

IgG4-Related Disease: Beyond Glucocorticoids

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Abstract IgG4-related disease is a heterogeneous immune-mediated fibroinflammatory condition that can affect every single organ. This disease is more prevalent in the elderly (the mean age of patients is above 60 years) and the prevalence rate is estimated to be over 4.6 per 100,000 population. Before making a diagnosis, the exclusion of malignancies, lymphoma, anti-neutrophil cytoplasmic antibody-associated vasculitis, multicentric Castleman disease, and other mimickers is crucial for appropriate treatment. Broad management guidelines have been published emphasizing the need for prompt treatment and the use of glucocorticoids as first-line drug therapy for induction of remission. However, the toxic effects of glucocorticoids are problematic because IgG4-related disease is more prevalent in patients above 60 years of age, a population with frequent comorbid conditions and polypharmacy. Immunosuppressants (cyclophosphamide, methotrexate, leflunomide, and tacrolimus) and targeted immunomodulators (rituximab, XmAb5871, and abatacept) are appealing to overcome potential toxic effects of glucocorticoids and as emerging glucocorticoid-sparing and/or maintenance treatments. In this review, we provide an overview of our understanding of the pathophysiology of the disease (T follicular helper cells, CD4⁺ cytotoxic T cells, plasmablasts, and alternatively activated M2 macrophages) and clinical characteristics, and highlight the potential targets for treatment intervention.

Key Points

IgG4-related disease is a fibroinflammatory disease characterized by elevated serum IgG4, infiltration of IgG4⁺ plasma cells, storiform fibrosis, and hyperplastic ectopic germinal center formation, which mimic many other diseases.

Follicular helper T cells and M2 macrophages are key players for inducing IgG4⁺ plasma cell differentiation and storiform fibrosis in IgG4-related disease.

Molecular-targeted agents are appealing with the aim of overcoming potential toxic effects of glucocorticoids in IgG4-related disease.

1 Introduction

IgG4-related disease is a fibroinflammatory disease characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4⁺ plasma cells, storiform fibrosis, hyperplastic ectopic germinal centers, and elevated serum IgG4 levels [1]. The disease can affect every single organ and mimics many malignancies, lymphomas, infectious diseases, autoimmune diseases, and inflammatory disorders. Greater understanding of this disease is essential to achieve an earlier, more accurate diagnosis and appropriate treatment, which can prevent severe irreversible organ damage. This review provides an overview of the clinical features and our understanding of the

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pathophysiology of the disease, and highlights the potential targets for treatment intervention.

2 Epidemiology

The overall prevalence rate and annual incidence rate in Japan of type 1 autoimmune pancreatitis (IgG4-related pancreatitis) was reported to be 4.6 per 100,000 population and 1.4 per 100,000 population, respectively, in 2011 and the mean age was 66 years [2]. Because these figures were derived early in the discovery of IgG4-related disease, which has since been shown to be a multi-organ immune-mediated condition, they are likely to be a substantial underestimate of its true prevalence. Although the prevalence of various organ manifestations is still unclear, autoimmune pancreatitis, dacryosialadenitis, and retroperitoneal fibrosis are the most common disease features. IgG4-related disease typically affects middle-aged and elderly people (the mean age is 64 years), in roughly equal male and female ratios [3].

3 Pathogenesis

Over a decade since the proposal of IgG4-related disease, our understanding of its pathophysiology has improved dramatically, including our knowledge of the related genetic risk factors, candidate antigens, the role of IgG4, and innate and adaptive immune responses (Fig. 1). As discussed in the below section, long-term exposure to multiple exogenous antigens leads to the stimulation of innate (alternatively activated M2 macrophages) and adaptive (T follicular helper cells, activated B cells, and CD4⁺ cytotoxic T cells) immune responses. Moreover, this leads to the recruitment of large numbers of associated immune cells required for anti-inflammatory or tolerance-inducing effects at locally affected sites in genetically susceptible individuals. The massive infiltration of those immune cells results in the swelling and hypertrophy of affected organs, and subsequent fibrosis.

3.1 Genetic Risk Factors

Several studies have used candidate-gene approaches and genome-wide association studies to identify the susceptibility genes for IgG4-related disease. Some of those identified include human leukocyte antigen (HLA) serotypes (HLA DRB1*04:05-DQB1*04:01 and HLA-A) and single-nucleotide polymorphisms (Fc gamma receptor 2B; Fc receptor-like 3; cytotoxic T-lymphocyte-associated antigen 4; and potassium voltage-gated channel, shaker-related subfamily, member 3) on Asian cohorts [4–8], while one

study on Caucasians reported HLA-B8 [9]. Larger global studies are required for the future.

3.2 Candidate Antigens

Exogenous antigens such as occupational antigens (industrial dust, gases, oils, solvents, pesticides, and asbestos), tobacco smoke, food and animal antigens, and neoantigens are candidate environmental risk factors associated with IgG4-related disease [10–13]. Furthermore, annexin A11 was recently identified as an IgG4-recognizing autoantigen in IgG4-related disease [14]. Because annexin A11 is an intracellular protein, it is likely that this antigen is only presented following cellular damage. Therefore, long-term exposure to occupational antigens or food and animal antigens may trigger tissue injuries in target organs and lead to aberrant expression of intracellular proteins such as annexin A11 in genetically susceptible individuals.

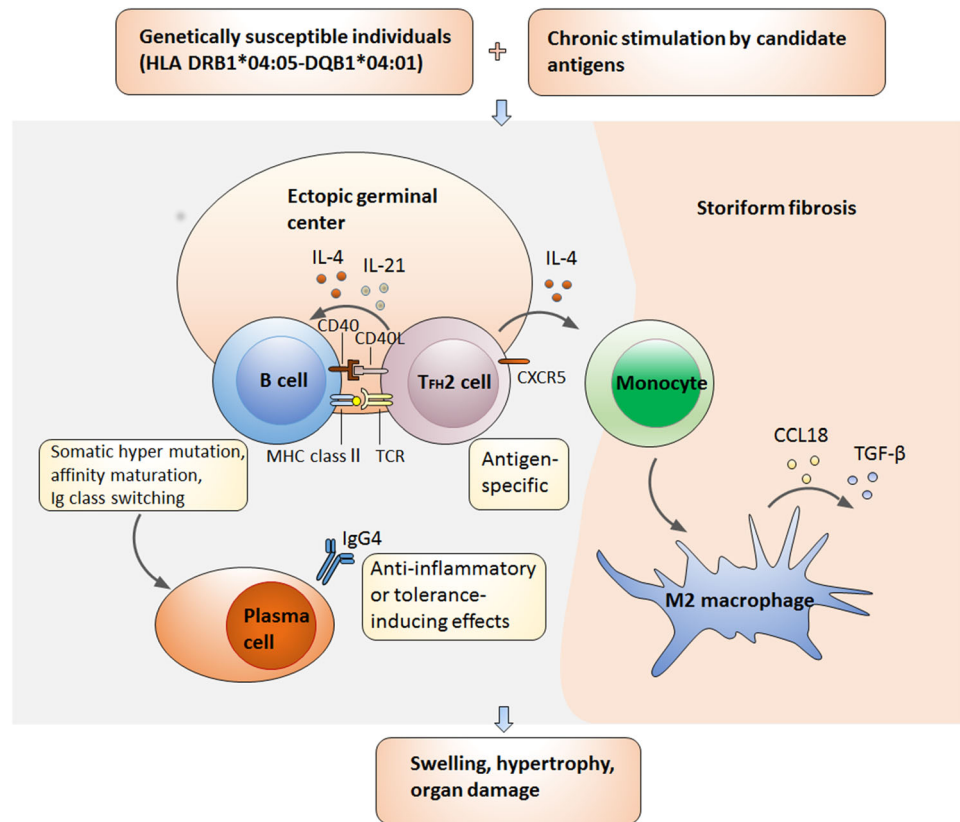
3.3 Role of IgG4

The IgG4 antibody itself has an anti-inflammatory role and tolerance-inducing effects owing to its structural (so-called ‘Fab arm exchange’) and functional characteristics (poor affinity to Fc-gamma receptors on effector cells and to C1q) [15]. IgG4-mediated immune tolerance is well known in beekeepers, who are exposed long term to high levels of the bee venom allergen. Venom-specific IgG4 is produced at high levels in tolerant individuals, which competitively binds to the allergen, inhibiting IgE-mediated immune complex formation and mast cell activation [16]. Patients who receive allergen-desensitizing immunotherapy also produce a high level of allergen-specific IgG4, which protects them against anaphylactic reactions and reduces allergic symptoms [16]. IgG4 in IgG4-related disease is also thought to have anti-inflammatory or tolerance-inducing effects because IgG4 inhibits the binding and pathogenic effect of IgG1 in IgG4-related disease and patients frequently have a history of long-standing atopic diseases [17].

3.4 Innate Immunity

A large number of interleukin (IL)-4- and IL-13-induced, alternatively activated M2 macrophages infiltrate fibrotic lesions in IgG4-related disease, and play a role in antigen recognition, Th2-type response enhancement, and stromal fibrosis formation. Toll-like receptor 7 and the macrophage receptor with collagenous structure on M2 macrophages recognize the disease-triggering antigens in IgG4-related disease [18, 19]. M2 macrophages produce IL-33 to enhance Th2-type responses at affected sites in IgG4-related disease [20]. Excessive amounts of CC-

Fig. 1 Schematic of the pathogenesis of IgG4-related disease. *CCL18* CC-chemokine ligand 18, *CXCR5* CXC chemokine receptor 5, *HLA* human leukocyte antigen, *Ig* immunoglobulin, *IL-4* interleukin-4, *IL-21* interleukin-21, *MHC* major histocompatibility complex, *TCR* T-cell receptor, *TFH2 cell* follicular helper type-2 cell, *TGF- β* transforming growth factor- β



chemokine ligand 18 and transforming growth factor- β produced by M2 macrophages also up-regulate collagen production by fibroblasts, resulting in storiform fibrosis [21–23].

3.5 Adaptive Immunity

Although Th2 and Treg cells were initially reported in the pathogenesis of IgG4-related disease [24, 25], more recent studies have emphasized follicular helper T (Tfh) cells and CD4⁺ cytotoxic T cells as the pathogenic players in IgG4-related disease [26]. Follicular helper T cells are a CD4⁺ T-cell subset responsible for germinal center formation, antigen-dependent B-cell maturation and activation, B-cell differentiation to antibody-producing plasmablasts/plasma cells, and Ig class switching [27]. IgG4-secreting plasmablasts in the circulation are oligoclonally increased, correlating with disease activity in patients with IgG4-related disease [28]. The increased plasmablasts coincide with somatic hypermutations, and the re-elevation of distinct plasmablast clones is associated with disease relapse [28]. Therefore, oligoclonally expanded plasmablasts are derived from germinal centers and are assisted by Tfh cells [27]. Abundant IgG4⁺ B-cell receptor clones in the circulation and tissues of IgG4-related disease also indicate that

Tfh cell-dependent responses play a significant role in the expansion of plasmablasts in IgG4-related disease [29].

In fact, we initially reported that Tfh cells, particularly Tfh2 cells, in the circulation are markedly increased and activated, and correlate with disease activity in IgG4-related disease [30–32]. Furthermore, these Tfh2 cells specifically induce the differentiation of IgG4-secreting plasmablasts from naïve B cells in IgG4-related disease [32]. The ability of Tfh2 cells to induce IgG4-secreting plasmablasts is greater in patients with IgG4-related disease than in healthy donors [32]. Interleukin-4 and IL-21 secreted by Tfh2 cells are the major cytokines in IgG4 class switching and plasmablast differentiation, respectively [27, 33, 34].

Other groups have replicated evidence of the involvement of Tfh2 cells in the pathogenesis of IgG4-related disease [35]. In addition, studies have reported hyperplastic ectopic germinal center formation and high expression levels of Tfh-related transcription factor B-cell lymphoma 6 at affected sites in IgG4-related disease [33, 36, 37]. Importantly, the majority of CD4⁺ T cells in locally affected tissues in IgG4-related disease are Tfh cells [38, 39]. Interestingly, the dramatically expanded population of Tfh cells that secrete IL-4 are located outside the ectopic germinal centers and are in contact with IgG4-secreting B cells [40]. Furthermore, tissue-infiltrating Tfh

cells also efficiently induce IgG4 production from B cells in IgG4-related disease [38]. The proportions of Tfh cells in circulation reflected the proportion of Tfh cells in the local affected sites, indicating that Tfh cells in circulation are derived from local affected areas [41]. Collectively, Tfh cells are responsible for inducing hyperplastic ectopic germinal center formation, IgG4 class switching, and plasmablast/plasma cell differentiation in IgG4-related disease.

CD4⁺ cytotoxic T cells are also oligoclonally expanded in the circulation, and a large number of CD4⁺ cytotoxic T cells infiltrate affected tissues in IgG4-related disease [42]. These CD4⁺ cytotoxic T cells produce a large number of cytotoxic inflammatory cytokines (perforin, granzyme A/B, IL-1 β , interferon- γ , and transforming growth factor- β). At affected sites of IgG4-related disease, activated B cells are thought to interact with and activate CD4⁺ cytotoxic T cells, which subsequently secrete profibrogenic cytokines to lead to storiform fibrosis.

4 Biomarkers of Disease Activity

In IgG4-related disease, the evaluation of systemic disease activity is crucial for early appropriate intervention to prevent irreversible organ damage [43]. Therefore, there is a clear need to identify potential biomarkers associated with disease activity in IgG4-related disease. The serum IgG4 level increases during disease progression, and is higher in patients with multi-organ involvement compared with those with single organ involvement. Several blood biomarkers associated with disease activity have been reported, including circulating activated follicular helper T cells [32], plasmablasts [44, 45], serum soluble IL-2 receptor [46], complement [47], and CC-chemokine ligand 18 [23]. Furthermore, ¹⁸F-fluorodeoxyglucose-positron emission tomography/computed tomography is a reliable radiologic method for assessing disease activity [48, 49].

5 Clinical Manifestations

Common characteristics of IgG4-related disease include organomegaly or hypertrophy, elevated serum IgG4 levels, and tissue infiltration by IgG4⁺ plasma cells, frequently accompanied by severe fibrosis (so-called storiform fibrosis). Hyperplastic ectopic germinal center formation is frequently observed in affected tissues. Obliterative phlebitis can be present, particularly in the pancreas and submandibular glands and less frequently in the lacrimal glands. The inflammatory infiltration is composed of an admixture of T cells, B cells, and macrophages. B cells are typically organized in ectopic germinal centers, while T

cells are distributed diffusely throughout the lesion. IgG4⁺ plasma cells are diffusely distributed outside the ectopic germinal centers. Large numbers of macrophages are located in fibrotic regions.

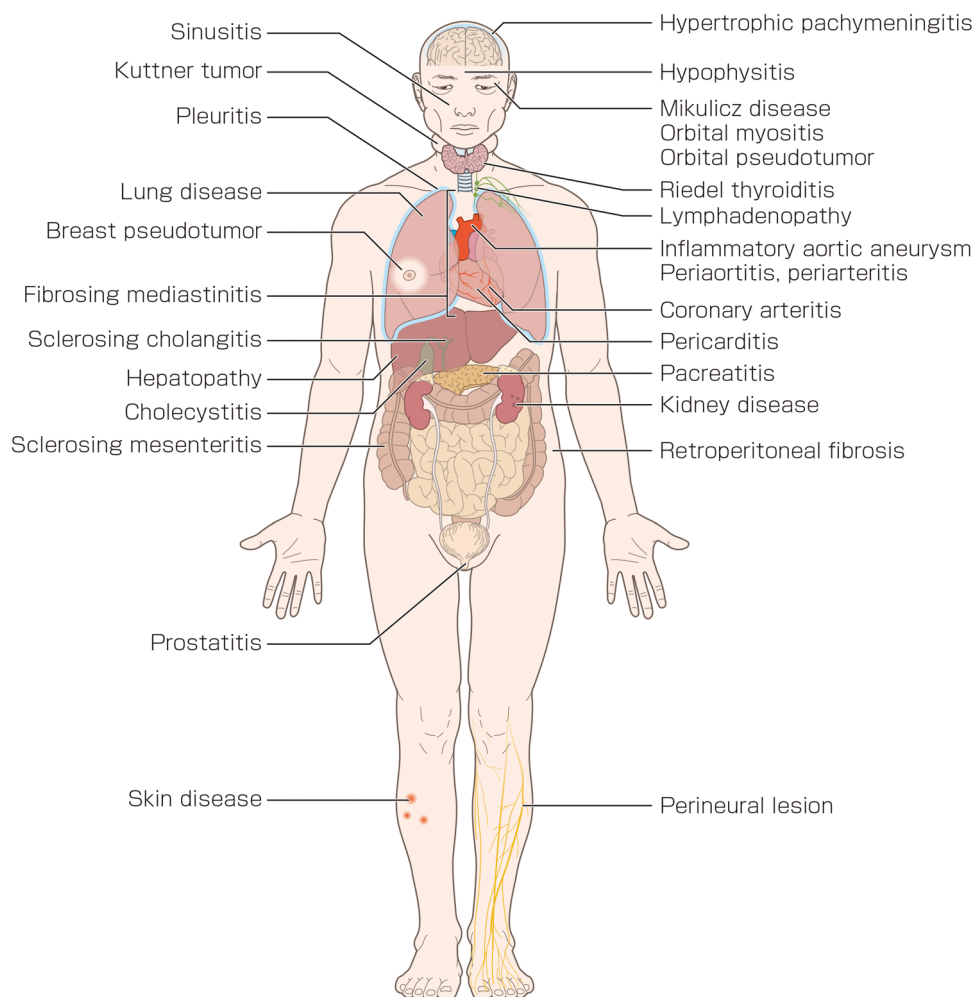
The clinical presentation is typically subacute or chronic, with symptoms and organ dysfunction evident for months to years before diagnosis. IgG4-related disease can affect every single organ and manifestations may present synchronously or metachronously (Fig. 2). Half of patients show multiple organ involvement, while the remainder show isolated lesions. As shown in Table 1, the clinical symptoms depend on the location of the affected organs, and the severity is variable among individuals. Patients frequently have an atopic history, elevated serum IgE levels, and eosinophilia.

Fever and elevated serum C-reactive protein are unusual. Destructive bone lesions in the sinuses, head, and middle-ear spaces are suggestive of mimickers such as granulomatosis with polyangiitis and tumors, and not true IgG4-related disease. Disease-specific autoantibodies such as anti-SSA, anti-SSB, anti-double-stranded DNA, and anti-neutrophil cytoplasmic autoantibodies are negative. Prominent neutrophilic inflammation, necrosis, granulomatous inflammation, and histiocytes in pathologic examination are unusual. Lack of response to glucocorticoid therapy is uncommon.

6 Diagnosis

Clinicians in every medical field can encounter IgG4-related disease in daily practice, making the development of proper diagnostic criteria essential. In 2011, comprehensive diagnostic criteria for IgG4-related disease was proposed in Japan [50], with the major characteristics being serum IgG4 levels > 135 mg/dL, infiltration of > 10 IgG4⁺ plasma cells per high-power field, and an IgG4⁺/IgG⁺ plasma cell ratio > 40%. However, universal diagnostic criteria for IgG4-related disease have not been established and the overemphasis on elevated serum IgG4 levels and pathologically proven IgG4⁺ plasma cell infiltration has led to the misdiagnosis of similar conditions as IgG4-related disease. It is therefore important for clinicians to be mindful that elevated serum IgG4 levels and IgG4⁺ plasma cell infiltration in lesions are not specific to IgG4-related disease. Furthermore, the low sensitivity of histologic analysis is also problematic owing to difficulties obtaining biopsy samples. Umehara et al. recently proposed that careful and intensive examination using a combination of comprehensive diagnostic criteria and organ-specific criteria is the best method for accurately diagnosing IgG4-related disease [51, 52].

Fig. 2 Systemic organ manifestations of IgG4-related disease



As shown in Table 2, other diseases that mimic IgG4-related disease must be excluded before concluding a diagnosis of IgG4-related disease [53]. For example, recent studies demonstrate that clinicians should note anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and multicentric Castleman disease as representative mimickers of IgG4-related disease [54–56]. Anti-neutrophil cytoplasmic antibody-associated vasculitis and multicentric Castleman disease not only have similar clinical presentations to IgG4-related disease but also exhibit IgG4⁺ plasma cell infiltration at affected sites and elevated serum IgG4 levels.

Additionally, orbital mass, chronic periaortitis, retroperitoneal fibrosis, tubulointerstitial nephritis, interstitial lung disease, pachymeningitis, hypophysitis, pleuritis, dacryosialadenitis, sinusitis, and prevertebral fibrosis are not only observed in IgG4-related disease but also in ANCA-associated vasculitis [54, 55, 57–60]. Of note, biopsy specimens of granulomatosis with polyangiitis frequently show lymphocytic infiltration that is rich in plasma cells, storiform fibrosis, and obliterated blood vessels [54].

Furthermore, granulomatosis with polyangiitis of the central nervous system, upper respiratory tract, or orbit usually lack classic morphologic features such as necrotizing vasculitis, parenchymal necrosis, and palisading granulomas [54]. Therefore, constitutional symptoms such as fever, ANCA positivity, and elevated serum C-reactive protein are clues for a diagnosis of ANCA-associated vasculitis.

Differentiating IgG4-related disease from multicentric Castleman disease is also essential because of the difference in required treatments. A moderate dose of glucocorticoids is effective for IgG4-related disease but not for multicentric Castleman disease, whereas anti-IL-6 receptor blockade is effective for multicentric Castleman disease [61]. Importantly, differentiating IgG4-related disease from multicentric Castleman disease is challenging because both diseases exhibit high serum IgG4 levels and IgG4⁺ plasma cell infiltration at affected sites. The important clue for a diagnosis of one disease over the other is in the underlying pathogenesis: while IL-4 and IL-21 are the culprit cytokines associated with IgG4-class switching and plasma cell proliferation in IgG4-related disease [34], excessive IL-6

Table 1 Summary of clinical manifestations of IgG4-related disease

Organ	Clinical manifestations
Orbits and lacrimal glands	Gradually progressing exophthalmia, limited mobility of the eyeball, and bilateral swelling of the lacrimal glands. Radiologic enlargement of the extra-ocular muscles, mass lesions of the pterygopalatine fossa infiltrating along the trigeminal nerve, and mass lesions of the lacrimal glands. Serum C-reactive protein level is within the normal range
Nose and sinuses	Nasal obstruction, nasal discharge, postnasal discharge, hyposmia, and dull headache. Radiologic nasal polyps, swelling of mucosal surfaces, and thickening of sinus walls. Serum C-reactive protein level is within the normal range. Destructive lesions are unusual
Salivary gland	Enlargement of submandibular gland, parotid gland, and minor salivary gland. Mild-to-moderate sicca symptoms. Serum C-reactive protein level is within the normal range
Meninges	Headache, radiculopathy, and cranial nerve palsies. Radiologic thickening of the cerebral and/or spinal dura mater. Serum C-reactive protein level is occasionally elevated
Pituitary	Anterior hypopituitarism, diabetes insipidus, and panhypopituitarism. Radiologic pituitary gland and stalk enlargement. Serum C-reactive protein level is occasionally elevated
Thyroid gland	Thyroid gland enlargement and hypothyroidism (Riedel thyroiditis). Diffuse low echogenicity on ultrasound. Serum C-reactive protein level is within the normal range
Mediastinal tissue	Paravertebral band-like soft-tissue mass in thorax. Serum C-reactive protein level is occasionally elevated
Lymph nodes	Enlargement of lymph node. Serum C-reactive protein level is within the normal range
Lungs	Asymptomatic finding on lung imaging or respiratory symptoms (dry cough or dyspnea). Radiologic mass lesion (lymphoplasmacytic type of inflammatory pseudotumor), consolidation, small nodules, thickening of bronchovascular bundles and interlobular septa, ground-glass opacities similar to multicentric Castleman disease or sarcoidosis, and pleural thickening/effusion. Serum C-reactive protein level is occasionally elevated
Biliary tree	Mild abdominal pain, weight loss, or acute obstructive jaundice. Radiologic diffuse or multi-focal narrowing or smooth wall thickening of the biliary tract. If untreated, progression to end-stage liver disease occurs. Serum C-reactive protein level is within the normal range
Liver	Obstructive jaundice and elevated liver enzyme level. Radiologic mass lesion (lymphoplasmacytic type of inflammatory pseudotumor) involving hilar and perihilar bile ducts. IgG4-related autoimmune hepatitis or hepatopathy is rare but reported. Serum C-reactive protein level is within the normal range
Pancreas	Mild abdominal pain, weight loss, acute obstructive jaundice, and acute glucose intolerance. Radiologic ‘sausage-shaped pancreas’ with loss of normal lobularity, capsule-like rim with decreased enhancement, and diffuse narrowing of pancreatic duct. Serum C-reactive protein level is within the normal range
Aorta and artery	Periaortitis, periarteritis, and inflammatory aortic aneurysm. Radiologic diffuse thickening of the aortic wall or artery. Coronary artery is occasionally affected. Serum C-reactive protein level is occasionally elevated
Retroperitoneum	Backache, lower abdominal pain, lower extremity edema, hydronephrosis from ureteral involvement, or asymptomatic finding on radiologic studies. Serum C-reactive protein level is occasionally elevated
Kidney	Proteinuria, hematuria, elevated serum creatinine level, and asymptomatic radiologic abnormalities. Tubulointerstitial nephritis is typical, but glomerulonephritis can also occur. Hypocomplementemia is frequent. Multiple round- or wedge-shaped radiologic low-density areas in both renal cortices, markedly enlarged bilateral kidneys, a rim-like lesion of the kidney, pelvis thickening, and multiple and bilateral tumor lesions. Serum C-reactive protein level is within the normal range
Other	Gallbladder (lymphoplasmacytic sclerosing cholecystitis), breast pseudotumor, prostatitis, pericarditis (constrictive pericarditis), sclerosing mesenteritis, skin disease, IgG4-related gastrointestinal disease, and perineural lesions

production is the key feature of multicentric Castleman disease [62]. These differences result in elevated serum C-reactive protein and IgA levels (laboratory markers linked to IL-6) in patients with multicentric Castleman disease, but not in most cases of IgG4-related disease [56]. Although both diseases commonly involve the lymph nodes, lungs, retroperitoneum, kidneys, and skin, IgG4-related disease more commonly affects the orbits, lacrimal glands, salivary glands, and pancreas than multicentric Castleman disease [56]. We recently reported that the combination of orbit, lacrimal gland, salivary gland, or

pancreas involvement, an atopic history, or a lack of involvement of lymph nodes; and C-reactive protein ≤ 0.8 mg/dL or IgA ≤ 330 mg/dL are useful criteria for distinguishing IgG4-related disease from multicentric Castleman disease in daily clinical practice [56]. Therefore, the diagnosis of IgG4-related disease should be based on a combination of clinical features, serum characteristics, and pathologic findings.

Table 2 Representative IgG4-related disease mimickers

Tumors
Malignancies
Malignant lymphoma (mucosa-associated lymphoid tissue lymphoma, angioimmunoblastic T-cell lymphoma)
Inflammatory myofibroblastic tumor
Inflammatory pseudotumor (fibrohistiocytic type)
Autoimmune diseases
Anti-neutrophil cytoplasmic autoantibody-associated vasculitis
Large-vessel vasculitis
Systemic lupus erythematosus
Sjögren syndrome
Rheumatoid arthritis (synovitis and lymphadenopathy)
Others
Multicentric Castleman disease
Cutaneous plasmacytosis
Angiolymphoid hyperplasia with eosinophilia
Rosai–Dorfman disease
Kimura disease
Hypereosinophilic syndrome
Primary sclerosing cholangitis
Inflammatory bowel disease
Sarcoidosis
Erdheim–Chester disease

7 Treatment

Assessing disease involvement of organs is important, and whole body computed tomography scan and ^{18}F -fluorodeoxyglucose-positron emission tomography/computed tomography are recommended if possible before treatment. All patients with symptomatic active IgG4-related disease require treatment, sometimes urgently in cases where important organs/tissues are affected, such as the meninges, lungs, pancreas, bile duct, kidney, and aorta, and for hydronephrosis due to retroperitoneal fibrosis. A subset of patients with asymptomatic IgG4-related disease also require treatment, where delayed intervention can lead to impossible recovery of organ function as a result of fibrosis progression [43].

7.1 Glucocorticoids

An international consensus guidance statement on the management and treatment of IgG4-related disease recommends the use of glucocorticoids as first-line therapy [63]. Despite being effective for patients with IgG4-related disease, a glucocorticoid treatment regimen has yet to be standardized owing to limited global retrospective observational evidence. Recently, the first prospective, phase II

clinical trial of glucocorticoids for the treatment of patients with newly diagnosed IgG4-related disease was reported by the members of the Japanese IgG4-related disease research group [64]. All patients received prednisolone at a dose of 0.6 mg/kg/day as induction therapy, with the dose reduced by 10% every 2 weeks. The maintenance dose was 10 mg/day for at least 3 months. The authors reported that the overall response rate was 93.2% and only 1.7% of patients were refractory to primary glucocorticoid treatment at 1 year. Despite maintenance treatment using prednisolone (median dose, 7 mg/day), about 10% of patients relapsed during the observation period. Adverse events were glucose intolerance (41%), dyslipidemia (26%), infection (18%), hypertension (15%), psychosis (5%), glaucoma (3%), pathologic fracture (3%), myopathy (3%), femur head necrosis (2%), and cataract (2%).

The first randomized controlled study to compare the efficacy and safety of high vs. medium doses of glucocorticoids as induction therapy for IgG4-related disease was reported in 2017 [65]. Although the remission rate was similar in high- and medium-dose groups at week 12, a higher relapse rate was observed at week 24 in the medium-dose group. Patients with a higher number of involved organs and higher IgG4-RD Responder Index scores at baseline were more likely to relapse and may therefore require high-dose glucocorticoids.

The first randomized controlled study of long-term maintenance glucocorticoid therapy was conducted in patients with autoimmune pancreatitis to clarify the efficacy and necessity of maintenance glucocorticoid therapy [66]. The relapse rate over 3 years was significantly lower in the maintenance therapy group than in the cessation group. Relapse-free survival was also significantly longer in the maintenance therapy group than in the cessation group. Thus, maintenance glucocorticoid therapy for 3 years may decrease the occurrence of relapse in patients with autoimmune pancreatitis compared with those who discontinue the therapy.

Yamamoto et al. reported that glucocorticoid discontinuation is achieved in only 5.7% of patients in daily clinical practice [67]. Furthermore, half of IgG4-related disease cases experience relapse within 7 years of initial glucocorticoid treatment [67]. Therefore, glucocorticoid treatment alone is not sufficient to cure patients with IgG4-related disease. In addition, glucocorticoid toxicity is problematic because IgG4-related disease usually affects the elderly. Evaluation of glucocorticoid-sparing agents or treatment alternatives is warranted and the search for a better alternative represents a major challenge in the management of patients with IgG4-related disease.

7.2 Conventional Immunosuppressants

It remains unclear whether combining glucocorticoids and conventional immunosuppressants is more efficacious than glucocorticoids alone for preventing the relapse of IgG4-related disease. A recent study reported that combining cyclophosphamide (50–100 mg/day) with glucocorticoids resulted in a significantly higher relapse-free rate in 1 year than with glucocorticoids alone [68]; however, long-term cyclophosphamide toxicity assessment is warranted in the future. A small case series with no control group reported methotrexate or leflunomide as a promising option for maintaining glucocorticoid-induced remission and tapering glucocorticoids [69, 70]. In contrast, another retrospective study reported similar relapse-free rates between patients treated with glucocorticoids plus immunosuppressants (azathioprine, mycophenolate mofetil, or 6-mercaptopurine) and those treated with glucocorticoids alone [71]. To date, there is limited evidence for the efficacy of calcineurin inhibitors such as tacrolimus as corticosteroid-sparing agents in IgG4-related disease [72]. Prospective randomized controlled trials are required to evaluate the efficacy of conventional immunosuppressants for achieving sustained remission in IgG4-related disease and enabling the tapering of glucocorticoids.

7.3 Targeted Agents

7.3.1 Anti-CD20 Antibody

B-cell depletion with rituximab (anti-CD20 antibody) is effective as induction therapy for IgG4-related disease. Carruthers et al. reported in their prospective single-arm pilot trial that most patients (87%) were successfully treated with rituximab alone and disease response occurred in 97% at 6 months [73]. A clinical response occurred within 4 weeks of rituximab treatment. Considering that IgG4-related disease usually affects middle-aged to elderly patients who might have comorbidities contraindicating long-term glucocorticoids, B-cell depletion is an appealing alternative to glucocorticoids. Maintenance therapy with rituximab is required because relapse has been frequently observed after B-cell reconstitution. In fact, maintenance therapy with rituximab was associated with longer relapse-free survival in a nationwide database study in France [74]. The optimal dose, frequency, and duration of maintenance therapy with rituximab should be explored in future studies. Adverse events such as infusion reactions and severe infections were noted.

7.3.2 Anti-CD19 Antibody

XmAb5871 is a humanized monoclonal antibody that targets CD19 via the Fc γ RIIb. The Fc portion of XmAb5871

was designed to increase its affinity (400-fold over native IgG) to Fc γ RIIb, a receptor that inhibits B-cell function. An open-label single-arm trial (a phase II pilot study) of XmAb5871 for the treatment of IgG4-related disease conducted at Massachusetts General Hospital by Stone et al. [75] administered intravenous XmAb5871 to enrolled patients every 2 weeks for 6 months. This treatment showed promising efficacy in patients with active IgG4-related disease [75], and was well tolerated with good safety and immunogenicity profiles.

7.3.3 T-Cell Co-stimulation Blockade

T cells that receive both T-cell receptor-mediated signals and CD28-mediated co-stimulation are activated and differentiate into effector cells. CD80/CD86 on antigen-presenting cells such as dendritic cells, macrophages, and activated B cells binds as a co-stimulatory molecule to CD28 on the surface of T cells. Abatacept is a fusion protein composed of the extracellular domain of cytotoxic T lymphocyte-associated antigen 4 and the Fc region of IgG1. Cytotoxic T lymphocyte-associated antigen 4 binds to CD80/CD86 on antigen-presenting cells, interfering with ligation to CD28 on T cells, thereby acting as a negative regulator of CD28-mediated T-cell activation. A recent report proposed a second mechanism of abatacept, whereby it directly depletes expanded CD80/86-expressing plasmablasts through Fc-mediated mechanisms (complement- or cell-dependent cytotoxicity) [76]. Yamamoto et al. reported a case of long-standing and relapsing IgG4-related disease successfully treated with 500 mg of abatacept intravenously every 4 weeks [77]. It remains unclear whether the effectiveness of abatacept in this case was owing to its interference with CD28 co-stimulation of Tfh cells and/or CD4⁺ cytotoxic T cells, or its more direct effect on activated B cells, macrophages, or dendritic cells. The safety profile of abatacept makes it a useful molecular-targeted therapy in the treatment of IgG4-related disease. The efficacy of abatacept should be clarified by examining its use in more cases of IgG4-related disease.

7.4 Ongoing Clinical Studies of Interventions

Several studies of interventions are ongoing in IgG4-related disease in clinicaltrials.gov. We found four studies currently evaluating igitatimod (NCT03368274), leflunomide (NCT02703194), rituximab plus lenalidomide (NCT02705638), and mycophenolate mofetil (NCT02458196), with completion dates of May 2018 to April 2019. It is an urgent task to develop an ideal treatment method with fewer side effects and less relapse.

Table 3 Summary of current evidence of immunosuppressive therapies for IgG4-related disease

Drug	Number of participants	Study design	Dose	Observation period (mo)	Response rate	Relapse	References
Glucocorticoids	61	Open-label, prospective, phase II clinical trial	0.6 mg/kg/day of prednisolone as induction therapy, with the dose reduced by 10% every 2 weeks	12	93.2%	14.6% during the 5-y maintenance period	[63]
	40	Open-label randomized controlled trial	High doses of prednisolone (0.8–1.0 mg/kg/day) vs. medium doses (0.5–0.6 mg/kg/day)	6	95% (high-dose group) and 80% (medium-dose groups)	5% (high-dose group) and 20% (medium-dose groups)	[64]
	49	Open-label randomized controlled trial	Maintenance dose of 5–7.5 mg/day until 26 weeks (short-term maintenance group) or until 3 years (long-term maintenance group)	36	100%	58% (short-term maintenance group) and 23% (long-term maintenance group)	[65]
Conventional immunosuppressant							
Cyclophosphamide	102	Retrospective observational study	Prednisolone monotherapy (0.5–1.0 mg/kg/day, tapered gradually) or prednisolone with cyclophosphamide (50–100 mg/day)	12	59.6% (prednisolone monotherapy) and 88.0% (prednisolone and cyclophosphamide)	24% (prednisolone monotherapy) and 2% (prednisolone and cyclophosphamide)	[67]
Methotrexate	10	Case series	Oral or subcutaneous methotrexate (10–20 mg/week) was introduced on average 5 wk after initiation of prednisolone	21	100%	0%	[68]
Leflunomide	18	Case series	10 or 20 mg/day of leflunomide after starting prednisolone	6	100%	16.7%	[69]
Tacrolimus	1	Case report	A target level of 5–7 ng/mL	16	100%	0%	[71]
Targeted therapy							
Rituximab (anti-CD20)	30	Prospective, open-label clinical trial	Two 1000-mg doses of rituximab, administered approximately 15 days apart	12	97%	23%	[72]
	33	Retrospective observational study	Two 1000-mg doses of rituximab, administered approximately 15 days apart in the majority of patients (76%)	24	94%	42%	[73]
XmAb5871 (anti-CD19 and FcγRIIb)	15	Open-label, prospective, phase II clinical trial	Intravenous XmAb5871 every 2 wk	6	93%	7%	[74]
Abatacept (cytotoxic T lymphocyte-associated antigen 4)	1	Case report	500 mg of abatacept intravenously every 4 weeks	8	100%	0%	[76]

8 Prognosis

8.1 Risk Factors for Relapse

Patients with IgG4-related disease respond well to glucocorticoids, but the majority of patients experience disease relapse during follow-up [67]. Investigations into the risk factors for disease relapse identified a greater number of involved organs, higher levels of serum IgG4, and lower levels of serum IgA and IgM at baseline [78]. Re-elevation of serum IgG4 levels during glucocorticoid tapering may also be associated with disease relapse in IgG4-related disease [78].

8.2 IgG4-Related Disease and Malignancies

Various lines of evidence have recently suggested the presence of an association between IgG4-related disease and malignancies. First, a history of malignancy is 2.5 times more frequent in patients with IgG4-related disease compared with the general US population. Furthermore, the frequency of a history of malignancy is more than three-fold higher in patients with IgG4-related disease than matched disease controls, indicating that malignancies are associated with subsequent IgG4-related disease development in a subgroup of patients [79]. Importantly, no cases of IgG4-related disease involving an organ previously affected by malignancy have been reported.

Second, malignancies are frequently found at the time of diagnosis or during follow-up of patients with IgG4-related disease [80]. The cumulative rate of malignancy in patients with IgG4-related disease is significantly higher than that for the general Japanese population up to 12 years after diagnosis. Interestingly, the occurrence of malignancies is significantly more frequent within the first year after diagnosis of IgG4-related disease compared with that of subsequent years. Gastric, lung, prostate, and pancreatic cancers are prevalent. Importantly, serum levels of IgG, IgG4, soluble IL-2 receptor, and circulating immune complex are significantly higher in patients with malignancies than in those without. These findings suggest that clinicians should screen for malignancies after diagnosis of IgG4-related disease and during follow-up, particularly in patients with high disease activity at baseline. The pathologic mechanisms underlying the association between IgG4-related disease and malignancy remain unclear.

8.3 IgG4-Related Disease and Lymphoma

Lymphoma can develop on a background of chronic inflammation or lymphoid hyperplasia. While the risk of developing lymphoma in patients with IgG4-related

disease remains unclear, lymphoma can arise from pre-existing IgG4-related ophthalmic disease [81, 82]. An early clue to the diagnosis of B-cell lymphoma is the presence of predominant B-cell infiltration, while massive infiltration of both T cells and B cells is more suggestive of IgG4-related disease. Therefore, clinicians should perform clonality tests for detecting immunoglobulin light-chain restriction and clonal immunoglobulin gene arrangement to exclude lymphoma when diagnosing IgG4-related ophthalmic disease. Furthermore, when patients with IgG4-related ophthalmic disease experience relapse in the same regions, clinicians should perform a re-biopsy to exclude the development of lymphoma. Interestingly, the development of lymphoma has not been convincingly reported at pre-existing sites of other IgG4-related disease such as the pancreas, suggesting that the ophthalmic site has a higher propensity for lymphoma development in IgG4-related disease.

9 Conclusions

Recent advances in the understanding of the pathogenesis of IgG4-related disease have identified the importance of activated B cells, Tfh cells, CD4⁺ cytotoxic T cells, and M2 macrophages. Glucocorticoids are currently used as a remission induction therapy for IgG4-related disease, and in most cases, maintenance therapy is necessary and disease relapses are frequent with tapering glucocorticoid doses. Furthermore, considering IgG4-related disease usually affects older people, toxic effects of glucocorticoids are considerable. There is accumulating evidence of the efficacy of targeted therapies such as rituximab, XmAb5871, and abatacept in IgG4-related disease (Table 3). Considering the safety profiles reported for the treatment for patients with rheumatoid arthritis, abatacept may be the most desirable molecular-targeted therapy, although the evaluation of treatment should be performed carefully. In patients with IgG4-related aortic aneurysms, anti-IL-6 blockade may be appealing as glucocorticoid-sparing agents because an IgG4-related aortic aneurysm was recently recognized as a unique clinicopathologic entity of IgG4-related disease that is different from other types of IgG4-related disease in terms of hyper IL-6 synthesis [83, 84]. New therapeutic alternatives to glucocorticoids in the form of targeted therapies show promise and warrant further study to examine their incorporation into treatment algorithms for IgG4-related disease.

Compliance with Ethical Standards

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