Correlations between IgG4-related disease and allergic reactions: implications for future therapeutic strategies

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ABSTRACT

IgG4-related disease (IgG4-RD) is a chronic multi-organ immune fibroinflammatory disorder. It can affect almost any organ, with the primary treatment being corticosteroids, sometimes supplemented with conventional immunosuppressants or biological agents, such as rituximab therapy. The occurrence of this disease is associated with aberrant adaptive immune responses, but its specific pathological mechanisms remain unclear. Patients with IgG4-RD often have allergic diseases such as asthma, rhinitis, and urticaria. Allergic reactions and IgG4-RD may share similar pathological mechanisms, including activation of Th2 immune responses, excessive secretion of IgG4 and IgE, and increased blood/tissue eosinophils. The aim of this article is to review the allergy-like characteristics of IgG4-RD and emphasise the potential of allergy-targeted therapies in the treatment of IgG4-RD patients.

Introduction

IgG4-RD is a rare and serious fibroinflammatory disorder characterised by dense lymphoplasmacytic infiltration of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis (1). This disease can affect multiple organs, such as the salivary glands, lymph nodes, lacrimal glands, pancreas, thyroid, kidneys, lungs, retroperitoneum, and meninges, resulting in a wide range of clinical manifestations (2-10). Although the occurrence of IgG4-RD is associated with abnormal adaptive immune responses, the specific pathogenesis is still unclear. Patients with IgG4-RD often have concurrent allergic diseases such as asthma, sinusitis, and urticaria (11-14).

Allergy refers to an abnormal adaptive immune response that occurs when the body is exposed to certain antigens, typically resulting in symptoms such as itching, rash, asthma, and allergic rhinitis (15). Allergic reactions and IgG4-RD may have similar pathogenic mechanisms. In this review, we investigate the potential connections and interactions between IgG4-RD and allergy. We explore the pathogenesis, clinical features, and therapeutic approaches of IgG4-RD, while also discussing emerging findings and future research directions in the realm of allergic reactions. By comprehensively examining these seemingly disparate yet possibly interconnected immune phenomena, we aim to offer fresh insights into the mechanisms governing the immune system and provide inspiration for future clinical practice and therapeutic strategies.

Immunopathological mechanisms of IgG4-RD and allergy

IgG4-RD and allergic diseases share some common immunopathological features. The relationship between type 2 immune response with allergy and IgG4-RD is closely associated. The type 2 immune response primarily involves antibody-mediated immune reactions, particularly targeting parasitic infections and allergic reactions. Type 2 T helper (Th2) cells and group 2 innate lymphoid cells (ILC2s) play a crucial regulatory role in these processes by producing and releasing type 2 cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). These cytokines facilitate the differentiation of B cells into plasma cells, leading to the production of specific types of antibodies (such as IgE, IgG1, and IgA), and enhancing the growth and activation of eosinophils. In allergies and IgG4-RD, the activation of type 2 immune response plays a crucial role in disease onset and progression.

Type 2 immunity in IgG4-RD and allergy

The type 2 immune response is not only mediated by Th2 cells but also by ILC2s, which are activated by cytokines like interleukin-33 (IL-33), thymic stromal lymphopoietin (TSLP), and interleukin-25 (IL-25). Th2 cells and ILC2s are important sources of type 2 cytokines such as IL-4, IL-5, and IL-13 (16). When the organism elicits an aberrant or exaggerated immune response towards ordinarily innocuous substances, such as pollen, dust mites, food proteins, etc., it instigates an allergic reaction. This hypersensitivity reaction typically implicates the type 2 immune response within the immune system (17). In numerous studies, IgG4-RD patients have been found to exhibit type 2 cytokines in both their circulation and affected organs, indicating the involvement of type 2 immune response in the pathogenesis of IgG4-RD. Research has revealed upregulation of type 2 cytokines IL-4, IL-5, and IL-13 in the serum and tissues of patients afflicted with IgG4-RD (18-20). In IgG4-RD, these cytokines activate B cells to undergo class switching from IgM to IgE and/or IgG4, concurrently promoting an increase in peripheral blood eosinophils (21-23). Additionally, in patients with IgG4-related dacryoadenitis and sialadenitis-circulating Th2 cells have been detected-along with significant of Th2 cells in the affected tissues (24). Thymus and activation-regulated chemokine (TARC), also known as CCL17, is a chemokine, which involves in immune responses and inflammatory processes, primarily expressed by Th2 cells (25). Higher TARC levels have been found in individuals diagnosed with atopic dermatitis and asthma, suggesting its potential significance as a key mediator in allergic diseases (26). Additionally, increased TARC levels have been detected in the serum of patients with IgG4-RD (27, 28), correlating with IgG4-RD responder index (IgG4-RD RI) scores and the number of affected organs, but not with blood IgG4 levels or peripheral eosinophil counts (29). IL-33 and TSLP promote the occurrence of acute type 2 immune responses and are upregulated in the plasma and submandibular glands of IgG4-RD patients (30-34). IL-10 produced by Th2 cells is also elevated in IgG4-RD (18).

The role of IgG4 in allergy and IgG4-RD

IgG comprises four subclasses: IgG1, IgG2, IgG3, and IgG4, with IgG4 exhibiting the lowest concentration (35). However, IgG4 possesses a series of unique characteristics compared to other IgG subclasses. IgG4 can undergo Fab-arm exchange, endowing it with bispecific antigen-binding properties. Due to the presence of amino acid residues at specific positions that are distinct from those observed in other IgG subclasses, IgG4 exhibits a unique binding pattern with Fcγ receptors. Particularly, mutations such as L234F, A327G, and P331S in IgG4 result in decreased affinity for Fcγ and C1q, relative to IgG1. However, IgG4 binding to the inhibitory receptor FcγRIIb remains unaffected, leading to a tendency for IgG4-induced Fcγ receptor signalling to be inhibitory. These characteristics of IgG4 impede its immunological response or target protein blockade have led to its widespread recognition as an anti-inflammatory antibody with beneficial functions in allergic diseases. The clinical significance of IgG4 in allergic diseases remains controversial. Mounting evidence suggests that IgG4 may also plays a pathogenic role in a range of diseases, including IgG4-RD-eosinophilic esophagitis (EoE) (36-38). The balance between IgG4 and IgE is implicated in the occurrence of allergy and immune tolerance. IgG4 production initiates approximately 6-8 weeks after allergen-specific immunotherapy (AIT) (39), and increases following a decline in IgE levels (40). This may suggest that AIT serves as an inducer for IgG4-RD. However, a study investigating the relationship between AIT and IgG4-RD revealed that although atopic manifestations did not increase in IgG4-RD, a higher prevalence of AIT treatment history was observed among IgG4-RD patients compared to the general population. This observation might not necessarily imply a pathogenic role of AIT in IgG4-RD but rather suggests a higher incidence of refractory allergic diseases among IgG4-RD patients. Furthermore, some patients who underwent AIT were diagnosed with IgG4-RD a decade after AIT cessation, making it challenging to establish a causal relationship between the two events (41). EoE is a chronic esophageal disorder mediated by Th2 cells, characterised by oesophageal dysfunction and eosinophilic infiltration. Although EoE is considered a form of food allergy, its pathogenesis is not IgE-mediated (42). Serum IgG4 levels are significantly elevated in patients with EoE (43), and IgG4 deposition has also been observed in esophageal biopsy specimens (44), suggesting that IgG4 may play a role in the pathogenesis of EoE. The exact role of AIT in EoE is yet to be fully elucidated. While AIT treatment may be associated with the progression of EoE, and clinical and histological improvements have been noted following the cessation of therapy (45, 46), many EoE patients develop the disease before undergoing AIT (47, 48), indicating that AIT may not be a direct trigger for EoE.

The role of IgE in allergy and IgG4-RD

IgE, a pivotal antibody in allergic reactions, plays a crucial role in immune responses to allergens. Upon entry of allergens into the body, antigen-presenting cells such as macrophages and dendritic cells ingest and process the antigens, presenting antigen fragments to T helper cells. Activated Th2 cells produce IL4 and IL13, stimulating B cells to differentiate into plasma cells that produce specific IgE antibodies. IgE circulates in the bloodstream and binds with high affinity to FcεRI receptors on the surface of mast cells and basophils. Upon re-exposure to the same allergen, these cells release a cascade of inflammatory mediators, leading to the occurrence of allergy (49). IgE-mediated allergic reactions are prevalent in the majority of IgG4-RD patients (50-57). A prospective study in the United Kingdom suggests that IgE levels may serve as diagnostic and predictive markers for IgG4-RD recurrence (50), with IgG4-RD patients with higher baseline IgE levels possibly exhibiting

Table I. Incidence of allergic disease.

no. and ref.	Nation	Study design	Study population	Incidence of allergic disease
1 (78)	China	Retrospective cohort study	622 IgG4-RD	Allergic diseases:310(49.8%)
2 (51)	China	Retrospective cohort study	459 newly diagnosed IgG4-RD patients	Allergic diseases: 201(43.8%) Rhinitis: 99(49.3%) Drug allergy: 30(14.9%) Bronchial asthma: 20(1%) Food allergy: 3(1.5%) Contact allergy: 7(3.5%) Mixed allergy: 11(5.5%)
3 (61)	China	Case-control study	434 IgG4-RD	Allergic diseases: 214 (49.3%) Rhinitis: (74.3%) Conjunctivitis: (3.7%) atopic dermatitis: (8.9%) Asthma: (34.6%) Urticaria: (27.6%) Food allergy:(1.9%)
4 (66)	China	Retrospective study	428 IgG4-RD	Allergic diseases: 172(40.2%)
5 (79)	Japan	Retrospective study	235 IgG4-RD	Allergic diseases: 70 (29.8%) Rhinitis: 29(41.4%) Bronchial asthma: 25(35.7%) Drug allergy: 16(22.9%)
6 (53)	America	Case-control study	231 IgG4-RD	Allergic diseases165: (71.4%) Aero-allergen symptoms: 135 (81.8%) Food allergy symptoms and hypersensitivities: 47 (28.5%) Skin allergy symptoms: 97(58.8%) Anaphylaxis: 20(12.1%)
7 (80)	Japan	-	123 IgG4-RD	Allergic diseases: 57(46.3%) Rhinitis: 39 (68.4%) atopic dermatitis: 1 (1.8%) Asthma: 9(15.8%)
8 (56)	China	Prospective study	118 IgG4-RD	Allergic diseases: 73(61.9%) Sinusitis: 15(20.5%)
9 (41)	Italy	Retrospective study	116 patients with biopsy-proven IgG4-RD	Allergic diseases: 29 (25%) Inhalants: 15(51.7%) Foods allergy: 3 (10.3%) Drugs allergy: 18(62.1%) Contact allergens: 3(10.3%) Anaphylaxis: 3(10.3%)
10 (81)	Japan	Cross-sectional study	114 IgG4-RD	Allergic diseases: 22(19.3%) Rhinitis: 2(9.1%) Sinusitis: 4(18.2%) Bronchial asthma: 14(66.7%) Drug allergy: 2(9.1%)
11 (82)	America	-	74 IgG4-RD	Allergic diseases: 33(44.6%) Rhinitis: 18(54.5%) Conjunctivitis: 5(15.2%) Bronchial asthma: 9(27.3%) Hives: 3(9.1%) Oral allergic syndrome: 1(3%) Eczema: 2(6.1%) Hay fever: 2(6.1%)
12 (52)	America	Retrospective cohort study	70 sequential patients with biopsy-proven IgG4-RD	Allergic diseases: 22(31.4%) Rhinitis: 16(72.7%) Conjunctivitis: 5(22.7%) Bronchial asthma: 8(36.4%) Hives: 3(13.6%) Oral allergic syndrome: 1(4.5%)
13 (55)	Japan	Retrospective study	51 IgG4-RD	Allergic diseases: 22(43.1%) Rhinitis: 15 (68.2%) Conjunctivitis: 4 (18.2%) Bronchial asthma: 13(59.1%)
14 (83)	America	-	39 IgG4-RD	Allergic diseases: 18(46.2%) Rhinitis: 12(66.7%) Conjunctivitis: 3(16.7%) Bronchial asthma: 5(27.8%) Hives: 3(16.7%) Gastrointestinal symptoms: 1(5.6%)

increased disease activity and recurrence risk (51, 52). In a cohort study, compared to patients with normal IgE levels, those with elevated IgE levels in IgG4-RD commonly presented with involvement of the submandibular glands and pancreas, as well as multiple affected organs and higher IgG4-RD RI scores (51). However, some IgG4-RD patients without atopy also demonstrated elevated IgE levels, suggesting that IgE elevation may be independent of allergy or atopy and instead be a reactive process in IgG4-RD (52).

The role of eosinophils in allergy and IgG4-RD

In patients with IgG4-RD, there is an elevation of eosinophils in the circulation (50, 52-56, 58-61), and the presence of eosinophils has also been observed in the tissues of IgG4-RD patients (50, 62, 63). Researches show elevated eosinophils are an independent risk factor for IgG4-related systemic respiratory diseases (64), and are associated with pancreato-biliary disease of IgG4-RD (65). Compared to patients without salivary gland involvement, those with salivary gland involvement in IgG4-RD demonstrate higher eosinophil counts and a higher prevalence of allergic diseases (66).A cohort study involving 425 patients revealed that the coexistence of IgG4-RD and eosinophilia is more common in male patients, who exhibit longer disease duration, increased occurrence rates of dacryoadenitis, sialadenitis, lymphadenopathy, and rash, elevated IgG4-RD RI scores, involvement of a greater number of organs, and higher serum IgG4 levels. Nevertheless, there is no notable discrepancy in the prevalence of allergic conditions between IgG4-RD patients with and without eosinophilia, suggesting that the elevated eosinophils levels in IgG4-RD may not be directly associated with allergic processes (58). However, contrasting results from another study indicate a correlation between elevated eosinophils and allergies (53).

Genetic susceptibility to IgG4-RD and allergy

Genetic susceptibility to IgG4-RD is currently under investigation, with specific susceptible genes yet to be fully elucidated. Genome-wide association studies have identified HLA-DRB1 and FCGR2B as two susceptibility loci for IgG4-RD(67), while genetic variations in the IL1R1 gene are associated with IgG4-related periaortitis/periarteritis (68). The HLA-DRB1 locus is implicated in cefaclor-induced immediate hypersensitivity reactions (69), iodinated contrast medium-related systemic allergic reactions (70), chronic spontaneous urticaria (71, 72), and allergic rhinitis (73). Proteomic analysis has shown upregulation of HLA-DRB1 protein in urine of allergic rhinitis patients (74). The functional polymorphism of FCGR2B may play a role in the pathogenesis of allergy (75). Additionally, elevated IL1R1 protein levels are associated with increased risk of allergic diseases (76), with an increase of one standard deviation in plasma IL1R1 linked to heightened asthma risk (77). These findings suggest common immunopathogenic mechanisms between IgG4-RD and allergy.

Clinical association between allergy and IgG4-RD

The prevalence of allergic diseases associated with IgG4-RD

There is a significant difference in the prevalence of concurrent allergic diseases in IgG4-RD across different studies. Allergic symptoms are documented in 19.3–71.4% of IgG4-RD patients, with rhinitis (9.1–74.3%), bronchial asthma (1–66.7%), drug allergies (9.1–62.1%), food allergies (1.5–28.5%), conjunctivitis (3.7–22.7%), and skin allergies (9.1–58.8%) being the most commonly reported allergies (Table I). Among patients with allergies, age appears to be a significant factor. According to a study, patients aged 40 to 59 years are more likely to suffer from allergies than younger or older patients (54).

IgG4-RD organ involvement and allergy

According to the research findings, allergies are more common in IgG4-RD patients with head, neck, and chest involvement. Patients diagnosed with IgG4-related ophthalmic diseases exhibit a higher prevalence of allergies compared to those not affected by the disease (84). Researchers found that patients with concurrent salivary gland involvement were more likely to experience allergic symptoms in both a retrospective and prospective study (66, 85). Furthermore, patients with IgG4-related chronic rhinosinusitis have a higher incidence of allergies compared to those unaffected by this condition (86). Allergies are also more prevalent in patients with intrathoracic lesions (87). A large cross-sectional study involving 756 patients with IgG4-RD indicates that multi-organ involvement is more common among those who have allergic rhinitis and chronic sinusitis compared to those without these conditions (13). Another large case-control study encompassing 434 patients observed that more organ involvement in allergic IgG4-RD patients compared to those without allergies (61).

Allergic reactions contribute to the relapse of IgG4-RD

IgG4, IgE, elevated eosinophils, and allergies may be risk factors for IgG4-RD relapse. Some studies suggest that allergies are a risk factor for relapse (88-90), while others do not support this finding (51, 80, 91, 92). Similarly, elevated eosinophils have been implicated in relapse in some studies (51, 54, 89, 92), yet others have not corroborated this association (88, 91). Two studies on IgG4-ROD propose that allergies, eosinophils and IgE are not predictive of relapse (84, 93). There is also controversy over whether elevated IgG4 can cause disease relapse. Serum IgG4 levels show no correlation with relapse in IgG4-ROD (93); however, other studies suggest that higher IgG4 levels may lead to a higher risk of relapse in IgG4-RD and IgG4-ROD (94-97). Research currently indicates that IgG4 ≥6.5g/L is a predictive factor of relapse in IgG4-RD (94). According to a study of 60 patients suffering from IgG4-RD who were treated with rituximab, elevated eosinophils, IgE, and IgG4 were associated with recurrence risk (60). Despite higher relapse rates among patients with baseline IgE levels >60 KU/L, follow-up levels of IgE were not predictive of relapse (51).

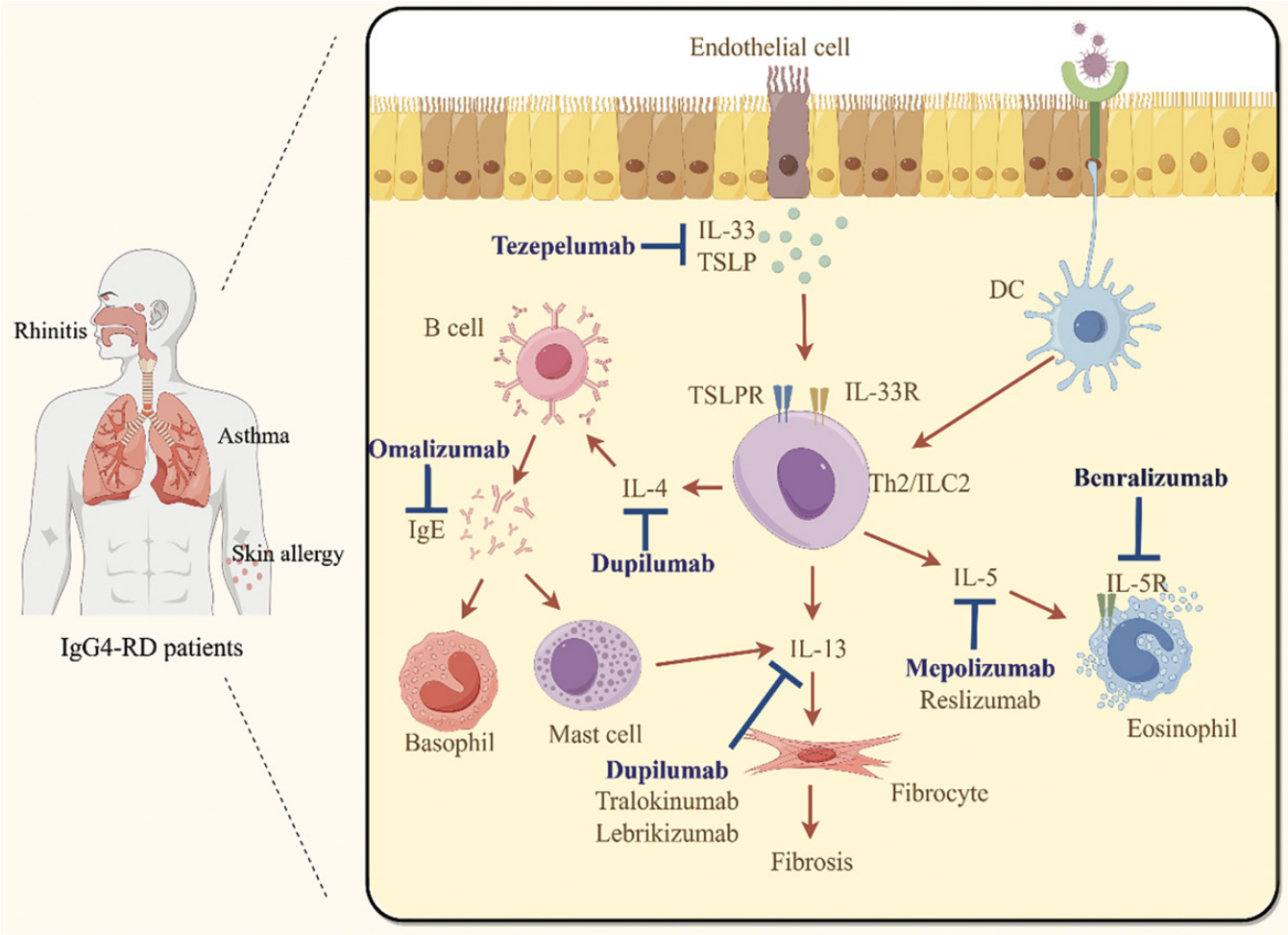

Fig. 1. Pathogenesis and potential allergy-related therapeutic targets in IgG4-RD.
Type 2 immune responses, primarily characterised by antibody-mediated reactions, are closely associated with allergy and IgG4-RD. When DCs are activated, they have the capacity to stimulate Th2 cell activation. Concurrently, damaged endothelial cells secrete factors such as IL-33 and TSLP to activate ILC2/Th2 cells. Th2 cells produce and release type 2 cytokines including IL-4, IL-5, and IL-13. IL-4 promotes B cell maturation and differentiation, induces class-witching of immunoglobulins, and secretion of specific antibodies such as IgE, thereby promoting activation and degranulation of eosinophils and mast cells. IL-5 primarily activates eosinophils. IL-13 sustains Th2 cell responses, induces fibrosis, and plays a critical role in the pathogenesis of IgG4-RD. Dupilumab, by blocking the IL-4 and IL-13 signalling pathways, effectively controls inflammation and fibrosis in IgG4-RD patients, reduces serum IgG4 levels and IgG4-RD RI, and improves enlargement of lacrimal and submandibular glands. Tralokinumab and lebrikizumab inhibit IL-13 signalling and show potential therapeutic effects in improving organ fibrosis in IgG4-RD patients. Mepolizumab and reslizumab are monoclonal antibodies targeting IL-5, while benralizumab is a recombinant monoclonal antibody targeting IL5Rα. They hold potential therapeutic efficacy in treating peripheral blood or tissue eosinophilia-associated IgG4-RD. Omalizumab, a humanised anti-IgE antibody, effectively reduces serum-free IgE levels and inhibits FcεRI expression on the surface of mast cells and basophils, thereby attenuating their activation, which may benefit IgG4-RD patients with elevated IgE levels. Tezepelumab, a humanised monoclonal antibody against TSLP, reduces inflammation in Lat^{Y136F} knock-in mouse lungs and represents a potential novel therapeutic approach for future IgG4-RD treatment.
DC: dendritic cells; ILC2 cell: group 2 innate lymphoid cell; Th2 cell: T helper cell; IgG4-RD: IgG4-related disease; TSLP: thymic stromal lymphopoietin; IL4: interleukin 4; IL-5: interleukin 5; IL-13: interleukin 13; IL-33: interleukin 33.

The future therapeutic directions for IgG4-RD

IgG4-RD is a chronic inflammatory disorder characterised by fibrosis affecting multiple organs and systems throughout the body. At present, This disease is initially treated with glucocorticoids. For patients experiencing relapse or refractory cases, treatment options include traditional immunosuppressive agents such as methotrexate, azathioprine, leflunomide and mycophenolate mofetil, as well as biologics like rituximab (98). However, despite these treatments, there remains a risk of relapse (99), highlighting the urgent need to explore more effective treatment modalities. IgG4-RD shares similar pathogenic mechanisms with allergic diseases, involving activation of type 2 immune responses. Monoclonal antibodies targeting the type 2 immune response pathway may thus emerge as novel therapeutic options for IgG4-RD.

Dupilumab, a fully humanised monoclonal antibody (mAb), interacts with the interleukin-4 receptor alpha (IL-4Rα) subunit to disrupt IL-4 and IL-13 signalling pathways via binding to their shared IL-4Rα, thereby suppressing type 2 inflammation. Approved indications for dupilumab include atopic dermatitis, moderate to severe asthma, and chronic rhinosinusitis with nasal polyposis (100-102). Dupilumab has been shown in prior studies to effective-

ly control inflammation and fibrosis in patients diagnosed with IgG4-RD (103-105), reduces serum IgG4 levels and IgG4-RD RI, and improves enlargement of lacrimal and submandibular glands (106-109). However, further research is necessary to evaluate its efficacy and safety in treating IgG4-RD.

Tralokinumab and lebrikizumab are monoclonal antibodies that inhibit IL-13 signalling. Tralokinumab functions by blocking the binding of IL-13 to IL13Rα1 and IL13Rα2, which can alleviate pulmonary fibrosis in a humanised mouse model of idiopathic pulmonary fibrosis (IPF) (110) and has been used to treat atopic dermatitis (111). Lebrikizumab inhibits IL13Rα1/IL-4Rα heterodimer receptor signalling and has demonstrated effectiveness in asthma (112) and atopic dermatitis (113). Nevertheless, studies have indicated that lebrikizumab, whether administered alone or in combination with pirfenidone, does not demonstrate significant efficacy in patients with IPF (114). Therefore, anti-IL-13 monoclonal antibodies also demonstrate potential therapeutic effects in IgG4-RD, particularly regarding organ fibrosis.

Mepolizumab and reslizumab are synthetic monoclonal antibodies against interleukin-5 (IL-5), while benralizumab is a recombinant IL5Rα monoclonal antibody. These agents are currently used in severe eosinophilic asthma therapy, effectively reducing eosinophil counts in the blood (115, 116). In a multicenter, double-blind, phase 3, randomised, active-controlled non-inferiority trial, benralizumab and mepolizumab were evaluated for their efficacy in treating eosinophilic granulomatosis with polyangiitis (EGPA), showing a reduction in eosinophil counts in EGPA patients (117). Moreover, among patients receiving benralizumab for EGPA, a reduction in serum IgG4 levels was noted (118). Currently, 300 mg of mepolizumab is approved for the treatment of EGPA. In a case of EGPA combined with IgG4-RD, combined immunosuppressive therapy with mepolizumab improves the patient's neuropathy and cardiac dysfunction (119), implying potential efficacy of anti-IL5 monoclonal antibodies in treating IgG4-RD associated with peripheral blood or tissue eosinophilia. Omalizumab, a humanised anti-IgE antibody, binds to IgE molecules, effectively reducing free IgE levels in serum. Additionally, it inhibits FcεRI expression on the surface of mast cells and basophils, thus mitigating their activation (120). Mast cell and basophil activation are possible mechanisms of fibrosis in IgG4-RD. Omalizumab is approved for the treatment of chronic urticaria and severe allergic asthma (121), potentially benefiting IgG4-RD patients with elevated IgE levels.

Tezepelumab is a humanised monoclonal antibody targeting thymic stromal lymphopoietin (TSLP). TSLP drives dendritic cells to promote the differentiation of naïve T cells into Th2 cells. Additionally, TSLP can directly drive mast cells to secrete Th2 cell cytokines. Tezepelumab blocks the binding of TSLP to its receptor, thereby reducing the production of eosinophils, among other cells (122). In Lat^{Y136F} knock-in mice, anti-TSLP therapy mitigates pulmonary inflammation (33). It holds promise as a potential new treatment option for IgG4-RD in the future.

Conclusion

In summary, IgG4-RD is characterised as a fibroinflammatory disorder of unknown aetiology that frequently coexists with allergic conditions. However, the specific mechanisms by which allergic processes influence IgG4-RD development remain poorly understood. It is hypothesised that common immunological pathways, such as the activation of type 2 immune responses, may underlie the pathogenesis of both IgG4-RD and its associated allergic manifestations. Future therapeutic strategies that target distinct elements of the type 2 inflammatory pathway could provide innovative treatment options for IgG4-RD. Nevertheless, extensive clinical research is essential to substantiate the effectiveness and safety of these therapeutic interventions in patients suffering from IgG4-RD.

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