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REVIEW

The spectrum of B cells in the pathogenesis, diagnosis and therapeutic applications of immunoglobulin G4-related disease

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Abstract

Immunoglobulin G4 (IgG4)-related disease is a chronic fibroinflammatory disease mediated by immune disorders. Given the challenging clinical diagnosis and treatment, knowledge of the pathogenesis of IgG4-related disease is important. The typical elevation of serum IgG4 concentrations and infiltration of IgG4-positive plasma cells in the involved tissues indicate the involvement of B lymphocytes in the pathogenesis of IgG4-related disease. Mass production of autoantibodies reflects abnormal activation of B cells, which causes tissue damage. Circulating plasmablasts are recently discovered markers that correlate with serum IgG4 concentration, the extent of organ involvement and disease activity. B-cell depletion therapy is an emerging curative strategy that can significantly alleviate clinical manifestations and achieve remission in patients with IgG4-related disease. These findings highlight the potential role of B cells in IgG4-related disease. In this review, we discuss the pathogenic impact of B lymphocytes on IgG4-related disease and describe novel therapies targeting B cells.

Keywords: B cells, fibrosis, IgG4-related disease, plasmablast, rituximab, therapy

INTRODUCTION

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is an immunological chronic inflammatory disease characterised by mass-forming organs, high serum IgG4 concentrations, abundant infiltration of IgG4-positive ($IgG4^+$) plasma cells, storiform fibrosis and obliterative phlebitis of the involved tissue. IgG4-RD was first described in a patient with sclerosing pancreatitis and elevated IgG4 levels.[1] Recently, multiple single-organ conditions have been recognised as manifestations of IgG4-RD, including Mikulicz's disease, IgG4-related sialadenitis, autoimmune pancreatitis (AIP), IgG4-related sclerosing cholangitis, Riedel's thyroiditis, retroperitoneal fibrosis and IgG4-related periarteritis.[2–4] Pathological manifestations are similar across organs regardless of the site of involvement. Inflammation and fibrosis in the affected tissues can result in organ impairment and functional failure.

Glucocorticoids (GCs) are the preferred medications for the clinical remission of active IgG4-RD.[5–7] Most patients respond swiftly to GC, regardless of the organ involved. However, disease relapse may occur when GC is tapered to low doses or discontinued.[5,8,9] Clinicians should monitor the potential side effects of GC, especially infections

and osteoporosis, during long-term maintenance treatments. Immunosuppressants improve therapeutic efficacy when combined with GC.[9,10] Combination therapy with mycophenolate and GC is commonly used to treat IgG4-RD. The efficacy of the combination therapy in reducing disease relapse was greater than that of monotherapy.[11] Additional steroid-sparing agents effectively induce remission.[12–14] However, these steroid-sparing medications are not recommended for routine use because of inadequate knowledge of their individual efficacy and therapeutic strategies. Due to a result of the unpredictable relapse patterns of IgG4-RD, treatment remains challenging. Recently, accumulated data have identified satisfactory efficacy and safety of B-cell depletion treatment for recurrent or refractory conditions of IgG4-RD.[15–18] The CD20 monoclonal antibody rituximab (RTX) has been used as an effective second-line therapy for IgG4-RD by eliminating B cells.[16,17,19] Patients treated with RTX rapidly achieve remission, with a prompt decline in circulating plasmablasts and lowered IgG4 serum concentrations.

Exploration of the mechanisms underlying IgG4-RD is important in the search for curative strategies that can maintain long-term remission and prevent disease recurrence. Recent advances in the understanding of IgG4-RD have clarified its potential immunological pathogenesis. High serum IgG4 concentrations, hypergammaglobulinemia and a unique increment of $IgG4^+$ plasma cells in the involved tissues are observed in most patients, indicating that humoural immunity may contribute to IgG4-RD.[20] Circulating plasmablasts are positively related to disease activity and have the potential to act as a new biological index with high diagnostic value.[21–23] In IgG4-RD, the expansion of antibody-producing cells and the prominent response to B-cell depletion therapy intensify the significance of B cells. Collective evidence supports the notion that B lymphocyte lineage plays an important role in the pathogenesis of IgG4-RD. The central aim of this review is to discuss the pivotal effects of B cells on IgG4-RD, as shown in Figure 1. Experimental findings in B-cell subsets are also presented to reveal the correlation between B-cell heterogeneity and clinical phenotypes. Finally, we provide an overview of emerging B-cell targeted therapies for IgG4-RD.

ANTIGENS AND ANTIBODY REACTION

B cells participate in antigen presentation and antibody production. Triggers of IgG4-RD are unclear. The expansion of serum antibodies in IgG4-RD suggests an autoantigen-antibody response that represents clones of autoreactive B cells.

Several potential autoantigens have been identified in patients with IgG4-RD. These include prohibitin, annexin A11, laminin 511-E8, galectin-3, amylase α-2A and interleukin (IL)-1 receptor antagonists.[24–32] Autoantigens have only been reported in the specific organs involved in IgG4-RD. Among these, IgG1 and IgG4 autoantibodies specifically bind to annexin A11 in IgG4-associated cholangitis and IgG4-AIP.[26] Laminin 511-E8 and galectin-3 co-localise with IgG in the pancreatic tissues of patients with AIP.[27,29] Anti-prohibitin antibodies are mainly detected in patients with IgG4-RD with pancreatic, salivary and retroperitoneal involvement.[24] To validate these findings, Liu *et al*.[33] evaluated antibody responses to these antigens in a clinical cohort of 100 IgG4-RD patients. A poor IgG4-specific autoantibody response was observed. No organ-specific enrichment was observed for the autoantibodies against annexin A11 or laminin 511-E8. However, patients with more than two specific autoantibody responses presented with more severe manifestations than those without or with only one autoantibody response.

In addition to autoantibodies, previous studies have demonstrated significant elevations in serum IgG1, IgG4, and IgE levels in patients with IgG4-RD. The concentrations of these antibodies are closely related to the disease conditions and the clinical phenotype of IgG4-RD. Shiokawa *et al*.[34] induced histological pancreatic injury in mice by infusing IgG1 or IgG4 derived from patients with IgG4-RD to explore the pathogenicity of IgG. Pathogenic injury is caused by injections of IgG1, IgG4, or IgG1 combined with IgG4 into the pancreas. The results showed that IgG1 led to severe pathological activity, whereas IgG4 suppressed the pathogenic effects of IgG1. These findings suggest a bilateral role of IgG4. IgG4 cannot activate the complement system or participate in activating FCγ receptors on immune cells and is therefore considered to have anti-inflammatory properties.[35] However, whether IgG4 antibodies are involved in the pathogenesis of IgG4-RD or are immunoreactive products remains unclear. IgE is another critical mediator that correlates with the IgG4 concentration and disease activity in IgG4-RD.[36] Serum IgE levels are elevated in patients with atopic manifestations. IgG4 and IgE levels decrease after GC treatment.[37,38] Furthermore, serum IgG4 and IgE baseline levels independently predict disease relapse after treatment.[39]

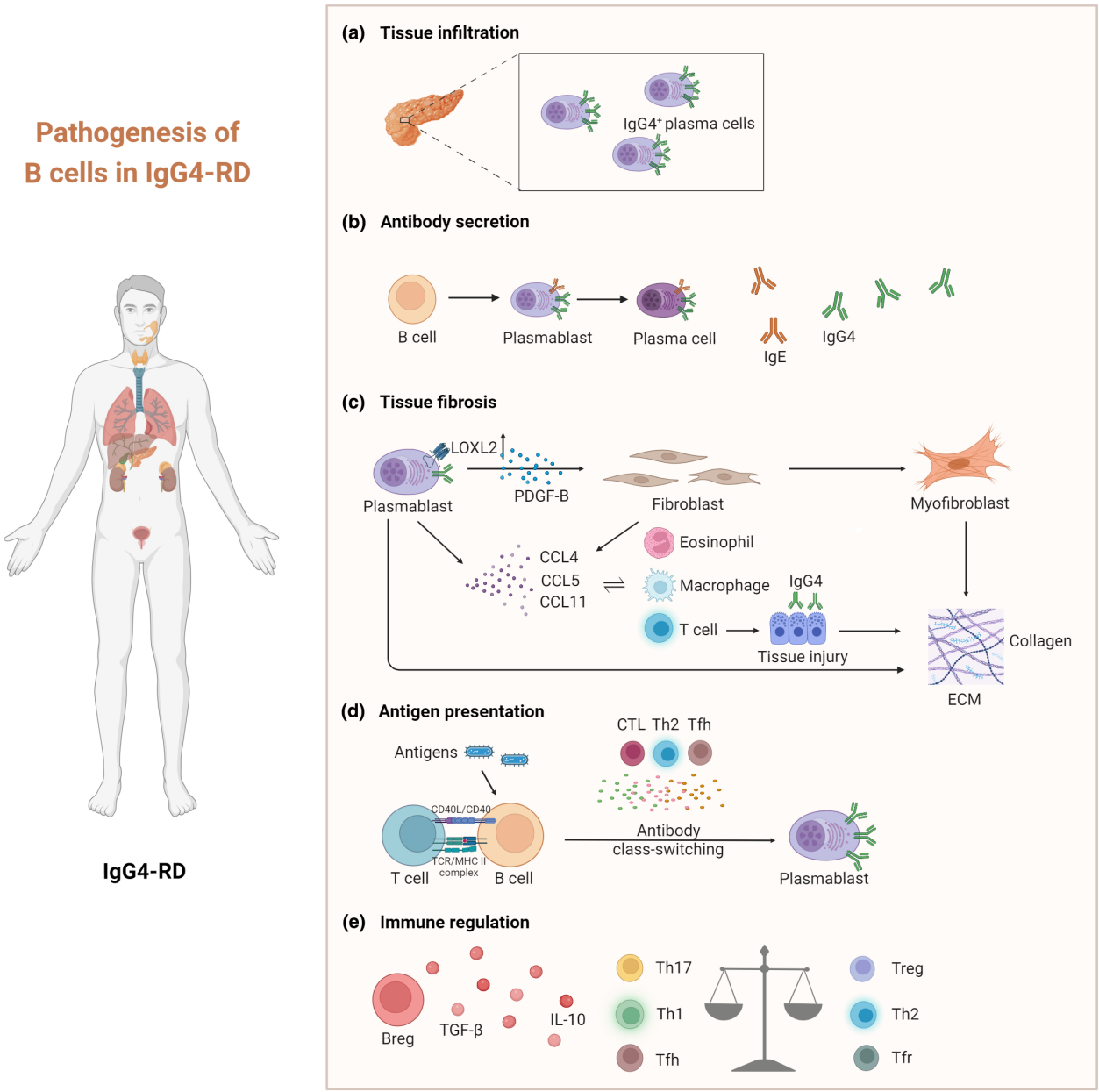

Figure 1. Pathogenesis of B lymphocytes in IgG4-RD. **(a)** Abundant infiltration of IgG4$^+$ plasma cells in affected tissues. **(b)** Mature B cells can produce antibodies like IgE and IgG4, whose levels are significantly increased in IgG4-RD. **(c)** Plasmablasts highly express the collagen-related gene LOXL2 and secrete profibrotic cytokines, such as PDGF-B, which activate the differentiation of fibroblasts to myofibroblasts. The secreted inflammatory cytokines CCL4, CCL5 and CCL11 recruit other immune cells involved in fibrosis or tissue damage. Under these comprehensive influences, collagen produced by myofibroblasts accumulates, which results in ECM stiffness and tissue fibrosis. **(d)** Interaction between T and B cells involves the differentiation of naïve B cells to class-switched plasmablasts/plasma cells. **(e)** Bregs produce IL-10 and TGF-β to maintain the balance of Th1/Th2 and Treg/Th17. The figure was created with BioRender.com. Breg, regulatory B cell; CCL, C-C chemokine ligand; CTL, cytotoxic T lymphocyte; ECM, extracellular matrix; IgG4-RD, IgG4-related disease; IL, interleukin; LOXL2, lysyl oxidase homologue 2; PDGF-B, platelet-derived growth factor-B; Tfh, T follicular helper cell; Tfr, follicular regulatory T cell; TGF-β, transforming growth factor-β; Th, T helper; Treg, regulatory T cell.

B CELLS IN TISSUE FIBROSIS REGULATION

Fibrosis is the aberrant extracellular matrix (ECM) accumulation secreted by activated myofibroblasts after inflammatory stimuli in reparative or reactive processes.[40] Immune cells secrete profibrotic cytokines that modulate myofibroblast activation through various cellular and molecular mechanisms. Fibrosis has attracted considerable attention because of its adverse effects on organ function.

Previous studies have reported the contribution of B lymphocytes to IgG4-RD fibrogenesis. In an exploratory study, Della-Torre *et al.*[41] were the first to emphasise the alleviation of pathological manifestations, especially fibroblast activation and lymphocyte infiltration, following RTX treatment. Experiments were performed using a co-culture system involving B cells from patients with IgG4-RD AIP and fibroblasts to determine the profibrotic properties of B cells.[42] B cells and activated fibroblasts secrete profibrotic factors, including platelet-derived growth factor-B and inflammatory chemokines, such as C–C chemokine ligand (CCL)-4, CCL-5 and CCL-11. Platelet-derived growth factor B stimulates collagen synthesis in fibroblasts, whereas chemokines recruit inflammatory cells with fibrotic potential to strengthen the fibrotic process. Further transcriptome analysis of different B-cell subsets showed that circulating plasmablasts highly expressed collagen genes compared with naïve or memory B cells. Among them, the pivotal enzyme lysyl oxidase homologue 2 is closely associated with the epithelial-to-mesenchymal transition and can regulate ECM stiffness. These findings provide important insight into the fibrogenic properties of B cells in patients with IgG4-RD. The depletion of B-cell subsets with profibrotic properties may reduce the activity of myofibroblasts, collagen production and the interaction of B cells with inflammatory cells, thus partly providing an explanation for the attenuation of fibrosis by RTX.

INTERACTION OF T CELLS AND B CELLS IN IGG4-RD

The dynamic interaction between T and B cells has important implications for adaptive immune responses in IgG4-RD. Many autoimmune diseases are associated with a T helper (Th) cell imbalance. Increments in the circulating Th2 and Th2-related cytokines IL-4, IL-5 and IL-13 have been widely identified in IgG4-RD,[43] which promote the proliferation, differentiation and antibody production of B cells. T follicular helper cells (Tfh) are involved in the germinal centre response and IgG4/IgE isotype class switching. Under the stimulation of Tfh, B cells differentiate into mature cells for antibody production. In IgG4-RD, Tfh, especially Tfh2 cells, were upregulated in the involved tissues and peripheral blood of IgG4-RD.[44–46] In addition to plasmablasts, cytotoxic T cells (CTLs) are inflammatory cells that heavily infiltrate IgG4-RD-involved tissues.[47] $CD4^+$ CTLs can secrete profibrotic molecules, such as transforming growth factor-β (TGF-β), to aggravate the fibrosis. Other T cell subsets, such as regulatory T cells (Tregs),[48] follicular regulatory T cells[49] and peripheral Th[50,51] also play a conceivable role in IgG4-RD. Complex interactions between T and B cells contribute to the inflammatory and fibrotic processes in IgG4-RD.

B-CELL SUBSETS AND IGG4-RD CHARACTERISTICS

B cells are indispensable mediators at the onset of IgG4-RD. B-cell subsets have diverse correlations with clinical phenotypes. However, the heterogeneity of B lymphocytes requires further investigation. Table 1 presents an overview of the various roles of the B-cell subpopulations in IgG4-RD.

Plasmablasts

Plasmablasts are the precursors of antibody-secreting plasma cells that develop from immature B cells in response to antigen stimulation and Th-cell activation. Mattoo *et al.*[23] first observed oligoclonal expansion and extensive somatic hypermutation of circulating $CD19^+CD27^+CD20^-CD38^{high}$ plasmablasts in patients with IgG4-RD using next-generation sequencing. Lin *et al.*[52] reported that circulating plasmablasts present with higher levels of IgG4-RD than those in Sjögren's syndrome. Moreover, the ratio of circulating plasmablasts is positively related to the levels of serum IgG4, inflammatory indicators and the number of organs involved.[21,52] Circulating $CD19^+CD27^+CD20^-CD38^{high}$ plasmablasts significantly decrease after efficient treatment and re-elevate when disease relapse.[21,23,45,53,54] Zhang *et al.* elucidated B-cell heterogeneity based on the immunophenotype and identified three subgroups using cluster analysis of active IgG4-RD.[55] Among these, the subgroup with high plasmablast and low naïve B-cell ratios tended to present with high disease severity and poor therapeutic response, suggesting that the B-cell subsets varied in their

Table 1. B-cell subsets in IgG4-RD

B-cell subsets	Findings in IgG4-RD	Roles in IgG4-RD
Plasmablasts	Plasmablasts aberrantly expand in IgG4-RD[53]	Novel diagnostic biomarker of IgG4-RD
	The level of plasmablasts is positively correlated with serum IgG4,[21,53] ESR,[21] number of involved organs,[21,22,53] and IgG4-RI[21,53]	Indicator of disease activity
	Decreased level of plasmablasts reflects efficient treatment[14,21–23,53,54]	Profibrotic mediator for tissue fibrosis
	Increase of plasmablasts level after treatment suggests disease relapse[23]	
	Plasmablasts could upregulate the expression of collagen genes[42]	
Memory B cells	Ratios of $CD19^+CD24^+CD38^-$ memory B cells increase in IgG4-RD[52] and negatively correlate with serum IgG4	Potential predictor for disease recurrence
	Elevated ratios of $CD19^+CD20^+CD27^+CD38^-$ memory B cells are accompanied with disease remission[53,54]	
	The percentage of $CD19^+IgD^-CD27^+CD38^-$ memory B cells is reduced after treatment[14]	
	Ratios of $IgG4^+$ memory B cells increase and IgM^+IgD^+ memory B cells decrease in IgG4-RD[57]	
	$CD19^+CD20^+CD27^+CD38^-$ memory B cells increase in relapsing patients[54]	
Bregs	Ratios of $CD19^+CD24^{hi}CD38^{hi}$ Bregs decline in IgG4-RD[52]	Potential biomarker with clinical phenotype
	Ratios of $CD19^+CD24^{hi}CD38^{hi}$ Bregs increase in type 1 AIP[63]	
	Ratios of $CD19^+CD24^{hi}CD27^+$ Bregs decrease in type 1 AIP[63]	
	Patients with low frequency of Bregs respond poorly to treatment[55]	
Naïve B cells	The B cells decline after treatment[54]	Indicator of disease activity
	Patients with high plasmablasts and low naïve B-cell levels seem to suffer high disease severity[55]	

AIP, autoimmune pancreatitis; Bregs, regulatory B cells; ESR, erythrocyte sedimentation rate; IgG4-RI, IgG4-related disease response index.

clinical characteristics. The diagnostic utility of serum IgG4 levels for IgG4-RD is widely recognised. However, 37–49% of patients with IgG4-RD have a general range of serum IgG4 levels.[8,17,56] Circulating plasmablasts are more robust diagnostic indicators than serum IgG4 concentrations and are considered novel biomarkers of IgG4-RD. Plasmablast levels are useful in evaluating disease activity and predicting clinical flares. The excellent performance of circulating plasmablasts makes them promising biomarkers of IgG4-RD. However, flow cytometry measurement remains challenging because of the limitations of research centres and irregular applications. Further investigation into convenient diagnostic methods for the clinical practice of IgG4-RD is expected.

Memory B cells

Upon repeated stimulation with antigens, memory B cells rapidly differentiate into mature antibody-secreting cells and exert immune effects. Memory B cells with different immunophenotypes appear to exhibit variations in IgG4-RD. Lin *et al.*[52] observed a higher proportion of $CD19^+CD24^+CD38^-$ memory B cells in patients with active IgG4-RD than in patients with primary Sjögren's syndrome and healthy individuals, while Lanzillotta *et al.*[53] identified a similar level among these groups. No correlation between memory B cells and IgG4 levels has been reported in patients with IgG4-RD.[57] $CD19^+IgD^-CD38^-CD27^+$ memory B cells were reduced following the combination remedy of GC plus iguratimod.[14] Evidence suggests that $CD19^+CD20^+CD27^+CD38^-$ memory B cells significantly increase above the baseline value in relapsing patients, whereas other B-cell subsets decline uniformly in the relapse and non-relapse groups.[54] Further survival analysis confirmed the value of memory B cells as potential predictors of disease recurrence. Signalling lymphocytic activation molecule 7 (SLAMF7) is a receptor expressed on CTLs and activated B cells that modulate immune responses. $CD4^+SLAMF7^+$CTLs expand in the peripheral blood and fibrotic tissues of a small number of patients with IgG4-RD and secrete numerous profibrotic cytokines.[47] Higashioka *et al.*[58] found that the expression of SLAMF7 was markedly upregulated in memory B cells compared with naïve B cells. The result was attributed to the interaction with Tfh1 and inflammatory cytokines, such as interferon-γ and IL-21. The mutual effect of $SLAMF7^+$-activated cTfh1 cells and $IgG4^+$ memory B cells through SLAMF7 may assist in the differentiation of memory B cells into IgG4-secreting plasma cells.

Regulatory B cells (Bregs)

Among B-cell subsets, Bregs suppress immune response depending on IL-10 and TGF-β in several autoimmune diseases.[59] Through these anti-

inflammatory cytokines, Bregs restore the Th1/Th2, Th17/Treg and Tfh/follicular regulatory T cell balance, further interrupting the inflammatory cascade reactions.[60] In patients with active rheumatoid arthritis and systemic lupus erythematosus, a significant decline in peripheral Bregs indicates an impaired capacity to suppress the inflammatory response.[61,62]

Regarding IgG4-RD, $CD19^{+}CD24^{high}CD38^{high}$Bregs and $CD19^{+}CD24^{high}CD27^{+}$Bregs in peripheral blood were evaluated in AIP. The former phenotype of Bregs was elevated, while the latter was reduced in IgG4-RD AIP.[63] The cell counts of IL-10-producing Bregs were comparable between IgG4-RD patients with AIP and healthy controls. Thus, no correlation between the frequency of Bregs and the IgG4 levels was identified.[52] Zhang *et al*. classified three subgroups based on B-cell heterogeneity in IgG4-RD.[55] The subgroup with high levels of memory B cells and low levels of Bregs showed a poor response to treatment. TGF-β is generally considered to exhibit a remarkable role in fibrogenesis. However, its precise contribution has not been confirmed in IgG4-RD. The role of Bregs in IgG4-RD remains unclear. Further investigation is required to better understand the underlying pathogenesis of IgG4-RD.

B-CELL OMICS IN IGG4-RD

The omics approach can explore key molecules related to disease conditions based on clinical samples, thereby providing valuable clues for exploring mechanisms. Numerous serological biomarkers of IgG4-RD have been identified using metabolomics. Serum α-1 antitrypsin was significantly elevated in patients with IgG4-RD and was decreased after treatment.[64] It promotes B-cell differentiation and induces the secretion of IgE and IgG4 *via* IL-4 and CD40. An investigation of the proteomic atlas of IgG4-RD revealed that several B-cell related pathways and proteins involved in antigen presentation and B-cell receptor signalling are enriched in IgG4-RD tissue.[65] In another proteomic analysis, proteins associated with the complement system were upregulated in exosomes isolated from IgG4-RD plasma samples.[66] This analysis revealed that the extracted exosomes activated B cells *via* the oxidative stress pathway. Single-cell RNA sequencing is a novel method for evaluating transcriptional information at the single-cell level. Wu *et al*.[67] identified five B-cell subclusters based on immunophenotypes using single-cell RNA sequencing: naïve B (cluster 1), memory-unswitched B (cluster 2), memory-switched B (cluster 3), plasma B (cluster 4) and SOX4 naïve B (cluster 5). Distinct clusters differed in their functional enrichment. Among these clusters, glycolysis/gluconeogenesis and protein processing pathways were enriched in cluster 4, suggesting a potential metabolism mechanism in antibody production. Metabolomic, lipidomic and other omics data with B cells in IgG4-RD are limited and relevant studies are warranted.

B-CELL TARGETED THERAPY

The expression of transmembrane proteins CD19 and CD20 on B cells differs in the differentiation phase. B cells play an important role in the pathophysiology of IgG4-RD, suggesting their potential as novel therapeutic targets. Various B-cell depletion therapies are undergoing continuous development with satisfactory curative effects on clinical remission and fibrotic alleviation.

Targeting CD20

RTX, a monoclonal anti-CD20 antibody, is widely used as a biological agent to promote clinical and histological improvements in IgG4-RD.[17,19,23,41,68] In a clinical study, 83% of patients with IgG4-RD AIP exhibited steroid or immunosuppressant resistance but achieved complete remission under RTX therapy.[16] Carruthers *et al*.[17] also verified the favourable efficacy of RTX, up to 97% of patients rapidly achieved remission within half a year without combination with GC. However, a few patients remain poorly responsive to RTX treatment.[39] The clinical efficacy of RTX varies among patients, including therapeutic response and remission time.[17] The authors reported that the experimental indicators of IgG4-RD simultaneously responded to treatment with clinical improvement. Serum IgG4 concentration and erythrocyte sedimentation rate rapidly decline after RTX therapy.[17,18,23,68] The RTX biosimilar agent, CT-P10, has also been proven to be effective and safe for the induction of remission.[69] Another targeted agent, binutuzumab, is considered an alternative treatment for patients resistant to RTX.[70] This humanised type II anti-CD20 monoclonal antibody directly induced cell death *via* antibody-dependent cell-mediated cytotoxicity. Few relevant adverse reactions reflect the low immunogenicity of the antibody. Ginthör *et al*.[71] reported that one patient with IgG4-related membranous nephropathy achieved

complete remission with obinutuzumab therapy due to RTX allergy.

RTX exerts its therapeutic effects by modulating the immune response. $CD19^{+}CD27^{+}CD20^{-}CD38^{high}$ plasmablasts are oligoclonally expanded in patients with active IgG4-RD. A significant decline in the number of circulating plasmablasts after RTX treatment and disease remission has been previously described.[18,22,23,47] Although the therapeutic efficacy of RTX is widely established, its mechanism of action remains unclear. Mature B cells lack CD20 expression on their surfaces. One possible explanation for this remission is that RTX induces plasma cell deficiency by depleting the $CD20^{+}$ precursors. This may explain the decreased circulating plasmablasts and serum IgG4 levels after RTX treatment. In addition, B-cell depletion may interfere with T- and B-cell interactions, leading to decreased levels of inflammatory cytokines and further improving the disease conditions in IgG4-RD.[41,47,72]

Targeting CD19

In addition to anti-CD20 antibodies, antibodies targeting CD19 can potentially affect the B-cell pool. Anti-CD19 blocks the cell signalling *via* the B-cell receptor by the combination with Fc-γ-RIIb on B cells. One completed open-label single-arm trial (clinicaltrials.gov: NCT02725476) evaluated the effects of obexelimab (Xmab5871) on IgG4-RD. The alleviation of disease activity was observed in all 15 patients. Another randomised, double-blind trial (clinicaltrials.gov: NCT04540497) is currently recruiting patients in phase III to explore the curative effect of inebilizumab in IgG4-RD. Despite the limited evidence on CD19 antibody-targeted therapy, these trials offer the prospect of novel B-cell targeted therapies.

Other targeted therapy

Bruton's tyrosine kinase (BTK) is a key molecule involved in B-cell growth, proliferation and differentiation *via* the B-cell receptor signal transduction pathway.[73] BTK inhibitors have shown promising effects in numerous rheumatic disorders.[74,75] Two phase 2 clinical trials of the BTK inhibitors, zanubrutinib (clinicaltrials.gov: NCT04602598) and rilzabrutinib (clinicaltrials.gov: NCT04520451), are ongoing. The elevation of serum IL-6 levels suggests an enhanced inflammatory response in IgG4-RD.[52,76] The blockage of Janus kinase 1/2 inhibitors on IL-6/IL-6 receptor signal implies its therapeutic potential.[76] Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, has shown good curative effects and tolerance in IgG4-RD.[77,78] Other feasible therapeutic strategies are emerging for the treatment of IgG4-RD.

The efficacy of B-cell targeted therapy has been broadly evaluated in several autoimmune diseases.[79] However, clinicians should consider the side effects of B-cell targeted therapy. Infusion reaction,[16] neutropenia[16] and infection[17,18] have been reported in patients with IgG4-RD receiving RTX treatment. Non-infectious events such as allergies and neutropenia are relatively common. Infections mainly occur in the respiratory and urinary tracts and mucocutaneous tissues.[80] Progressive multifocal leukoencephalopathy can occur with long-term use of RTX.[81] However, most adverse events are mild to moderate. Collective evidence indicates that RTX is an efficient therapeutic strategy that is well tolerated, with few severe adverse events. The safety of other emerging B-cell targeted therapies requires substantial evidence-based evaluation.

CONCLUSION

Multiple processes cooperate to induce inflammation and fibrosis in IgG4-RD. The pathogenicity of B lymphocytes is attributed to the production of antibodies and their profibrotic properties. The efficacy of B-cell depletion therapy represents the paramount role of B cells in the pathogenesis of IgG4-RD. The correlation with disease activity differed among different B-cell subsets. Among these cells, plasmablasts have been extensively explored and are acknowledged as valuable novel biomarkers. Nevertheless, other B-cell subsets require further investigation. The derivation and function of these autoantibodies remain unclear and need to be elucidated. However, the exploration of B cells provides new potential avenues for curative strategies against IgG4-RD, which are urgently needed and are under development.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Qiyuan Hao: Conceptualization; writing – original draft. **Meng Sun:** Conceptualization; writing – review and editing. **Yanying Liu:** Conceptualization; funding acquisition; writing – review and editing.

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