immunoglobulin E (IgE) concentrations, asthma, allergic rhinitis, eczema, or chronic rhinosinusitis, suggesting activation of T helper 2 (Th2)-mediated immune pathways. [9, 11] However, allergic predisposition alone does not adequately explain the development of IgG4-RD because a substantial proportion of patients have no history of atopic disease. Moreover, accumulating evidence demonstrates that disease pathogenesis involves a far more complex immunologic network encompassing B lymphocytes, plasmablasts, T follicular helper cells, cytotoxic $CD4^+$ T lymphocytes, regulatory T cells, macrophages, and multiple profibrotic cytokines, indicating that IgG4-RD extends well beyond the spectrum of conventional allergic disorders [9, 11].

Advancing age represents one of the most consistently recognized epidemiologic risk factors for IgG4-RD, with the majority of patients presenting during the fifth to seventh decades of life [9, 13]. Although the disease can occur in younger adults and, rarely, in children, its incidence increases progressively with advancing age. A male predominance has been consistently reported, particularly among patients with pancreatobiliary disease, retroperitoneal fibrosis, renal involvement, and large-vessel disease. In contrast, disease involving the lacrimal glands, salivary glands, and orbital tissues appears to demonstrate a more balanced sex distribution or a slight female predominance. These observations suggest that demographic characteristics may differ according to the predominant organ involved and clinical phenotype [9, 13].

Despite extensive research, no single biomarker has demonstrated sufficient sensitivity or specificity to reliably predict disease onset or identify individuals at increased risk before clinical manifestations become apparent. Rather, IgG4-RD is currently regarded as the consequence of a multifaceted interaction among genetic susceptibility, environmental influences, dysregulated innate and adaptive immune responses, persistent B-cell activation, pathogenic T-cell expansion, and progressive fibroblast-mediated tissue remodeling [8, 11]. This integrated pathogenic model provides the biological basis for the characteristic lymphoplasmacytic inflammation, storiform fibrosis, tumefactive lesions, and multisystem organ involvement that define this increasingly recognized fibroinflammatory disorder.

Immunopathogenesis

The immunopathogenesis of IgG4-related disease (IgG4-RD) is complex and incompletely understood, involving coordinated interactions between innate and adaptive immune responses that culminate in chronic inflammation, immune dysregulation, and progressive tissue fibrosis. Rather than representing a conventional antibody-mediated autoimmune disorder, IgG4-RD is increasingly recognized as an immune-mediated fibroinflammatory disease characterized by aberrant activation of B lymphocytes, plasmablasts, multiple $CD4^+$ T-cell subsets, macrophages, and fibroblasts, which collectively promote tissue remodeling and organ dysfunction [9, 15].

Although the initiating antigen remains unknown, current evidence suggests that chronic antigenic stimulation in genetically susceptible individuals triggers persistent immune activation. Antigen-presenting cells, including dendritic cells and macrophages, activate naïve $CD4^+$ T lymphocytes, leading to differentiation into specialized T-cell subsets that orchestrate the inflammatory response. Unlike classical autoimmune diseases dominated by T helper 1 (Th1) or T helper 17 (Th17) immunity, IgG4-RD demonstrates a distinctive immune profile characterized by expansion of T helper 2 (Th2) cells, regulatory T cells (Tregs), T follicular helper (Tfh) cells, T peripheral helper (Tph) cells, and cytotoxic $CD4^+$ T lymphocytes ($CD4^+$ CTLs), all of which contribute to disease progression through complementary immunologic pathways [10, 15].

B lymphocytes play a central role in disease pathogenesis. Following antigenic stimulation, activated B cells undergo differentiation into plasmablasts and plasma cells that

produce IgG4 antibodies. Circulating plasmablasts correlate closely with disease activity, the extent of organ involvement, and the likelihood of relapse, making them more reliable indicators of active disease than serum IgG4 concentrations alone. The pivotal role of B cells is further supported by the remarkable clinical efficacy of rituximab, an anti-CD20 monoclonal antibody that induces rapid depletion of B cells and results in clinical remission in many patients with refractory or relapsing disease [1, 13, 16].

T follicular helper cells are essential mediators of B-cell maturation and immunoglobulin class switching within germinal centers. Through the secretion of interleukin (IL)-4 and IL-21, these cells promote differentiation of B lymphocytes into IgG4-producing plasma cells and facilitate the expansion of plasmablast populations. In parallel, T peripheral helper cells provide additional B-cell help within inflamed tissues, thereby sustaining local antibody production and chronic inflammation. The expansion of these T-cell populations has emerged as a hallmark of active IgG4-RD and represents an important link between cellular immunity and humoral immune responses [12, 15]

Regulatory T cells, which normally function to maintain immune tolerance and suppress excessive inflammation, appear to exhibit paradoxical activity in IgG4-RD. While these cells produce anti-inflammatory cytokines such as IL-10 that favor immunoglobulin class switching toward IgG4, they also secrete transforming growth factor-beta (TGF-β), a potent profibrotic cytokine that stimulates fibroblast proliferation, extracellular matrix deposition, and collagen synthesis. Consequently, regulatory T cells may simultaneously limit acute inflammation while promoting the progressive fibrosis that characterizes advanced disease [10, 14, 15].

One of the most significant discoveries in recent years has been the identification of cytotoxic $CD4^+$ T lymphocytes as major drivers of tissue injury. These cells infiltrate affected organs and produce profibrotic and proinflammatory mediators, including interferon-γ, interleukin-1β, transforming growth factor-beta, perforin, and granzyme B. Their interaction with activated B cells, macrophages, and fibroblasts perpetuates chronic inflammation and accelerates tissue remodeling. The abundance of $CD4^+$ CTLs within affected tissues correlates with disease severity and has become a defining immunologic feature of IgG4-RD [13, 16].

Macrophages also contribute substantially to disease progression. Polarization toward alternatively activated M2 macrophages promotes secretion of profibrotic cytokines and growth factors, including TGF-β, platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF). These mediators stimulate fibroblast activation, angiogenesis, and extracellular matrix production, thereby facilitating the development of dense collagen deposition and storiform fibrosis. Persistent activation of fibroblasts ultimately results in irreversible architectural distortion and progressive organ dysfunction if treatment is delayed [10, 12, 15].

Although serum IgG4 concentrations are frequently elevated, increasing evidence suggests that IgG4 antibodies themselves are unlikely to be the principal pathogenic mediators of tissue injury. IgG4 possesses unique biological properties, including limited complement activation and the ability to undergo Fab-arm exchange, producing functionally monovalent antibodies with relatively weak inflammatory potential. These characteristics suggest that elevated IgG4 may represent a secondary immunologic response to chronic antigenic stimulation rather than the primary cause of tissue damage. Instead, the pathogenic process appears to be driven predominantly by cellular immune mechanisms involving activated B cells, plasmablasts, pathogenic T-cell subsets, and fibroblasts [9, 14].

Collectively, current evidence supports an integrated pathogenic model in which genetic susceptibility and environmental triggers initiate persistent immune activation, leading to coordinated interactions among antigen-presenting cells, B lymphocytes, plasmablasts, T-cell subsets, macrophages, and fibroblasts. These interactions promote cytokine-mediated inflammation, progressive extracellular matrix deposition, storiform fibrosis, and the development of tumefactive lesions that characterize IgG4-RD. A more comprehensive understanding of these immunologic pathways has not only improved diagnostic accuracy but has also facilitated the development of targeted therapies aimed at interrupting disease progression before irreversible organ fibrosis occurs [9, 16].

Histopathology

Histopathological examination remains the diagnostic cornerstone of IgG4-related disease (IgG4-RD) and is considered the most reliable method for confirming the diagnosis when interpreted alongside the clinical, serologic, and radiologic findings [14, 18]. Although elevated serum IgG4 concentrations and characteristic imaging abnormalities may support clinical suspicion, neither is sufficiently sensitive nor specific to establish the diagnosis independently. Tissue biopsy therefore plays a pivotal role in differentiating IgG4-RD from malignancies, infections, vasculitides, and other inflammatory disorders that frequently present with similar clinical and radiographic features [14, 16, 18].

The histopathological diagnosis of IgG4-RD is based on three characteristic morphological features: dense lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis. These features are regarded as the histopathological hallmarks of the disease, although their relative prominence may vary according to the organ involved and the stage of disease progression [15, 18].

Dense lymphoplasmacytic infiltration represents the earliest and most consistent microscopic finding. The inflammatory infiltrate consists predominantly of mature lymphocytes and plasma cells distributed throughout the affected tissue, often accompanied by scattered eosinophils. Plasma cells demonstrating strong immunohistochemical staining for IgG4 are markedly increased, reflecting the characteristic immune response associated with the disease. Nevertheless, increased numbers of IgG4-positive plasma cells alone are insufficient for diagnosis because similar findings may occur in several inflammatory, infectious, and neoplastic conditions. Consequently, immunohistochemical findings should always be interpreted within the broader histopathological and clinical context [15, 17, 19].

Storiform fibrosis is regarded as one of the most distinctive pathological features of IgG4-RD. Histologically, collagen bundles are arranged in an irregular whorled or cartwheel-like configuration surrounding inflammatory cells and spindle-shaped fibroblasts, producing the characteristic "storiform" appearance. This unique architectural pattern reflects chronic fibroblast activation and excessive

extracellular matrix deposition mediated by profibrotic cytokines, particularly transforming growth factor-beta (TGF-β). Storiform fibrosis is especially prominent in the pancreas, kidneys, retroperitoneum, salivary glands, and orbital tissues but may be less conspicuous in lymph nodes and certain other organs [14, 18].

Obliterative phlebitis, the third histopathological hallmark, is characterized by dense inflammatory infiltration and concentric fibrosis involving the walls of medium-sized and small veins, resulting in partial or complete obliteration of the vascular lumen. Arteries are generally spared or only minimally affected, a feature that helps distinguish IgG4-RD from systemic vasculitides. Although obliterative phlebitis is highly characteristic of IgG4-RD, it may not be observed in every biopsy specimen, particularly when tissue samples are small or obtained from organs in which this feature is less frequently encountered [15, 18].

Eosinophilic infiltration is another supportive histopathological finding observed in a substantial proportion of patients. The presence of eosinophils is consistent with activation of type 2 immune pathways and correlates with the increased prevalence of allergic disorders, peripheral eosinophilia, and elevated serum IgE concentrations reported in many patients with IgG4-RD. However, eosinophilic infiltration is typically mild to moderate and should not be considered a defining diagnostic feature [15, 17].

Immunohistochemical staining plays a crucial role in confirming the diagnosis by demonstrating increased numbers of IgG4-positive plasma cells within affected tissues.

Current consensus recommendations emphasize that both the absolute number of IgG4-positive plasma cells per high-power field and the ratio of IgG4-positive to total IgG-positive plasma cells should be assessed. An IgG4+/IgG+ plasma cell ratio greater than 40% is generally considered supportive of the diagnosis, although the diagnostic thresholds for absolute plasma cell counts differ among organs because normal tissue-specific plasma cell populations vary considerably [16, 19].

Histopathological findings also provide valuable information regarding disease stage. Early lesions are characterized predominantly by active lymphoplasmacytic inflammation with relatively limited fibrosis, whereas long-standing disease demonstrates extensive collagen deposition, tissue remodeling, and irreversible organ fibrosis. Recognition of these temporal changes has important therapeutic implications because patients with predominantly inflammatory lesions generally respond more favorably to immunosuppressive therapy than those with advanced fibrotic disease [14, 18].

Despite its diagnostic importance, histopathological interpretation requires considerable expertise. Increased numbers of IgG4-positive plasma cells have been reported in several conditions, including multicentric Castleman disease, Rosai-Dorfman disease, granulomatosis with polyangiitis, inflammatory bowel disease, chronic infections, and certain malignancies. Consequently, the diagnosis of IgG4-RD should never be based solely on immunohistochemical staining but rather on the combined assessment of clinical presentation, radiologic findings, serologic investigations, and the characteristic histopathological triad. [15, 19] The histopathological characteristics are summarized in table 2 below;

Table 2: Characteristic Histopathological Features of IgG4-Related Disease

Histopathological feature	Microscopic characteristics	Diagnostic significance
Dense lymphoplasmacytic infiltrate	Abundant mature lymphocytes and plasma cells with scattered eosinophils	Essential diagnostic feature; reflects active immune-mediated inflammation
Storiform fibrosis	Whorled ("cartwheel") arrangement of collagen fibers surrounding inflammatory cells and fibroblasts	One of the most characteristic histopathological hallmarks of IgG4-RD
Obliterative phlebitis	Dense inflammatory infiltrate and fibrosis causing partial or complete venous lumen obliteration	Highly characteristic finding that helps distinguish IgG4-RD from many mimicking disorders
Increased IgG4-positive plasma cells	Elevated IgG4-positive plasma cell count with an IgG4+/IgG+ plasma cell ratio generally >40%	Supports the diagnosis when interpreted with histological and clinical findings
Mild to moderate eosinophilic infiltration	Variable tissue eosinophilia accompanying lymphoplasmacytic inflammation	Supportive but nonspecific feature associated with type 2 immune responses

Clinical Manifestations

IgG4-related disease (IgG4-RD) is a heterogeneous multisystem fibroinflammatory disorder capable of affecting virtually every organ system. Clinical manifestations vary considerably depending on the anatomical site involved, the extent of fibroinflammatory changes, and the stage of disease progression. Patients may present with isolated organ involvement or synchronous disease affecting multiple organs, with the latter occurring in approximately 60–90% of patients during the disease course [9, 14, 18]. The onset is generally insidious, and constitutional symptoms such as fever, night sweats, and significant weight loss are relatively uncommon when compared with infectious, malignant, or systemic autoimmune diseases. Instead, patients typically present with painless enlargement of affected organs, tumefactive lesions, progressive fibrosis, or organ dysfunction secondary to chronic inflammatory infiltration [9, 15].

Pancreatobiliary Manifestations

The pancreas represents one of the most frequently affected organs in IgG4-RD, with type 1 autoimmune pancreatitis (AIP) recognized as its prototypical manifestation [15, 18, 20]. Patients commonly present with painless obstructive jaundice, diffuse pancreatic enlargement, abdominal discomfort, weight loss, new-onset diabetes mellitus, or recurrent episodes of pancreatitis. Radiologic imaging frequently demonstrates diffuse enlargement of the pancreas, delayed enhancement, narrowing of the main pancreatic duct, and the characteristic "sausage-shaped" appearance. Because these findings often mimic pancreatic

adenocarcinoma, careful clinicopathologic correlation is essential to avoid unnecessary pancreatic resection [18, 20].

IgG4-related sclerosing cholangitis frequently coexists with autoimmune pancreatitis and typically manifests with obstructive jaundice, cholestatic liver enzyme abnormalities, pruritus, or recurrent cholangitis. The disease may closely resemble primary sclerosing cholangitis or cholangiocarcinoma, making histopathological evaluation and multidisciplinary assessment essential for accurate diagnosis [15, 20].

Salivary and Lacrimal Gland Manifestations

Head and neck involvement is among the most common clinical presentations of IgG4-RD. Patients frequently develop painless bilateral enlargement of the submandibular, parotid, and lacrimal glands, resulting in facial swelling, xerostomia, xerophthalmia, or orbital fullness [9, 18]. Unlike primary Sjögren syndrome, severe glandular dysfunction is less prominent during the early stages of IgG4-RD, while persistent gland enlargement and tumefactive lesions are more characteristic. Mikulicz disease, previously considered a subtype of Sjögren syndrome, is now recognized as part of the spectrum of IgG4-RD because of its characteristic histopathologic and immunologic features [14, 18].

Orbital Manifestations

Orbital disease may involve the lacrimal glands, extraocular muscles, orbital fat, infraorbital nerves, or trigeminal branches. Patients commonly present with painless orbital swelling, proptosis, diplopia, eyelid edema, blurred vision, or restricted extraocular movements [15, 18]. Chronic inflammation may result in compressive optic neuropathy or irreversible visual impairment if left untreated. Radiologic imaging often demonstrates bilateral lacrimal gland enlargement and diffuse orbital soft tissue infiltration.

Renal Manifestations

Renal involvement most commonly manifests as IgG4-related tubulointerstitial nephritis, although membranous nephropathy, renal cortical nodules, renal pelvic lesions, and retroperitoneal fibrosis-associated obstructive nephropathy may also occur [15, 19]. Patients may present with asymptomatic renal dysfunction, proteinuria, microscopic hematuria, sterile pyuria, or progressive chronic kidney disease. Imaging studies frequently reveal multiple low-attenuation cortical lesions, diffuse renal enlargement, or thickening of the renal pelvis. Early recognition is essential because prompt immunosuppressive therapy may prevent irreversible renal fibrosis [18, 19].

Pulmonary Manifestations

Thoracic involvement exhibits considerable radiologic variability and may affect the lung parenchyma, pleura, mediastinum, or hilar lymph nodes. Clinical manifestations include chronic cough, exertional dyspnea, chest discomfort, wheezing, or asymptomatic pulmonary nodules detected incidentally during imaging [15, 18]. High-resolution computed tomography may demonstrate pulmonary nodules, ground-glass opacities, bronchovascular thickening, interstitial infiltrates, pleural thickening, or mediastinal lymphadenopathy. Because these findings overlap with pulmonary malignancy, sarcoidosis, vasculitis, and interstitial lung disease, histologic confirmation is frequently required [18].

Retroperitoneal and Vascular Manifestations

Retroperitoneal fibrosis represents one of the hallmark manifestations of IgG4-RD and frequently involves the abdominal aorta, iliac vessels, and ureters. Progressive fibroinflammatory tissue may encase the ureters, resulting in hydronephrosis, obstructive uropathy, and progressive renal insufficiency [15, 18]. Large-vessel involvement includes IgG4-related aortitis, peri-aortitis, and inflammatory aneurysm formation involving the thoracic or abdominal aorta. Patients may remain asymptomatic or present with abdominal pain, back pain, constitutional symptoms, or vascular complications requiring urgent intervention [18, 20].

Neurological Manifestations

Neurological involvement is relatively uncommon but may produce significant morbidity. Hypertrophic pachymeningitis represents the most characteristic neurological manifestation and commonly presents with chronic headache, cranial neuropathies, visual disturbances, hearing impairment, seizures, or focal neurological deficits resulting from inflammatory thickening of the dura mater [15, 18]. Additional manifestations include hypophysitis, orbital apex syndrome, peripheral neuropathy, hypoglossal nerve involvement, and inflammatory pseudotumors affecting the central nervous system. Because these presentations often mimic neoplastic, infectious, or granulomatous disorders, histopathological confirmation is frequently necessary [15].

Endocrine Manifestations

The endocrine organs may also be affected, particularly the thyroid and pituitary glands. IgG4-related thyroid disease encompasses Riedel thyroiditis and a subset of Hashimoto thyroiditis characterized by extensive fibrosis and abundant IgG4-positive plasma cell infiltration [15, 18]. Pituitary involvement may result in hypophysitis, presenting with headache, hypopituitarism, diabetes insipidus, fatigue, and visual impairment secondary to pituitary enlargement.

Lymph Node and Other Organ Manifestations

Lymphadenopathy is frequently encountered in IgG4-RD and may occur either as isolated disease or in association with multiorgan involvement. Enlarged lymph nodes are generally painless and may involve cervical, mediastinal, hilar, abdominal, or inguinal nodal stations [18, 19]. Less commonly affected organs include the skin, breast, prostate, pericardium, mesentery, sinonasal cavity, middle ear, and gastrointestinal tract. The wide spectrum of organ involvement contributes substantially to delayed diagnosis because the disease frequently mimics malignancy, chronic infection, or other immune-mediated inflammatory disorders.

Overall, the clinical presentation of IgG4-RD is determined by the distribution and severity of fibroinflammatory lesions rather than by systemic inflammatory activity. Consequently, maintaining a high index of clinical suspicion is essential, particularly in middle-aged or older adults presenting with unexplained tumefactive lesions, multiorgan disease, elevated serum IgG4 concentrations, or characteristic histopathological findings [14, 20]. The clinical presentations are summarized in the table 3 below;

Table 3: Clinical Presentations in Various Organs

Organ system	Common clinical manifestations	Major complications
Pancreas	Autoimmune pancreatitis, abdominal pain, obstructive jaundice	Pancreatic insufficiency, diabetes mellitus
Biliary tract	IgG4-related sclerosing cholangitis, cholestatic jaundice	Biliary obstruction, recurrent cholangitis
Salivary/lacrimal glands	Painless gland enlargement, xerostomia, xerophthalmia	Chronic gland fibrosis
Orbit	Proptosis, diplopia, orbital swelling	Optic nerve compression, vision loss
Kidney	Tubulointerstitial nephritis, proteinuria, renal dysfunction	Chronic kidney disease
Lung	Pulmonary nodules, cough, dyspnea	Progressive pulmonary fibrosis
Retroperitoneum	Retroperitoneal fibrosis, ureteric obstruction	Hydronephrosis, renal failure
Aorta	Aortitis, peri-aortitis, aneurysm	Aortic aneurysm, vascular rupture
Central nervous system	Hypertrophic pachymeningitis, hypophysitis, cranial neuropathies	Permanent neurological deficits
Thyroid/Pituitary	Riedel thyroiditis, hypophysitis	Endocrine dysfunction

Diagnosis

The diagnosis of IgG4-related disease (IgG4-RD) remains challenging because of its heterogeneous clinical manifestations, variable organ involvement, and remarkable ability to mimic malignant, infectious, and autoimmune disorders. No single clinical feature, laboratory investigation, imaging modality, or histopathological finding is sufficiently sensitive or specific to establish the diagnosis independently. Instead, diagnosis requires a comprehensive multidisciplinary approach that integrates clinical presentation, serologic evaluation, radiologic findings, histopathological examination, immunohistochemical analysis, and careful exclusion of alternative diagnoses [7, 14, 21].

A high index of clinical suspicion is essential, particularly in middle-aged and older adults presenting with unexplained tumefactive lesions, painless enlargement of exocrine glands, autoimmune pancreatitis, retroperitoneal fibrosis, tubulointerstitial nephritis, orbital inflammatory disease, or multisystem fibroinflammatory lesions. The simultaneous or sequential involvement of multiple organs should further raise suspicion for IgG4-RD, especially when imaging demonstrates characteristic inflammatory masses or diffuse organ enlargement and when patients exhibit an excellent response to glucocorticoid therapy [14, 19].

Laboratory Evaluation

Laboratory investigations provide supportive rather than diagnostic evidence. Elevated serum IgG4 concentrations are among the most recognized laboratory abnormalities and are observed in approximately 60–70% of patients with biopsy-confirmed IgG4-RD [15, 18, 20]. Nevertheless, normal serum IgG4 concentrations do not exclude the diagnosis because a substantial proportion of patients have values within the normal reference range despite active disease. Conversely, elevated serum IgG4 levels are not specific and may also occur in allergic disorders, chronic infections, primary sclerosing cholangitis, multicentric Castleman disease, ANCA-associated vasculitis, rheumatoid arthritis, systemic lupus erythematosus, and several malignancies [15, 18].

Additional laboratory abnormalities may include elevated total IgG concentrations, peripheral eosinophilia, increased serum IgE levels, hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR), and mildly increased C-reactive protein (CRP) concentrations, although inflammatory markers are frequently normal or only minimally elevated. Hypocomplementemia may occur, particularly in patients with IgG4-related kidney disease, and is associated with more extensive systemic involvement [18, 20].

Recent studies have demonstrated that circulating plasmablasts correlate more closely with disease activity than serum IgG4 concentrations. Flow cytometric quantification of plasmablast populations has therefore emerged as a promising biomarker for monitoring disease activity, assessing treatment response, and detecting relapse, although its routine clinical use remains limited to specialized centers [13, 16].

Imaging Evaluation

Radiologic imaging plays a crucial role in identifying organ involvement, determining disease extent, guiding biopsy, and monitoring treatment response. Computed tomography (CT) and magnetic resonance imaging (MRI) are commonly employed to evaluate organ enlargement, inflammatory masses, vascular involvement, and retroperitoneal fibrosis. Organ-specific imaging characteristics often provide valuable diagnostic clues but should always be interpreted alongside clinical and pathological findings [15, 18].

In autoimmune pancreatitis, CT and MRI frequently demonstrate diffuse pancreatic enlargement with delayed enhancement and narrowing of the main pancreatic duct, producing the characteristic "sausage-shaped" pancreas. Magnetic resonance cholangiopancreatography (MRCP) is particularly useful for assessing associated IgG4-related sclerosing cholangitis and biliary strictures. High-resolution chest CT is valuable for evaluating pulmonary involvement, whereas contrast-enhanced CT and MRI are preferred for assessing renal lesions, orbital disease, retroperitoneal fibrosis, and large-vessel inflammation [18, 20].

Fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) has emerged as a useful imaging modality for detecting occult organ involvement, identifying appropriate biopsy sites, evaluating disease distribution, and monitoring therapeutic response. Because PET/CT detects metabolically active inflammatory lesions throughout the body, it is particularly valuable in patients with suspected multisystem disease [18, 20].

Histopathological Evaluation

Histopathological examination remains the gold standard for confirming IgG4-RD whenever tissue can be safely

obtained. Diagnosis relies on identifying the characteristic histopathological triad of dense lymphoplasmacytic infiltrates, storiform fibrosis, and obliterative phlebitis together with increased numbers of IgG4-positive plasma cells demonstrated by immunohistochemistry [14, 19].

Immunohistochemical analysis should include both the absolute number of IgG4-positive plasma cells per high-power field and the ratio of IgG4-positive to total IgG-positive plasma cells. Although an IgG4+/IgG+ plasma cell ratio exceeding 40% is generally considered supportive of the diagnosis, organ-specific thresholds should be applied because normal plasma cell density varies among different tissues. Importantly, increased IgG4-positive plasma cells alone are insufficient for diagnosis and should always be interpreted within the context of the characteristic histopathological architecture and clinical presentation [16, 19].

2019 ACR/EULAR Classification Criteria

The 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria represent the most widely accepted framework for the classification of IgG4-RD in research settings [7]. The criteria utilize a three-step approach consisting of entry criteria, exclusion criteria, and weighted inclusion criteria encompassing clinical findings, serologic abnormalities, imaging characteristics, and histopathological features. A cumulative score meeting the established threshold supports classification as IgG4-RD after exclusion of alternative diagnoses. Although these criteria were developed primarily for research classification rather than routine clinical diagnosis, they have substantially improved diagnostic consistency and facilitate standardized patient selection in clinical studies [7].

Ultimately, the diagnosis of IgG4-RD should be based on the integration of clinical assessment, laboratory investigations, imaging studies, histopathological findings, and multidisciplinary clinical judgment rather than reliance on any single diagnostic test. Early recognition and prompt diagnosis remain essential because timely initiation of therapy may prevent irreversible fibrosis and permanent organ dysfunction. The diagnostic modalities are summarized in table 4 below;

Table 4: Diagnostic Modalities in IgG4-Related Disease

Diagnostic modality	Principal findings	Clinical significance
Clinical assessment	Multiorgan fibroinflammatory disease, tumefactive lesions, painless gland enlargement	Raises initial clinical suspicion
Serum investigations	Elevated serum IgG4, hypergammaglobulinemia, eosinophilia, elevated IgE, hypocomplementemia	Supportive but not diagnostic
CT/MRI	Organ enlargement, inflammatory masses, retroperitoneal fibrosis, vascular involvement	Defines disease extent and guides biopsy
MRCP	Pancreatic duct narrowing, biliary strictures	Essential in pancreatobiliary disease
18F-FDG PET/CT	Multiorgan metabolic activity and occult disease	Detects systemic involvement and monitors treatment response
Histopathology	Dense lymphoplasmacytic infiltrates, storiform fibrosis, obliterative phlebitis	Diagnostic cornerstone
Immunohistochemistry	Increased IgG4-positive plasma cells and elevated IgG4+/IgG+ ratio	Confirms tissue involvement when interpreted with histology
2019 ACR/EULAR criteria	Composite classification incorporating clinical, serologic, imaging, and pathological findings	Standardized classification framework for research and clinical support

Differential Diagnosis

The diagnosis of IgG4-related disease (IgG4-RD) requires careful exclusion of numerous disorders that share similar clinical, radiologic, serologic, and histopathological features. Because the disease frequently presents as tumefactive lesions, diffuse organ enlargement, or progressive fibrosis, it is commonly mistaken for malignancy, chronic infection, granulomatous disease, or other systemic autoimmune disorders. Failure to recognize these mimicking conditions may result in delayed diagnosis, inappropriate immunosuppressive therapy, or unnecessary surgical intervention. Consequently, a comprehensive differential diagnostic evaluation is an essential component of the diagnostic work-up and should integrate clinical findings, laboratory investigations, imaging studies, histopathology, immunohistochemistry, and, when appropriate, microbiological and molecular testing [7, 15, 20].

One of the most important differential diagnoses is malignancy, particularly pancreatic adenocarcinoma, cholangiocarcinoma, lymphoma, salivary gland tumors, renal cell carcinoma, pulmonary malignancies, and metastatic disease. Autoimmune pancreatitis, the pancreatic manifestation of IgG4-RD, frequently presents with painless obstructive jaundice, pancreatic enlargement, weight loss, and elevated serum carbohydrate antigen 19-9 (CA 19-9), closely resembling pancreatic cancer. Similarly, IgG4-related sclerosing cholangitis may mimic cholangiocarcinoma or primary sclerosing cholangitis because of biliary strictures and obstructive jaundice. Imaging findings alone are often insufficient to distinguish these entities, making tissue biopsy and histopathological examination indispensable in patients with suspected malignancy [15, 18, 20].

Sjögren syndrome: represents another important consideration, particularly in patients presenting with bilateral enlargement of the salivary and lacrimal glands. Although both diseases may manifest with xerostomia and xerophthalmia, glandular enlargement in IgG4-RD is typically persistent, painless, and associated with dense IgG4-positive plasma cell infiltration and storiform fibrosis. In contrast, Sjögren syndrome is characterized by autoimmune destruction of exocrine glands, positive anti-SSA/Ro and anti-SSB/La antibodies, and prominent lymphoepithelial lesions without the characteristic histopathological triad of IgG4-RD [16, 18].

ANCA-associated vasculitides: particularly granulomatosis with polyangiitis, may also resemble IgG4-RD because both conditions can involve the upper respiratory tract, lungs, kidneys, orbit, and cranial structures. However, granulomatosis with polyangiitis is characterized by necrotizing granulomatous inflammation, small-vessel vasculitis, and positive anti-neutrophil cytoplasmic antibodies (ANCA) in many patients, whereas IgG4-RD typically demonstrates dense lymphoplasmacytic infiltrates, storiform fibrosis, obliterative phlebitis, and abundant IgG4-positive plasma cells without granulomatous inflammation [15, 18].

Sarcoidosis: should likewise be considered in patients presenting with lymphadenopathy, pulmonary infiltrates, orbital disease, or multiorgan involvement. Although both disorders may affect numerous organs simultaneously, sarcoidosis is characterized histologically by well-formed non-caseating granulomas rather than lymphoplasmacytic inflammation and storiform fibrosis. Elevated serum angiotensin-converting enzyme (ACE) concentrations and typical bilateral hilar lymphadenopathy may further support the diagnosis of sarcoidosis, although neither finding is entirely specific [18, 20].

Multicentric Castleman disease: frequently enters the differential diagnosis because it may present with generalized lymphadenopathy, constitutional symptoms, elevated serum IgG4 concentrations, and abundant IgG4-positive plasma cells within lymph nodes. Nevertheless, Castleman disease typically exhibits marked systemic inflammation, significantly elevated interleukin-6 concentrations, thrombocytosis, anemia, hypoalbuminemia, and characteristic lymph node histopathology that differs substantially from IgG4-RD. Furthermore, storiform fibrosis and obliterative phlebitis are generally absent in Castleman disease [16, 19].

Several infectious diseases, including tuberculosis, fungal infections, syphilis, and chronic bacterial infections, may produce inflammatory masses, lymphadenopathy, or organ enlargement resembling IgG4-RD. These conditions should be excluded through appropriate microbiological investigations, culture, serologic testing, molecular diagnostics, and histopathological examination before initiating immunosuppressive therapy. Failure to recognize underlying infection may result in disease progression and serious treatment-related complications [18, 20].

Other immune-mediated disorders, including systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, Rosai-Dorfman disease, Erdheim-Chester disease, and idiopathic retroperitoneal fibrosis, may also exhibit overlapping clinical or pathological features. Comprehensive clinical assessment, disease-specific serologic testing, imaging findings, and careful histopathological interpretation are therefore essential to establish the correct diagnosis [15, 20].

Ultimately, the distinguishing feature of IgG4-RD is not any single laboratory or imaging abnormality but rather the combination of characteristic clinical presentation, multiorgan fibroinflammatory involvement, elevated serum IgG4 in many patients, dense lymphoplasmacytic infiltrates, storiform fibrosis, obliterative phlebitis, and increased tissue IgG4-positive plasma cells. Integration of these findings through multidisciplinary collaboration among rheumatologists, gastroenterologists, pathologists, radiologists, surgeons, nephrologists, neurologists, and other specialists remains the most reliable strategy for differentiating IgG4-RD from its numerous clinical mimics. [7, 14, 20] The major differential diagnoses are summarized in table 5 below;

Table 5: Major Differential Diagnoses of IgG4-Related Disease

Disease	Clinical overlap	Distinguishing features
Pancreatic adenocarcinoma	Pancreatic enlargement, obstructive jaundice, weight loss	Malignant cytology, invasive tumor, absence of storiform fibrosis and abundant IgG4-positive plasma cells
Cholangiocarcinoma	Biliary strictures, jaundice	Malignant biliary epithelium, absence of characteristic IgG4-RD histopathology
Primary Sjögren syndrome	Xerostomia, xerophthalmia, salivary gland enlargement	Anti-SSA/Ro or anti-SSB/La positivity, lymphoepithelial lesions, lack of storiform fibrosis
Granulomatosis with polyangiitis	Orbital disease, pulmonary and renal involvement	Positive ANCA, necrotizing granulomatous vasculitis
Sarcoidosis	Multiorgan disease, pulmonary involvement, lymphadenopathy	Non-caseating granulomas, elevated ACE levels, bilateral hilar lymphadenopathy
Multicentric Castleman disease	Generalized lymphadenopathy, elevated serum IgG4	IL-6–driven systemic inflammation, characteristic lymph node pathology
Tuberculosis	Mass lesions, lymphadenopathy, constitutional symptoms	Positive microbiological studies, caseating granulomas
Rosai-Dorfman disease	Lymphadenopathy, extranodal masses	S100-positive histiocytes with emperipolesis
Idiopathic retroperitoneal fibrosis	Retroperitoneal fibrosis, ureteric obstruction	Lacks characteristic IgG4-rich lymphoplasmacytic infiltrates in many cases
Lymphoma	Mass lesions, constitutional symptoms, lymphadenopathy	Monoclonal lymphoid proliferation confirmed by immunophenotyping and histopathology

Treatment and Management

The management of IgG4-related disease (IgG4-RD) aims to induce disease remission, preserve organ function, prevent irreversible fibrosis, minimize disease relapse, and reduce treatment-related adverse effects. Because IgG4-RD is a chronic immune-mediated fibroinflammatory disorder with highly variable organ involvement, treatment should be individualized according to the organs affected, disease severity, extent of fibrosis, comorbid conditions, and the risk of permanent organ damage. Early diagnosis and timely initiation of therapy are essential because established fibrosis responds less favorably to immunosuppressive treatment than active inflammatory lesions [9, 15, 20].

A multidisciplinary approach involving rheumatologists, gastroenterologists, nephrologists, pulmonologists, neurologists, ophthalmologists, pathologists, radiologists, surgeons, and primary care physicians is often required to optimize patient outcomes. Management should address both active disease and long-term surveillance because relapse remains common, particularly among patients with multiorgan involvement, elevated serum IgG4 concentrations, or incomplete remission following initial therapy [15, 20].

Glucocorticoids

Glucocorticoids remain the cornerstone of initial treatment for most patients with active IgG4-RD and are highly effective in inducing clinical remission. Most patients demonstrate rapid improvement in constitutional symptoms, reduction in organ swelling, improvement in laboratory abnormalities, and regression of inflammatory lesions within several weeks of treatment initiation [15, 18, 20].

Prednisone or prednisolone is generally recommended as first-line therapy for patients with symptomatic disease, significant organ involvement, or progressive fibroinflammatory lesions. Initial treatment is commonly followed by gradual tapering over several months according to the patient's clinical response, laboratory parameters, and imaging findings. Although many patients achieve remission with corticosteroid therapy, disease relapse after dose reduction or discontinuation remains a significant clinical challenge, emphasizing the need for careful long-term follow-up [15, 20].

Conventional Immunosuppressive Therapy

Conventional immunosuppressive agents are primarily used as glucocorticoid-sparing therapies in patients with relapsing disease, corticosteroid dependence, or contraindications to prolonged steroid use. Commonly utilized agents include azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclophosphamide, and, less frequently, leflunomide. Although these medications have demonstrated variable clinical benefit in observational studies, high-quality randomized controlled trials remain limited, and their efficacy appears less consistent than that of B-cell-depleting therapy [15, 19].

Selection of immunosuppressive therapy should be individualized according to disease severity, organ involvement, patient comorbidities, reproductive considerations, and potential adverse effects. Regular monitoring of hematologic, hepatic, and renal function is essential throughout treatment to minimize drug-related toxicity [18, 20].

Rituximab and B-cell-Targeted Therapy

The recognition of B lymphocytes and plasmablasts as central mediators of disease pathogenesis has transformed the therapeutic landscape of IgG4-RD. Rituximab, a chimeric monoclonal antibody targeting the CD20 antigen expressed on B lymphocytes, has demonstrated remarkable efficacy in inducing remission, reducing circulating plasmablast populations, improving organ function, and decreasing relapse rates in patients with refractory, relapsing, or glucocorticoid-dependent disease [11, 16, 20].

Clinical improvement following rituximab therapy often occurs within weeks and is accompanied by reductions in serum IgG4 concentrations and inflammatory activity. Rituximab is increasingly considered a preferred therapeutic option for patients with multiorgan disease, recurrent relapses, contraindications to prolonged corticosteroid therapy, or organ-threatening manifestations involving the kidneys, retroperitoneum, central nervous system, orbit, or large vessels [16, 20].

Several emerging biologic therapies targeting B-cell maturation, plasmablast survival, cytokine signaling, and T-cell activation are currently under investigation. Although preliminary studies have demonstrated encouraging results, additional randomized clinical trials are required before these agents can be incorporated into routine clinical practice [18, 20].

Organ-Specific Management

Management strategies should be tailored according to the organs affected and the severity of disease. Patients with autoimmune pancreatitis and IgG4-related sclerosing cholangitis often require close collaboration between gastroenterologists, hepatobiliary surgeons, and interventional endoscopists to relieve biliary obstruction while avoiding unnecessary surgical intervention. Renal involvement requires careful monitoring of kidney function, urinary protein excretion, and imaging findings to prevent irreversible chronic kidney disease. Retroperitoneal fibrosis may necessitate ureteric stenting or surgical decompression in addition to immunosuppressive therapy when significant urinary tract obstruction is present [15, 20].

Patients with orbital disease, hypertrophic pachymeningitis, pituitary involvement, or aortitis require prompt specialist assessment because delayed treatment may result in irreversible neurological deficits, endocrine dysfunction, vision loss, vascular complications, or permanent organ damage. Early intervention is particularly important in these patients because inflammatory lesions generally respond more favorably to treatment than advanced fibrotic disease [15, 20].

Monitoring and Follow-up

Long-term clinical follow-up is essential because relapse remains common even after successful remission induction. Disease monitoring should include periodic clinical assessment, laboratory investigations, imaging studies, and evaluation of organ function according to the pattern of disease involvement. Although serum IgG4 concentrations may decline following treatment, they do not consistently correlate with disease activity and should not be used as the sole marker of therapeutic response. Increasing evidence suggests that circulating plasmablast levels may provide a more reliable indicator of disease activity and relapse, although this investigation is not universally available [11, 16].

Treatment-related complications, including glucocorticoid-induced osteoporosis, diabetes mellitus, hypertension, opportunistic infections, and immunosuppressant toxicity, should be actively monitored throughout long-term follow-up. Preventive strategies, including vaccination, bone health assessment, cardiovascular risk modification, and infection prophylaxis when appropriate, should be incorporated into routine patient care [18, 20].

Overall, the successful management of IgG4-RD requires early recognition, individualized treatment, multidisciplinary collaboration, and continuous long-term surveillance. Advances in understanding disease immunopathogenesis have facilitated the development of

targeted therapies, particularly B-cell-directed treatment, which has significantly improved outcomes in patients with refractory or recurrent disease. The current treatment options are summarized in table 6 below;

Table 6: Current Therapeutic Options for IgG4-Related Disease

Treatment	Clinical role	Major limitations
Glucocorticoids (prednisone/prednisolone)	First-line induction therapy for active disease	Relapse after tapering, long-term adverse effects
Azathioprine	Steroid-sparing maintenance therapy	Myelosuppression, hepatotoxicity, variable efficacy
Mycophenolate mofetil	Maintenance therapy in relapsing disease	Gastrointestinal adverse effects, infection risk
Methotrexate	Alternative steroid-sparing agent	Hepatotoxicity, bone marrow suppression
Tacrolimus	Selected refractory cases	Nephrotoxicity, neurotoxicity
Cyclophosphamide	Severe organ-threatening disease	Cytopenias, infertility, malignancy risk
Rituximab	Refractory, relapsing, multiorgan, or steroid-dependent disease	Infusion reactions, hypogammaglobulinemia, infection risk
Supportive and organ-specific interventions	Management of complications such as biliary obstruction, hydronephrosis, or endocrine dysfunction	Dependent on organ involvement and disease severity

Prognosis

The prognosis of IgG4-related disease (IgG4-RD) has improved considerably over the past two decades owing to earlier recognition, standardized classification criteria, advances in diagnostic imaging, and the introduction of targeted immunomodulatory therapies [7, 15, 20].] Most patients respond favorably to glucocorticoid therapy, particularly when treatment is initiated during the early inflammatory phase of the disease before the development of extensive fibrosis. Clinical remission is frequently accompanied by regression of organ enlargement, improvement in laboratory abnormalities, restoration of organ function, and resolution of radiologic abnormalities. Nevertheless, long-term prognosis remains highly variable and is influenced by the extent of organ involvement, disease chronicity, degree of fibrosis, and response to therapy [15, 20].

Early diagnosis is one of the most important determinants of favorable clinical outcomes. Patients treated before irreversible fibrotic remodeling develops generally experience substantial improvement and preservation of organ function. Conversely, delayed diagnosis may result in permanent structural damage involving the pancreas, kidneys, biliary tract, retroperitoneum, lungs, cardiovascular system, or central nervous system. Once advanced fibrosis has become established, immunosuppressive therapy may successfully suppress ongoing inflammation but often fails to reverse pre-existing tissue damage [15, 19].

Disease relapse remains a major challenge in the long-term management of IgG4-RD. Relapses may occur months or years after successful induction of remission and frequently involve either previously affected organs or new anatomical sites. The reported frequency of relapse varies considerably among published studies because of differences in patient populations, organ involvement, treatment protocols, and duration of follow-up. Patients with multiorgan disease, persistently elevated serum IgG4 concentrations, high circulating plasmablast levels, delayed initiation of therapy, or incomplete response to initial treatment appear to have an increased risk of disease recurrence [11, 15, 20].

Prognosis also varies according to the organs involved. Patients with isolated salivary or lacrimal gland disease generally have an excellent prognosis following appropriate therapy, whereas involvement of the pancreas, kidneys, retroperitoneum, aorta, or central nervous system may be associated with more significant morbidity because of irreversible fibrosis, vascular complications, chronic kidney disease, endocrine dysfunction, or neurological impairment [15, 20]. Large-vessel involvement, including IgG4-related aortitis and inflammatory aneurysm formation, requires close surveillance because delayed recognition may result in life-threatening vascular complications.

Long-term treatment is frequently required to maintain disease remission and prevent recurrent inflammation. Although glucocorticoids remain highly effective for remission induction, prolonged corticosteroid therapy is associated with well-recognized adverse effects, including osteoporosis, diabetes mellitus, hypertension, cataracts, opportunistic infections, and cardiovascular complications. Consequently, steroid-sparing immunosuppressive agents and B-cell-depleting therapies, particularly rituximab, have become increasingly important for patients with relapsing or glucocorticoid-dependent disease [11, 18, 20].

Overall survival among patients with IgG4-RD is generally favorable when the disease is recognized promptly and managed appropriately. However, chronic relapsing disease may substantially impair quality of life through recurrent hospitalizations, repeated imaging studies, long-term immunosuppressive therapy, progressive organ dysfunction, and treatment-related complications. Accordingly, lifelong clinical follow-up remains essential to monitor disease activity, detect relapse, assess treatment response, and identify irreversible organ damage before significant functional impairment develops [15, 20].

Discussion

IgG4-related disease (IgG4-RD) has emerged as one of the most significant advances in contemporary clinical immunology and inflammatory medicine. Since its recognition as a unified systemic fibroinflammatory disorder, considerable progress has been made in understanding its clinical spectrum, immunopathogenesis, diagnostic evaluation, and therapeutic management. Disorders that were previously regarded as isolated organ-specific diseases, including autoimmune pancreatitis, Mikulicz disease, IgG4-related sclerosing cholangitis,

Riedel thyroiditis, and retroperitoneal fibrosis, are now recognized as manifestations of a single multisystem disease process characterized by immune-mediated inflammation and progressive fibrosis [1, 7, 15].

One of the greatest challenges associated with IgG4-RD is its remarkable clinical heterogeneity. Virtually every organ system may be affected, resulting in a wide range of clinical presentations that frequently resemble malignancies, chronic infections, granulomatous disorders, vasculitides, and other autoimmune diseases. Consequently, diagnosis is often delayed, particularly in patients with isolated organ involvement or atypical clinical manifestations. Increasing awareness among clinicians across multiple specialties has improved recognition of the disease; however, IgG4-RD remains substantially underdiagnosed in many regions, highlighting the need for continued education and multidisciplinary collaboration [15, 20].

Advances in immunology have substantially improved understanding of the mechanisms underlying IgG4-RD. Earlier hypotheses focused primarily on elevated serum IgG4 concentrations and IgG4-positive plasma cell infiltration as the principal drivers of disease. More recent evidence indicates that the disease is predominantly mediated by dysregulated cellular immunity involving activated B lymphocytes, circulating plasmablasts, T follicular helper cells, regulatory T cells, cytotoxic $CD4^+$ T lymphocytes, macrophages, and fibroblasts. These complex cellular interactions promote persistent inflammation, cytokine dysregulation, and progressive extracellular matrix deposition, ultimately leading to the characteristic storiform fibrosis and organ dysfunction observed in affected tissues [16, 20]. Consequently, elevated IgG4 concentrations are now considered markers of the underlying immune response rather than the primary mediators of tissue injury.

Despite major advances in disease characterization, diagnosis remains challenging because no single laboratory investigation or imaging modality possesses adequate sensitivity and specificity to establish the diagnosis independently. Elevated serum IgG4 concentrations, although frequently observed, are neither universally present nor specific to IgG4-RD. Similarly, imaging findings often overlap with those of malignant, infectious, and inflammatory disorders. Histopathological examination therefore remains the cornerstone of diagnosis, particularly when the characteristic triad of dense lymphoplasmacytic infiltrates, storiform fibrosis, and obliterative phlebitis is identified together with increased tissue IgG4-positive plasma cells [7, 14, 19]. The introduction of the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria has improved diagnostic consistency in research settings and has facilitated more standardized patient selection for clinical studies [7].

Therapeutic management has evolved considerably with improved understanding of disease immunopathogenesis. Glucocorticoids continue to represent the standard first-line therapy for active disease because of their rapid anti-inflammatory effects and high rates of initial clinical remission. However, frequent relapse following corticosteroid tapering has emphasized the limitations of long-term steroid monotherapy. Recognition of the pivotal role of B lymphocytes in disease pathogenesis has led to the successful application of rituximab, which has demonstrated excellent efficacy in inducing remission, reducing circulating plasmablast populations, preserving organ function, and decreasing relapse rates in patients with refractory or recurrent disease [11, 16, 18].The development of additional targeted biologic therapies directed against B-cell survival pathways, cytokine signaling, and immune-cell interactions represents an important area of ongoing investigation.

Several important challenges remain. The initiating antigen responsible for disease onset has not been identified, and the precise mechanisms linking genetic susceptibility, environmental exposures, and immune dysregulation remain incompletely understood. Reliable biomarkers capable of predicting disease onset, identifying patients at increased risk of relapse, and monitoring treatment response are also lacking. Although circulating plasmablasts have emerged as promising indicators of disease activity, their clinical application remains limited by restricted availability and lack of standardized testing across institutions. [11, 16] Furthermore, high-quality randomized controlled trials evaluating long-term maintenance therapy, optimal treatment duration, and comparative effectiveness of emerging biologic agents remain relatively limited.

Another important consideration is the progressive nature of tissue fibrosis. While immunosuppressive therapy effectively controls active inflammation in many patients, established fibrosis often remains irreversible despite successful suppression of disease activity. These observations underscore the importance of early diagnosis, prompt initiation of therapy, and regular long-term follow-up to preserve organ function before irreversible structural damage occurs [15, 20].

Overall, current evidence supports a multidisciplinary approach to the diagnosis and management of IgG4-RD that integrates clinical expertise, advanced imaging, histopathology, immunology, and individualized therapeutic strategies. Continued advances in molecular immunology, precision medicine, and targeted biologic therapy are expected to further improve diagnostic accuracy and long-term clinical outcomes. Future research should focus on identifying disease-specific biomarkers, clarifying the initiating mechanisms of immune activation, refining risk stratification models, and developing personalized treatment strategies capable of preventing irreversible fibrosis while minimizing treatment-related toxicity.

Limitations

This descriptive review has several limitations that should be acknowledged. First, although the review synthesized evidence from studies published between January 2019 and June 2026, the quality of available evidence varied considerably, ranging from observational cohort studies and case series to systematic reviews and expert consensus statements. Consequently, some conclusions were derived from studies with relatively small sample sizes and heterogeneous patient populations, reflecting the rarity and clinical diversity of IgG4-related disease (IgG4-RD) [15, 20].

Second, because IgG4-RD is an uncommon multisystem disorder, many published studies have originated from specialized referral centers with extensive experience in disease diagnosis and management. This may introduce referral bias and limit the generalizability of reported clinical characteristics, treatment outcomes, and long-term prognosis to broader patient populations. Furthermore, the predominance of data from Asian, European, and North

American cohorts highlights the need for additional epidemiologic studies from underrepresented regions, including Africa, South America, and the Middle East.

Third, considerable heterogeneity exists among published studies regarding diagnostic criteria, definitions of disease activity, treatment protocols, follow-up duration, and outcome measures. Although the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria have improved standardization, differences in study methodology continue to complicate direct comparisons across investigations [7].

Finally, despite significant advances in understanding disease immunopathogenesis, important knowledge gaps remain regarding the initiating antigen, mechanisms underlying disease relapse, predictors of treatment response, and optimal long-term maintenance therapy. These limitations emphasize the continued need for well-designed multicenter prospective studies and randomized controlled trials to strengthen the evidence base supporting clinical decision-making in IgG4-RD.

Future Directions

Rapid advances in immunology and molecular medicine are expected to transform the diagnosis and management of IgG4-RD over the coming decade. Future research should prioritize identification of the initiating antigen or antigens responsible for triggering disease onset and should further clarify the complex interactions among B lymphocytes, plasmablasts, T follicular helper cells, cytotoxic $CD4^+$ T lymphocytes, macrophages, and fibroblasts that drive chronic fibroinflammatory responses. Improved understanding of these pathways may facilitate the development of highly specific targeted therapies capable of interrupting disease progression before irreversible fibrosis develops [10, 16].

The discovery of reliable biomarkers capable of facilitating early diagnosis, predicting disease relapse, monitoring treatment response, and assessing long-term prognosis remains an important research priority. Although circulating plasmablasts have demonstrated considerable promise as indicators of disease activity, additional validation is required before their widespread implementation in routine clinical practice. Advances in transcriptomics, proteomics, metabolomics, and single-cell sequencing may further improve understanding of disease heterogeneity and support the development of precision medicine approaches tailored to individual patients.

Future clinical research should also focus on large multicenter prospective cohort studies and randomized controlled trials evaluating optimal glucocorticoid tapering strategies, comparative effectiveness of steroid-sparing immunosuppressive agents, long-term safety of biologic therapies, and individualized maintenance treatment protocols. In addition, international collaborative registries should be expanded to improve understanding of disease epidemiology, ethnic variation, organ-specific phenotypes, and long-term outcomes across diverse populations.

The integration of artificial intelligence into diagnostic imaging, digital pathology, and clinical decision-support systems may further enhance early recognition of IgG4-RD and improve differentiation from malignant and other inflammatory disorders. Continued multidisciplinary collaboration among rheumatologists, gastroenterologists, nephrologists, neurologists, pulmonologists, radiologists, pathologists, and immunologists will be essential to accelerate translational research and improve patient outcomes.

Conclusions

IgG4-related disease is an increasingly recognized immune-mediated fibroinflammatory disorder characterized by multisystem organ involvement, chronic lymphoplasmacytic inflammation, and progressive tissue fibrosis. Although remarkable advances have been achieved in understanding its clinical manifestations, immunopathogenesis, diagnostic evaluation, and therapeutic management, significant challenges remain because of the disease's heterogeneous presentation and its ability to mimic numerous malignant, infectious, and autoimmune conditions. Early recognition and accurate diagnosis require careful integration of clinical findings, laboratory investigations, imaging studies, histopathological examination, and multidisciplinary clinical assessment.

Recent advances in immunology have fundamentally changed current concepts of disease pathogenesis, highlighting the central roles of B lymphocytes, plasmablasts, pathogenic T-cell subsets, macrophages, and fibroblasts in the development of chronic inflammation and fibrosis. These discoveries have facilitated the introduction of targeted B-cell-directed therapies, particularly rituximab, which have substantially improved treatment outcomes in patients with relapsing or refractory disease.

Despite these advances, important knowledge gaps remain regarding disease initiation, reliable biomarkers, predictors of relapse, and optimal long-term management strategies. Continued multidisciplinary collaboration, high-quality clinical research, and the development of precision medicine approaches are expected to further improve diagnostic accuracy, therapeutic effectiveness, and long-term patient outcomes. As understanding of the molecular mechanisms underlying IgG4-RD continues to evolve, future innovations in targeted immunotherapy and biomarker discovery hold considerable promise for preventing irreversible organ fibrosis and improving the quality of life of affected patients.

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Conflicts of Interest

The authors declare that they have no competing interests or conflicts of interest related to this work.

Author Contributions

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Ethics Approval and Consent to Participate

Not applicable. This manuscript is a descriptive review of published literature and did not involve human participants, animals, or identifiable patient data.

Data Availability

No new datasets were generated or analyzed during the preparation of this review. All information presented is derived from published studies cited in the reference list.

References

1. Wallace ZS, Naden RP, Chari S, Choi HK, Della-Torre E, Dicaire JF, *et al*. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. Arthritis & Rheumatology,2020:72(1):7–19. doi:10.1002/art.41120.
2. Perugino CA, Stone JH. IgG4-related disease: an update on pathophysiology and implications for clinical care. Nature Reviews Rheumatology,2020:16(12):702–714. doi:10.1038/s41584-020-0500-7.
3. Perugino CA, Wallace ZS, Meyersohn N, Oliveira G, Stone JR, Stone JH. Clinical perspectives on IgG4-related disease and its classification. Annual Review of Medicine,2022:73:545–562. doi:10.1146/annurev-med-050219-034449.
4. Wallace ZS, Perugino CA. Current and future advances in practice: IgG4-related disease. Rheumatology Advances in Practice, 2024, 8(2).
5. Chen Y, Zhao JZ, Feng RE, Shi JH, Liu J, Shi J, *et al*. Update on classification, diagnosis, and management of IgG4-related disease. Chinese Medical Journal,2022:135(12):1367–1377.
6. Hegade VS, Sheridan MB, Huggett MT. Diagnosis and management of IgG4-related disease. Frontline Gastroenterology,2019:10(3):275–283.
7. Zhang W, Stone JH. Management of IgG4-related disease. The Lancet Rheumatology,2019:1(1)–e65.
8. Floreani A, Okazaki K, Uchida K, Gershwin ME. IgG4-related disease: changing epidemiology and new thoughts on a multisystem disease. Journal of Translational Autoimmunity,2021:4:100074. doi:10.1016/j.jtauto.2020.100074.
9. Della-Torre E, Mancuso G, Lanzillotta M, Bozzolo EP, Milani R, Doglioni C, *et al*. Urgent manifestations of immunoglobulin G4-related disease. Scandinavian Journal of Rheumatology,2021:50(1):48–51.
10. Lanzillotta M, Mancuso G, Della-Torre E. Emerging therapy options for IgG4-related disease. Expert Review of Clinical Immunology,2021:17(5):471–483.
11. Lanzillotta M, Mancuso G, Della-Torre E. Efficacy and safety of rituximab for IgG4-related pancreato-biliary disease: a systematic review and meta-analysis. Pancreatology,2021:21(7):1396–1403.
12. Liu Z, Zhao J, Chen H, Li H, Zhang P, Zhang W, *et al*. The external validation of the 2019 ACR/EULAR classification criteria for IgG4-related disease in a large cohort. Rheumatology, 2023.
13. Kogami M, Watanabe T, Yamashita K, *et al*. Performance of classification and diagnostic criteria for IgG4-related disease and clinical differences between IgG4-related disease and mimickers. Scientific Reports,2023:13:3013.
14. Lopez-Gomez M, *et al*. Comparative analysis of classification criteria in IgG4-related disease. Diagnostics,2024:14(22):2583.
15. Peng L, Zhang P, Li J, *et al*. The development and initial validation of IgG4-related disease damage index. Rheumatology, 2024.
16. Tang J, Cai S, Ye C, Dong L. Biomarkers in IgG4-related disease: a systematic review. Seminars in Arthritis and Rheumatism,2020:50(2):354–359.
17. Iaccarino L, Talarico R, Scirè CA, *et al*. Blood biomarkers recommended for diagnosing and monitoring IgG4-related disease. Clinical and Experimental Rheumatology, 2022.
18. Choi SJ, Lee J, Kim JH, *et al*. Serum IgG4 level during initial treatment as a predictor of relapse-free outcomes in IgG4-related disease. Arthritis Research & Therapy,2023:25:48.
19. Peng Y, Li JQ, Zhang PP, *et al*. Clinical outcomes and predictive relapse factors of IgG4-related disease following treatment: a long-term cohort study. Journal of Internal Medicine,2019:286(5):542–552.
20. Liu Y, Xue M, Wang Z, *et al*. Relapse predictors and serologically unstable condition of IgG4-related disease: a large Chinese cohort. Rheumatology,2020:59(8):2115–2123.
21. Zongfei J, Lingying M, Lijuan Z, *et al*. Clinical and pathological predictors of relapse in IgG4-related disease. Arthritis Research & Therapy,2022:24:106.
22. Capecchi R, Puxeddu I, Pratesi F, *et al*. Renal involvement in IgG4-related disease: from sunlight to twilight. Frontiers in Medicine,2021:8:635706.
23. Mbengue M, Goumri N, Niang A, *et al*. IgG4-related kidney disease: pathogenesis, diagnosis, and treatment. Clinical Kidney Journal, 2021.
24. Kawano M, Saeki T. Recent advances in IgG4-related kidney disease. Modern Rheumatology,2023:33(2):242–251.
25. Towheed ST, Tangri N, Komenda P, Rigatto C. Renal manifestations of IgG4-related disease: a concise review. International Journal of Rheumatology,2024:2024:4421589. doi:10.1155/2024/4421589.
26. Buglioni A, Nasr SH, Said SM, *et al*. Clinicopathologic features of IgG4-related kidney disease. Kidney International Reports, 2024.
27. Matsui S, Yamamoto H, Minamoto S, Waseda Y, Mishima M, Kubo K. IgG4-related respiratory disease. Modern Rheumatology,2019:29(2):251–256.
28. Dragos C, Keir GJ, Nicholson AG, Renzoni EA, Wells AU, Maher TM, *et al*. Pulmonary manifestations, treatments and outcomes of IgG4-related disease: a systematic literature review. Rheumatology International, 2024.
29. Morales AT, Cignarella AG, Jabeen IS, Barkin JS, Mirsaeidi M. An update on IgG4-related lung disease. European Journal of Internal Medicine,2019:66:18–24.
30. Balaban DT, Ismail G, Jinga M, *et al*. Treatment of IgG4-related disease-associated hypertrophic pachymeningitis with intrathecal rituximab. Frontiers in Neurology,2023:14:1189778.
31. Musto A, *et al*. Hypertrophic pachymeningitis IgG4-related with antineutrophil cytoplasmic antibody positivity: case report and literature review. Medicine,2019:98:(30).
32. Sapkota B, *et al*. IgG4-related disease presenting as hypertrophic pachymeningitis. Cureus,2022:14(2).
33. Kamekura R, Takano K, Yamamoto M, *et al*. Recent evidence of the role of CD4-positive T cell subsets in IgG4-related disease. International Journal of Molecular Sciences,2024:25:1333.
34. Akiyama M, Yasuoka H, Yamaoka K, Suzuki K, Takeuchi T. The immunological pathogenesis of IgG4-related disease. Immunology and Medicine,2025:48(1):1–13. doi:10.1080/25785826.2024.2407224.

35. Cai S, Dong L. Omics in IgG4-related disease. Chinese Medical Journal, 2024.
36. Arias-Intriago M, *et al*. IgG4-related disease: current and future insights into pathogenesis, diagnosis, and treatment. International Journal of Molecular Sciences,2025:26:5105.
37. González-García A, *et al*. New developments in the treatment of IgG4-related disease. Journal of Clinical Medicine,2025:14(19):6774.
38. Stone JH, Khosroshahi A, Zhang W, *et al*. Inebilizumab for treatment of IgG4-related disease. New England Journal of Medicine,2025:392(12):1168–1177. doi:10.1056/NEJMoa2409712.
39. Hammitzsch A, Ferraro N, Bachmann Q, Heemann U, Moog P. Long-term treatment patterns and outcomes in IgG4-related disease: a retrospective single-center cohort study focusing on rituximab. Rheumatology International, 2026. doi:10.1007/s00296-025-06065-1.
40. Taranto S, *et al*. IgG4-related disease in childhood: clinical presentation, diagnosis, treatment, and outcomes. Pediatric Rheumatology Online Journal, 2025.