Review

Role of eosinophilia in IgG4-related disease

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ABSTRACT

Immunoglobulin G4-related disease (IgG4-RD) is a heterogeneous immune-mediated condition that can affect almost any organ and is now being recognised with increasing frequency. Laboratory abnormalities including peripheral eosinophilia, hypergammaglobulinaemia, elevated serum IgE level, and hypocomplementaemia often provide initial clues to the diagnosis of IgG4-RD. The distinctive histopathological hallmarks of IgG4-RD are a dense lymphoplasmacytic infiltration with a high percentage of IgG4$^+$ plasma cells, storiform fibrosis, obliterative phlebitis, and mild to moderate tissue eosinophilia. Around 20–40% of patients with IgG4-RD presented with peripheral eosinophilia and 51–86% are manifested as tissue eosinophilia. These data indicate an extensive involvement of eosinophil in IgG4-RD. Here, we review the biology of eosinophil, the discovery of eosinophilia in IgG4-RD, and its association with disease activity and relapse. We also discuss the possible functions and therapeutic potential of eosinophil in IgG4-RD.

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibro-inflammatory condition that was newly recognised in 2003 (1-3). With the increase of the awareness of IgG4-RD, the disease incidence in population is now increasing. Unexplained tissue swelling or mass, which may involve one or multiple organs, is usually the first clinical symptom of this disease (4). Typical features of IgG4-RD are elevated IgG4 level and pathological hallmarks such as a dense lymphoplasmacytic infiltration with a high percentage of IgG4$^+$ plasma cells, storiform fibrosis, obliterative phlebitis and mild to moderate tissue eosinophilia (5, 6). Persistent immune and inflammation response leading to irreversible fibrosis and space-occupying lesions are the major causes of the dysfunction of affected organs.

Eosinophils, cells of the innate immune system, are a minor (<5%) component of circulating leukocytes (7). In pathological conditions, eosinophils are mainly tissue-resident cells and have a broader tissue distribution (8), and are sources of a wide variety of cytokines and chemokines other than exocytotic degranulation (9). It has been reported that around 20–40% of patients with IgG4-RD present with peripheral eosinophilia and 51–86% are manifested as tissue eosinophilia (4). This eosinophilia was found not to be related to allergy, which might be induced by processes inherent to IgG4-RD itself (10). Knowledge associated with eosinophilia in IgG4-RD is increasing in recent years, and novel therapeutic strategies targeting eosinophil or IL-5 receptor are being explored in other diseases. As the characteristic feature showed with peripheral or tissue eosinophilia, the role of eosinophilia in IgG4-RD is lack of comprehensive discussion. In this review, we summarise the role of eosinophilia and its potential value as a therapeutic target for IgG4-RD.

Biology of eosinophil

Eosinophil is one of the minor leukocyte populations. Once mature and released from the bone marrow environment, eosinophils circulate in the blood stream for approximately one day and most of them reside in mucosal surfaces for days (8, 9, 11). Circulating eosinophil count ranges from 0 to 500 per microliter in human blood. In abnormal conditions, the value can increase by 10-fold or more (12). Eosinophils have a complex subcellular structure including lipid bodies, primary and secondary granules, and a dynamic intracellular vesicular system (13, 14).

Eosinophils richly expressed cell surface receptors. The expressions of IL-3Rα, IL-5Rα, and GM-CSF-Rα, receptors for IL-3, IL-5, and GM-CSF, respectively, are required for eosinophil differentiation, maturation, activation, and survival in the bone marrow and tissues (9). The eosinophil is endowed with multiple immunoglobulin receptors and related family members, such as FcγRII and CD89, which are involved in eosinophil-mediated functional activities in mucosal sites. The expression of pattern recognition receptors, such as TLR, NOD, P2X7, RAGE, allows eosinophils to be stimulated directly by pathogen and/or damage-associated molecular patterns from invading microorganisms or its tissue microenvironment during host innate immune responses (9, 15). Eotaxins, including eotaxin-1/CCL11, eotaxin-2/CCL24 and eotaxin-3/CCL26, and their receptor CCR3 are important in promoting eosinophil trafficking across the vascular endothelium and epithelium into tissues (11). Human eosinophils express high level of CCR3, a major receptor involved in eosinophil chemotaxis, migration and recruitment (16). IL-5 promotes the proliferation of eosinophil precursors in the bone marrow and the activation and survival of mature eosinophils in the periphery, whereas local eotaxin expression drives eosinophil recruitment into tissues. Eosinophils also express negative regulation receptors, including Siglec-8, leukocyte immunoglobulin-like receptor 3, RhoH, Olig2 and CD300A, which are important in eosinophil apoptosis and suppression of eosinophil function (11, 17). The tissue accumulation of eosinophils *in vivo* is ultimately determined by a complex balance between pro-survival factors and signalling through inhibitory receptors.

Discovery of eosinophilia in IgG4-RD

IgG4-RD was recognised as a unified disease in 2003. Hamano *et al*. firstly reported elevated serum IgG4 concentration and infiltration of IgG4-positive plasma cells in pancreatic and retroperitoneal tissues in patients with autoimmune pancreatitis (AIP) (18, 19). Kamisawa *et al*. reported infiltration of IgG4-positive cells in multiple organs in patients with AIP and proposed a new clinicopathological entity of "IgG4-related autoimmune disease" (1). Meanwhile, researchers found elevated IgG4 level, IgG4-producing plasmacyte infiltration, lower frequency of apoptosis in glands compared with Sjögren's syndrome, and its good responsiveness to glucocorticoid in Mikulicz's disease (MD) (20, 21). The authors disclosed that MD represents a new entity (IgG4-related plasmacytic exocrinopathy) (21). Until 2011, this new disease entity and the nomenclature were accepted internationally as a new disease concept, IgG4-related disease (5, 22, 23). IgG4-RD includes a wide variety of diseases such as Mikulicz's disease, autoimmune pancreatitis, eosinophilic angiocentric fibrosis, riedel thyroiditis, hypophysitis, interstitial nephritis, interstitial pneumonitis, retroperitoneal fibrosis, prostatitis, lymphadenopathy, inflammatory aortic aneurysm, and inflammatory pseudotumour.

Early in 2005, it has been reported that inflammatory pseudotumour, an IgG4-related pulmonary disease, was histopathologically characterised by IgG4-positive plasma cells and lymphocytes infiltration, irregular fibrosis, obliterating phlebitis and arteritis, and eosinophilic infiltration (24). Deshpande *et al*. compared the histopathological characteristics of pancreatic and extrapancreatic tissues from patients with AIP, and found that distinguishing from type 2 AIP, type 1 AIP frequently showed a swirling/storiform pattern of growth, with eosinophils frequently interspersed within these zones of inflamed fibrous tissue (25). In 2010, a cross-sectional study of 114 IgG4-RD cases involving various organs found that eosinophilic infiltration presented in approximately 50–60% of the lesions regardless of the location of the affected organs (26). A consensus statement about the pathology of IgG4-RD was made in 2011, adding phlebitis without obliteration of the lumen and increased number of eosinophils as histopathological features of IgG4-RD (6). After the definition of IgG4-RD, researchers proposed comprehensive diagnostic criteria for IgG4-RD in 2011, stating that storiform or swirling fibrosis or obliterative phlebitis are characteristic of IgG4-RD and eosinophilic infiltration often occurs, along with infiltration of $IgG4^+$ cells (27). The 2019 ACR/EULAR classification criteria for IgG4-RD proposed that patients fulfilled the peripheral eosinophilia to a concentration of >3000 mm^3 should be excluded (28). Therefore, recent description of IgG4-RD morphologic feature is dense lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis, and mild-to-moderate tissue eosinophilia (2, 3, 5, 29).

Eosinophilia is also frequently occurred in other rheumatic conditions, especially eosinophilic granulomatosis with polyangiitis (EGPA). EGPA shows tissue eosinophilia, eosinophil-rich granulomatous inflammation, and necrotising vasculitis. Eosinophils are thought to play a critical role in EGPA, and eosinophil cationic protein has been found in serum and tissues of patients with active EGPA and is thought to cause tissue damage (30). IL-5 production is increased in EGPA patients. A random double-blind trial enrolled EGPA patients with a history of relapsing or refractory condition showed that mepolizumab, an anti-interleukin-5 monoclonal antibody, treatment reduced blood eosinophil counts and resulted in significantly more weeks in remission and a higher proportion of participants in remission (31). EGPA is considered within the family of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). A recent study has reported that AAV and IgG4-RD has overlap (32). A case has also reported that EGPA is a mimicker of IgG-RD (33).

The association of eosinophilia with IgG4-RD

There has been accumulating evidence for an involvement of eosinophil in the development of IgG4-RD. A prospective study of 48 patients with IgG4-RD showed that peripheral blood eosinophilia was detected in 38% of IgG4-RD patients compared with 9% of healthy controls, eosinophilia was also observed in lymphoid, biliary, and pancreatic tissue samples from 86% patients with

IgG4-RD (34). Furthermore, there was a positive correlation between blood eosinophil count and serum IgG4 level (34). Wallace *et al*. analysed the clinical and laboratory features of 125 biopsy-proven IgG4-RD patients, and found that patients with active disease and elevated serum IgG4 concentrations had higher blood absolute eosinophil counts compared to those with active disease but normal serum IgG4 concentrations (35). Li *et al*. established an IgG4-RD composite scoring system, which had four independent variables including blood eosinophil count, lymphocyte count, IgG levels, and the total number of involved organs. The results showed that this composite scoring had the potential to be complementary to the IgG4-RD responder index score to help assess disease severity (36). Wang *et al*. found that patients with dacryoadenitis and sialoadenitis (DS), previously referred to as MD, more commonly presented with increased number of blood eosinophils and higher serum IgG4 levels than those without DS (37). Wang *et al*. carried out a prospective study of 403 IgG4-RD patients and found that male sex was associated with higher peripheral eosinophil counts, CRP and IgG4 levels at baseline compared with female (38). Another study showed that eosinophilia, higher baseline responder index, having five or more organs involved, and dacryoadenitis were risk factors for remission induction failure with glucocorticoid monotherapy (39).

Relapse occurs frequently during the clinical course in IgG4-RD. This relapse includes recurrent organ involvement (ROI) and de novo organ involvement (DNOI). It has been shown that an elevation of peripheral blood eosinophil counts was related to DNOI (40). Wallace *et al*. concluded that high baseline of serum IgG4, IgE, and blood eosinophilia could predict IgG4-RD relapse independently (41). Peng *et al*. performed a long-term cohort study and found that elevation of blood eosinophil, higher serum IgG4 level, involvement of more organs and higher IgG4 responder index score were closely associated with disease relapse (42). A recent study compared the different clinical patterns of IgG4-RD patients with and without eosinophilia and found that peripheral eosinophil count was positively associated with disease duration, the number of involved organs, IgG4-RD responder index score, and serum IgG4 level (43). Moreover, higher recurrence rate was found during follow-up period in patients with eosinophilia (43). These data suggest the importance of eosinophilia in IgG4-RD relapse. Thus, the discovery of eosinophilia in periphery or affected tissues might be valuable in determining the prognosis and therapeutic options for IgG4-RD.

Eosinophilia in IgG4-RD is generally viewed as an integral part of the clinical feature, the causes of eosinophilia in IgG4-RD are not clear. Previous studies found that up to 40% of patients with IgG4-RD have allergic diseases (5, 44), and that IgG4-RD and allergic diseases have many features in common, including peripheral eosinophilia, high serum IgE level, eosinophil infiltration in tissues, and increased Th2 cytokines (10). These suggest that allergy may potentially play a potentially key role in the immunopathogenesis of IgG4-RD. On the contrary, Della Torre *et al*. in 2013 found that the prevalence of atopy in IgG4-RD was similar to that in the US general population, and that among patients who presented with peripheral blood eosinophilia, the mean eosinophil count was similar regardless of atopy (45). Saeki *et al*. retrospectively compared the clinical and laboratory features of IgG4-RD patients with and without allergic conditions in Japan and found that the absolute number of peripheral blood eosinophils, serum IgG4 level, the response to steroid, or the relapse rate were not significant different between the two groups (46). Recently, Zhang *et al*. analysed the IgG4-RD patients with and without eosinophilia and concluded that eosinophilia appeared independent of allergies in IgG4-RD (43). Lanzillotta *et al*. assessed the differences among the four clinical phenotype groups of IgG4-RD, including pancreato-hepato-biliary disease group, retroperitoneal fibrosis and/or aortitis group, head and neck-limited disease group, and classic Mikulicz syndrome with systemic involvement group (47), and found that increased blood eosinophil counts were similar among the four groups (48). These data suggested that eosinophilia was probably induced by a process inherent to IgG4-RD immune response itself, rather than allergies, and that Th2-related features (*e.g*., IL-5) may not be allergy mediated, but derive from IL-5 producing ILC2s as reported in other conditions (8). Studies have suggested that IgG4-RD mimics malignant, infectious, and inflammatory disorders (5, 49). There was substantial homology between human carbonic anhydrase II and the α-carbonic anhydrase of *Helicobacter pylori*, and between the plasminogen-binding protein of *H. pylori* and the ubiquitin-protein ligase E3 component n-recognin 2 expressed in pancreatic acinar cells (49). Moreover, various NOD-like receptor (NLR) and TLR ligands stimulation evoked more IgG4 and BAFF production in PBMCs isolated from patients with IgG4-related AIP (50). These innate immune responses against microbial antigens may be associated with the eosinophilia in IgG4-RD, although it needs to be further confirmed.

Eosinophils in the pathogenesis of IgG4-RD

Substantial strides have been made in understanding the pathogenesis of IgG4-RD. IgG4-RD is a multi-organ disease characterised by high serum IgG4 concentrations and $IgG4^+$ plasma cells infiltration, dominant production of Th2 cytokines (such as IL-4, IL-5 and IL-13), and an increase of IL-10 and TGF-β hyper-producing $CD4^+CD25^+Foxp3^+$ Tregs (51). The central role of B cells in this disease was demonstrated by the appearance of autoantibodies, identification of multiple self-antigens that promote B cell expansion, and robust clinical responsiveness to B cell depletion (3). T cells are the most abundant cells in the lymphoplasmacytic infiltration in IgG4-RD lesions, a recent study demonstrated that increased $CD4^+$ cytotoxic T lymphocytes (CTLs) in the blood and affected disease sites were involved in the pathogenesis of this disease (52). $CD4^+$ CTLs often represent about 80% of all infiltrating $CD4^+$ T cells in tissues from patients with IgG4-RD, the collaboration between clonal cytotoxic T cells

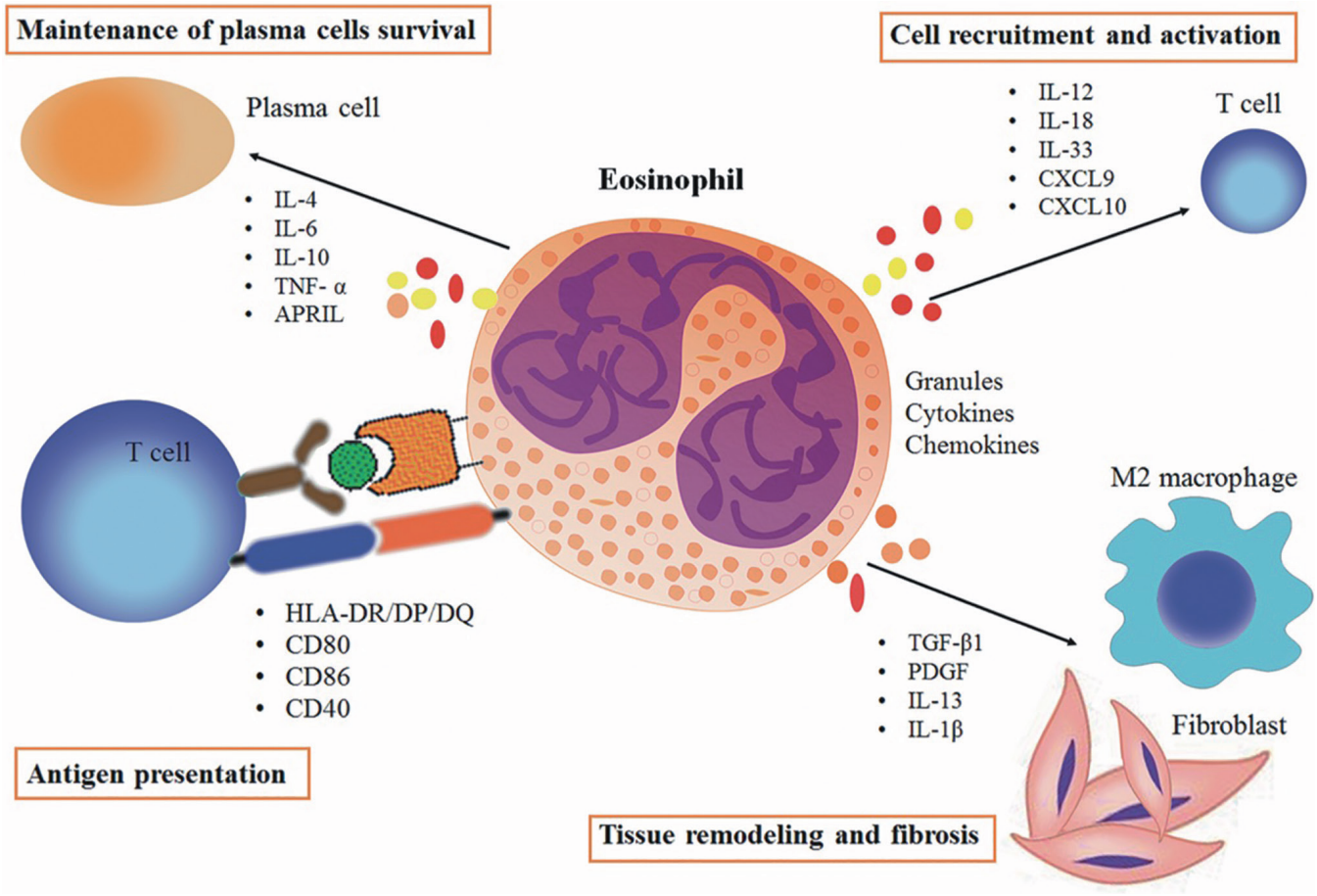

Fig. 1. Possible functions of eosinophils in the pathogenesis of IgG4-RD.
Eosinophils are capable of releasing granule proteins, cytokines, chemokines and growth factors. Eosinophils may have roles in the recruitment and activation of immune cells and fibroblasts, in promoting antigen presentation and survival of long-lived plasma cells, in tissue remodelling and fibrosis. Eosinophil-produced cytotoxic inflammatory mediators, such as TGF-β1, PDGF and IL-13, recruit and activate M2 macrophages and fibroblasts resulting in fibroinflammatory infiltration.
PDGF: platelet derived growth factor; APRIL: a proliferation inducing ligand.

and activated B-cell subsets is essential to drive the disease and its associated fibrotic processes by the secretion of key profibrotic cytokines, including interleukin (IL)-1β, interferon γ, and transforming growth factor β (3, 53). $CD4^+$ follicular T-helper cells are also involved in the disease via promoting the production of IgG4 from B cells (54).

Eosinophils have been commonly viewed as effector cells involved in the defense against parasites and in allergic inflammation conditions. But at times they have also been incriminated in various disease pathophysiology (8, 55). As sources of IL-23 and IL-17, eosinophils are considered as immunomodulatory effector cells in pulmonary aspergillosis (56). Eosinophils contribute to adaptive immunity through producing DC and effector Th cell chemoattractants such as CXC-chemokine ligand 9 (CXCL9) and CXCL10 (8, 57, 58), and by functioning as antigen-presenting cells (59, 60). After systemic IL-33 administration, IL-5-producing ILC2s and the associated eosinophil recruitment have been shown to promote severe pulmonary arterial occlusive hypertrophy (61). Study has also demonstrated a causal role for eosinophils in airway hyperreactivity and airway remodelling (55). After subcutaneous IL-33 administration, accumulation of eosinophils and subsequent eosinophil-derived IL-13 have been shown to contribute to IL-33-induced cutaneous fibrosis (62).

There has also been growing interest in the role of innate immune system, such as plasmacytoid dendritic cells (pDCs)-derived interferon (IFN)-α and interleukin (IL)-33 (63, 64), TLRs or NLR-induced monocyte and basophil activation (50, 65), and M2 macrophage activation (51, 66), in the formation of inflammatory masses composed of immune cells and fibrotic tissue in IgG4-RD. In addition to $IgG4^+$ plasma cells, the inflammatory lesions of IgG4-RD also contain $CD4^+$ T cells, macrophages, eosinophils, fibroblasts, and myofibroblasts.

On the basis of studies about eosinophilia in other fibroinflammatory disorders, we have exhibited a model of how the eosinophils play roles in the infiltrate situ of IgG4-RD (Fig. 1). It has been reported that eosinophils are capable of surviving in tissue for several weeks, depending on the presence of cytokines (67), thus the persistence of eosinophils may occur throughout the clinical course, as it was reported in eosinophilic angiocentric fibrosis, a firstly identified subtype of IgG4-RD (53). IL-5 produced by Th2 cells or IL-

Table I. Current therapies approved or in clinical trials to treat eosinophilia.

Strategy	Molecular target	Medication
Inhibition of eosinophil survival and promotion eosinophil clearance from tissues	Pro-eosinophil cytokines	Corticosteroids
Inhibition of recruitment	CCR3 IL-13 CCL11	Small molecule CCR3 antagonists Lebrikizumab/Tralokinumab/Dectrekumab eotaxin-1 specific antibody (bertilimumab)
Inhibition of survival	IL-5 IL-5R Siglec-8	IL-5 specific antibodies (mepolizumab, reslizumab) IL-5Ra specific antibody (benralizumab) Siglec-8 specific antibody (AK002)
Inhibition of activation	IL-33	Anti-IL-33 specific antibody
Inhibition of eosinophil production	IL-5R	IL-5Ra specific antibody (benralizumab)

C2s recruit eosinophils, which produce cytotoxic inflammatory mediators, such as TGF-β1, PDGF, and IL-13. These cytokines recruit and activate M2 macrophages and fibroblasts resulting in inflammatory fibrosis (29, 53, 67-69). Moreover, eosinophils have been proposed as an important source of plasma cell survival factors, including APRIL, IL-6, IL-4, IL-10 and TNF-α (55, 70-72). In addition, activated eosinophils within lesions could present antigens to $CD4^+$ T cells by upregulating class II MHC and costimulatory molecules (7, 73, 74). Human peripheral blood eosinophils pulsed with the antigens showed up-regulated surface expressions of HLA-DR/DP/DQ, CD80, CD86 and CD40 that were sustained over 5 days (60). Theoretically, these processes could occur within the fibroinflammatory infiltration thereby sustaining the inflammation. However, the precise roles of eosinophils in the immunopathogenesis of IgG4-RD need to be further confirmed.

Certain DAMPs, such as IL-33, may participate in the eosinophil associated fibroinflammatory lesions of IgG4-RD. A recent study reported that enhanced production of IFN-α and IL-33 by pDCs underlies the immunopathogenesis of IgG4-RD (75). Serum IFN-α and IL-33 concentrations were significantly higher and strongly correlated with IgG4 concentration and disease activity in IgG4-RD patients (64, 76). Diagnostic performance of serum IFN-α and IL-33 concentrations as markers of IgG4-RD was comparable to that of serum IgG4 concentration (76). It has been reported that eosinophil was involved in danger signal IL-33-induced cutaneous fibrosis by secreting IL-13 (62, 77). Chronic fibro-inflammatory responses in IgG4-related AIP depend on IFN-α and IL-33 produced from pDCs, which may be associated with the ability of IL-33 to promote the production of profibrogenic mediators such as IL-13 and TGF-β1 (63). Interestingly, studies have shown that IL-33 induces eosinophilia through enhancing Th2-derived IL-5 production (11) and group 2 innate lymphoid cell-derived type 2 cytokines (78). Moreover, eosinophil expressed ST2, a receptor of IL-33, which suggest that IL-33 could also directly interact with eosinophils (11, 79).

Intervention with eosinophil and associated signalling

Glucocorticoids are an effective and well-responsive treatment for IgG4-RD (80), but their long-term use is problematic. DMARDs are used with the intent to reduce glucocorticoid toxicity, although there is little evidence for their efficacy. For patients with refractory IgG4-RD, a biological agent such as rituximab, should be considered if available. Following rituximab therapy, a dramatic resolution of cellular infiltration and a partial reduction of fibrosis were observed (29, 41). However, these strategies could not inhibit the relapse of this disorder.

Eosinophil-targeted therapeutic agents have produced encouraging results (9, 11, 55, 81). These include several approaches (Table I): blocking the recruitment of eosinophils into organs and impairing the survival of mature eosinophils, blockade of eosinophil production in the bone marrow, and the inhibition of eosinophil activation. A randomised placebo-controlled double-blind trial enrolled EGPA patients with a history of relapsing or refractory disease showed that mepolizumab treatment resulted in significantly more weeks in remission and a higher proportion of participants in remission, thus allowing for reduced glucocorticoid use (31). Now that biologic agents targeting IL-5 or IL-5 receptor (mepolizumab, reslizumab, and benralizumab) that effectively and selectively deplete eosinophils in patients with asthma or other eosinophil-related disorders can be prescribed. Monoclonal antibodies to Siglec-8 are currently under assessment in clinical trials for nasal polyposis and systemic mastocytosis. Clinical trials might be performed in IgG4-RD associated with peripheral or tissue eosinophilia to confirm the potential of eosinophil inhibition in modifying disease.

Conclusions and future perspectives

In conclusion, eosinophilia is associated with the disease activity and relapse of IgG4-RD. Mild to moderate tissue eosinophilia is an importantly histopathological feature of IgG4-RD. Tissue eosinophils sense a large number of stimuli, including locally released mediators from other cells and cell-cell or cell-matrix interactions, to elicit specific regulated responses. However, the potential function of IgG4-RD associated eosinophilia remains largely unknown. Further studies are needed to illustrate the underlying mechanism of eosinophils (especially in tissue) in IgG4-RD, and to explore the therapeutic potential of eosinophil-targeting approaches in IgG4-RD.

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