

JAK inhibition as a therapeutic strategy for IgG4-RD

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Inhibición de las JAK.

To the Editor,

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

The autoimmune concept implies a perpetual cycle that is initiated by a cell damaging event that modifies self-antigens; the tissue-resident antigen presenting cells increase MHC Class II expression and present modified antigens onto T cells; the unique cytokine environment switches CD4+Th2 T cell differentiation which in turn drives an adaptive immune response towards IgG4 plasma cell differentiation and eventually end-organ damage with fibrosis [Figure 1].

The pathogenic role of IgG4 was shown by 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 hypocomplementaemia suggest activation of the lectin pathway on phagocytes to induce chronic inflammation [3, 4]. Interestingly, in the pancreatic ovalbumin mouse model (RIP-mOVA mice) no tissue inflammation was observed when animals were exposed to recombinant ovalbumin-specific human IgG4 monoclonal antibody only in contrast to co-transfer of OVA-specific CD8+ cytotoxic T cells which resulted in significant tissue damage suggesting the crucial role of T cells in the pathogenesis of IgG4-RD [5]. It is uncertain if IgG1 antibodies confer pathogenicity along with IgG4, especially with identification of annexin A11-specific IgG1 and IgG4 antibodies in patients with biliary tract/salivary gland/pancreas associated IgG4-RD [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 and perhaps providing an explanation to leptomenigeal IgG4-RD. Tsuboi and colleagues showed that patients with Sjogren's syndrome differ from IgG4-RD sialadenitis in which IL-10 and TGF- β were significantly elevated [7]. The pleiotropic effects of IL-4 and IL-13 produced by CD4+ invariant natural killer (iNKT) cells and/or group 2 innate lymphoid cells (ILC2) in IgG4-RD and signalling through type I (for lymphocytes) and type II (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, see Figure].

This cytokine model of self-sustained signalling implies that JAKinibs (small molecules that inhibit JAK1, JAK2, JAK3, Tyk2) may be useful in controlling tissue inflammation and preventing fibrosis in patients with IgG4-RD similar to recent clinical trials showing promising results in several other autoimmune diseases [8, 9]. Synovial fibroblasts when co-cultured with tofacitinib (first-generation JAK1/3 inhibitor with some anti-JAK2 activity) lost its ability to migrate to form networks and down-regulated 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 (GvHD) and offer endothelial cell protection 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 overall satisfactory safety profile and only small increase in the frequency of malignancies and serious infections. Baricitinib (JAK1/2 inhibitor) which inhibits expression of co-stimulating molecules CD80/CD86 on monocyte-derived dendritic cells and production of type-I interferons by plasmacytoid dendritic cells, including IL-6 production 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 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 showed improvement of skin and pulmonary inflammation in a mouse model that mimics scleroderma-associated interstitial lung disease [10]. JAKinibs therefore may have a significant role to play in IgG4-RD but physicians using these drugs will need to be mindful of the risks of novel as well as possible re-emergence of old infections.

Conflicting Interest:

None declared

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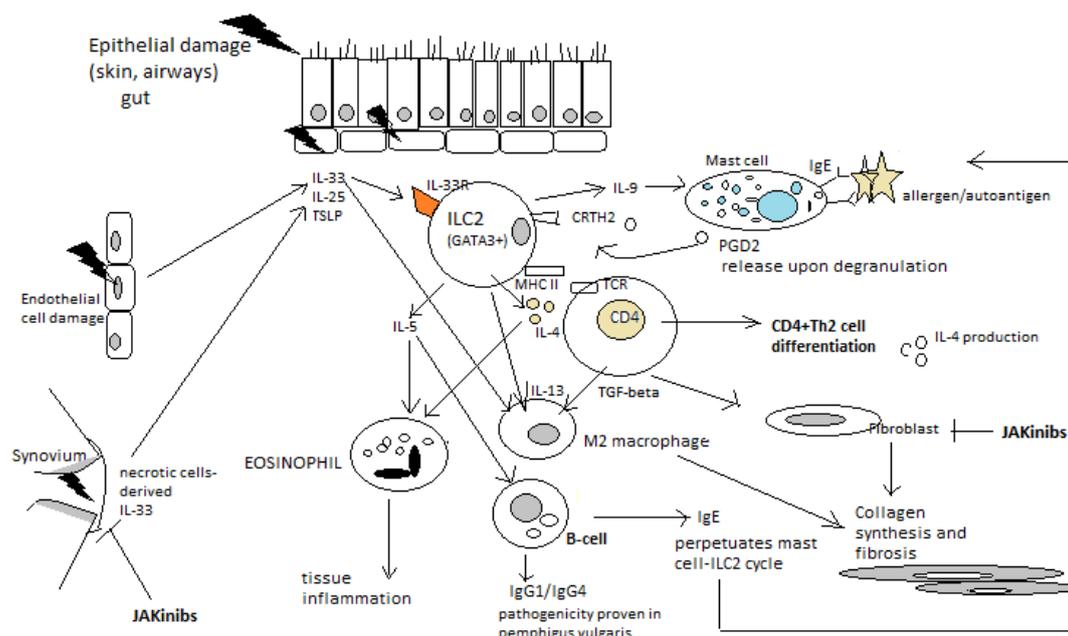
None

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FIGURE

Figure 1. Schematic representation of pathways involving innate lymphoid cells type 2 (ILC2) and cytokines in IgG4-RD



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 lead to eosinophil recruitment and macrophage polarization. MHC Class II upregulation on ILC2 interact with TCR on CD4+T cells (also CD80/86 and CD28; OX40L and OX40) to further produce IL-4 and GATA3 upregulation lead to CD4+Th2 cell differentiation. CD4+ cytotoxic lymphocytes release TGF- β 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 perpetuating the cycle of cytokine release. Endothelial damage results in production of IL-4, IL-12, TGF- β , IL-6, IL-33 that leads to fibroblast proliferation and macrophage polarization with survival signals for differentiation into myofibroblasts and extracellular matrix production. Necrotic cells from inflamed joints and fibroblast-like synoviocytes release IL-33 which expands synovial-resident ILCs and further feedback via arthritogenic Th17 cells amplify and lead to chronic joint inflammation.