JAK Inhibition as a Therapeutic Strategy for IgG4-RD

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To the Editor:

The review by Carballo et al [1] provides an excellent summary of the varied clinical presentations of IgG4-related disease (IgG4-RD), highlighting the role of clinicians and insisting on a detailed pathological description of affected organs with IgG4-stained plasmablasts infiltrating tissues to arrive at a diagnosis. However, the cytokine environment and what makes this "nonpathogenic" IgG isotype cause irreversible end-organ damage remains unknown. As the authors rightly discuss, both autoimmune and allergic aspects of IgG4-RD are involved. In addition to the general approach to managing the diverse clinical presentations of this disease, we would like to discuss the cytokine signalling involved in IgG4-RD in more detail and suggest Janus-associated kinase (JAK) inhibition as alternative therapeutic strategy to manage this condition.

Autoimmunity implies a perpetual cycle that is initiated by a cell-damaging event that modifies self-antigens. Tissue-resident antigen-presenting cells increase MHC class II expression and present modified antigens to T cells, and the unique cytokine environment switches $CD4^+$ T_H2 T-cell differentiation, which in turn drives an adaptive immune response towards IgG4 plasma cell differentiation and, eventually, end-organ damage with fibrosis (Figure).

The pathogenic role of IgG4 was shown to involve passive transfer of antibodies from patients with IgG4-RD causing pancreatic and salivary gland injury in neonatal Balb/c mice [2]. Distinct glycosylation changes on IgG4 with increased G0 and F1 glycans in patients with IgG4-RD and hypocomplementemia suggest activation of the lectin pathway on phagocytes to induce chronic inflammation [3,4]. Interestingly, in the pancreatic ovalbumin mouse model

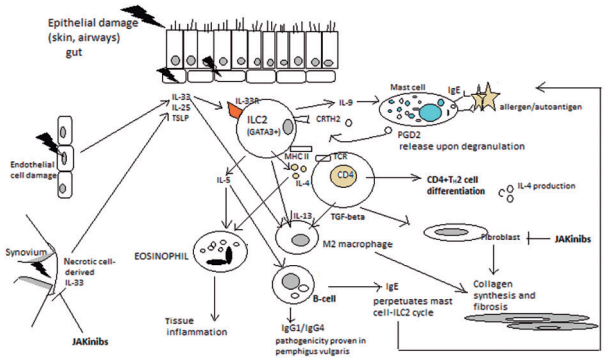

Figure. Schematic representation of pathways involving innate lymphoid cells type 2 (ILC2) and cytokines in IgG4-related disease. Epithelial damage leads to upregulation of IL-33, IL-25, and TSLP, with IL-33 acting via ST2 (IL-33R) on ILC2 cells and cytokines such as IL-4, IL-5 and IL-13 leading to eosinophil recruitment and macrophage polarization. MHC class II upregulation on ILC2 interacts with TCR on $CD4^+$ T cells (also CD80/86 and CD28; OX40L and OX40) to further produce IL-4. Upregulation of GATA3 upregulation leads to $CD4^+$ T_H2 cell differentiation. $CD4^+$ cytotoxic lymphocytes release TGF-ß that activate fibroblasts, including M2 macrophages, leading to collagen synthesis and fibrosis (CD206+ subset associated with fibrosis in systemic sclerosis). IL-5 can induce class-switching of B cells to produce IgG1/IgG4 or IgE that binds to mast cells. Upon further (auto)antigen cross-linking, the mast cells degranulate, releasing PGD2 that interacts with CRTH2 on ILC2s, thus perpetuating the cycle of cytokine release. Endothelial damage results in production of IL-4, IL-12, TGF-ß, IL-6, and IL-33 that leads to proliferation of fibroblasts and polarization of macrophages with survival signals for differentiation into myofibroblasts and production of extracellular matrix. Necrotic cells from inflamed joints and fibroblast-like synoviocytes release IL-33, which expands synovial-resident ILCs. Further feedback via arthritogenic TH17 cells amplify and lead to chronic joint inflammation.

(RIP-mOVA mice), no tissue inflammation was observed when animals were exposed to recombinant ovalbumin-specific human IgG4 monoclonal antibody only in contrast to cotransfer of OVA-specific $CD8^+$ cytotoxic T cells, which resulted in significant tissue damage, thus suggesting the crucial role of T cells in the pathogenesis of IgG4-RD [5]. It is uncertain whether IgG1 antibodies confer pathogenicity along with IgG4, especially with identification of annexin A11–specific IgG1 and IgG4 antibodies in patients with IgG4-RD affecting the biliary tract, salivary gland, or pancreas [6].

As the pathologic process in IgG4-RD can involve almost any tissue in the body, it is likely that the sustained cellular response is due to a ubiquitous cytokine signal(s). In this context, it is worthwhile noting that all cells in the body have the ability to respond to IL-4 and IL-13 cytokines, including astrocytes and microglial cells, which are macrophage-like cells in the central nervous system, thus perhaps providing an explanation for leptomeningeal IgG4-RD. Tsuboi et al [7] showed that patients with Sjögren syndrome differ from those with IgG4-RD sialadenitis, in which IL-10 and TGF-β were

significantly elevated. The pleiotropic effects of IL-4 and IL-13 produced by CD4+ in variant natural killer (iNKT) cells and/or group 2 innate lymphoid cells (ILC2) in IgG4-RD, as well as signalling through type 1 (for lymphocytes) and type 2 (for epithelial cells) IL-4 receptors via JAK1/JAK3 (IL-4) or Tyk2/JAK3 (IL-13) with downstream STAT6, are likely to drive chronic tissue inflammation and fibrosis [8] (Figure).

This cytokine model of self-sustained signalling implies that JAK inhibitors (small molecules that inhibit JAK1, JAK2, JAK3, and Tyk2) may be useful in controlling tissue inflammation and preventing fibrosis in patients with IgG4-RD and may prove to be as promising as the findings from recent clinical trials in several other autoimmune diseases [8,9]. When cocultured with tofacitinib (first-generation JAK1/3 inhibitor with some anti-JAK2 activity), synovial fibroblasts lost their ability to migrate to form networks and down-regulate production of inflammatory cytokines and metalloproteinases. Tofacitinib prevented bleomycin-induced skin and lung fibrosis in mice, including reduction of skin fibrosis in tight skin 1 (TSK1/+) mice, which is a model for the human fibrotic skin disorder scleroderma. It was also able to reverse graft-versus-host disease and provide endothelial cell protection, thus indicating its multiple effects on lowering tissue inflammation. Tofacitinib 5 mg twice daily was also effective in moderate-to-severe rheumatoid arthritis and psoriatic arthritis, with an overall satisfactory safety profile and only a small increase in the frequency of malignancies and serious infections. Baricitinib (JAK1/2 inhibitor), which inhibits expression of costimulating molecules CD80/CD86 on monocyte-derived dendritic cells and production of type 1 interferons by plasmacytoid dendritic cells, including production of IL-6 and differentiation of B cells into plasmablasts, may be an ideal candidate for managing IgG4-RD. It was effective in anti-TNF inhibitor–refractory rheumatoid arthritis, although it increased the risk of thromboembolic events. Ruxolitinib (JAK2/1 inhibitor), tofacitinib, and itacitinib (selective JAK1 inhibitor) decreased M2 macrophage activation by inhibiting IL-4 and IL-13 signalling and improved skin and pulmonary inflammation in a mouse model that mimics scleroderma-associated interstitial lung disease [10]. JAK inhibitors may therefore have a significant role to play in IgG4-RD. However, physicians prescribing these drugs will need to be mindful of the risks of novel infections, as well as the possible re-emergence of old infections.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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