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# IgG4-related disease: pathophysiologic insights drive emerging treatment approaches

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## ABSTRACT

*IgG4-related disease (IgG4-RD) is a fibroinflammatory condition that can affect essentially any organ. The disease shows similar histopathology findings across organ systems, consisting of a lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. IgG4 itself appears to be a reactive phenomenon rather than the primary disease driver. Recent investigations have focused on the interactions between cells of the B cell lineage and a novel CD4<sup>+</sup> SLAMF7<sup>+</sup> cytotoxic T cells capable of promoting fibrosis.*

*Plasmablasts appear to play a crucial role along with B cells in the presentation of antigen to this T cell. IgG4-RD is marked by responsiveness to glucocorticoids, but frequent disease relapse, the inability to taper glucocorticoids completely, and steroid toxicity are problematic. Targeted treatment approaches against the B cell lineage appear promising, and therapeutic efforts focused upon the CD4<sup>+</sup> SLAMF7<sup>+</sup> cytotoxic T cell may also be feasible.*

## Introduction

IgG4-related disease (IgG4-RD) is a fibroinflammatory condition that can involve essentially any organ (1). The disease was originally identified in 2003 following the recognition that a high percentage of patients with “sclerosing pancreatitis” – now known as type 1 or IgG4-related autoimmune pancreatitis (AIP) – had extra-pancreatic manifestations that shared similar pathologic features (2). IgG4-RD has now been described in essentially every organ. The most commonly involved organs are the major salivary glands, the orbital and periorbital tissues, the pancreas, the retroperitoneum, and lymph nodes (3).

A characteristic of IgG4-RD is the presence of similar histopathology findings

across organs (4). The hallmark features are a dense lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells, an irregularly whorled fibrotic pattern known as storiform fibrosis, obliterative phlebitis, and mild to moderate tissue eosinophilia (4). IgG4-RD is often associated with elevated peripheral IgG4 levels, but this finding is neither sensitive nor specific for the diagnosis (5). Similarly, high concentrations of IgG4-positive plasma cells within affected organs are also not diagnostic of IgG4-RD in and of themselves.

## Pathophysiology

Despite the fact that IgG4-RD has been recognized only recently as a discrete disease entity, a plausible pathophysiological scheme has been devised for this condition. Many of the advances in formulating novel treatment approaches stem directly from insights derived following observation of the effects of a targeted treatment approach – specifically, B cell depletion.

Although it is conceivable that the IgG4 molecule itself contributes directly to tissue injury in some fashion (*e.g.*, in the form of immune complexes), it now seems unlikely that IgG4 itself is the primary element driving the pathophysiology. T follicular helper cells appear to drive the class-switch toward IgG4, perhaps principally through the secretion of IL-4 (6), but the ultimate purpose of the class switch (and the effect of IgG4) is not known for certain. One possibility is that the high serum concentrations of IgG4 – long regarded as an anti-inflammatory antibody (7) – represents an ineffectual attempt to dampen an ongoing primary immune response, triggered by still unknown antigens.

B cells and other cells of their lineage, particularly plasmablasts, play an important role in IgG4-RD. Plasmab-

lasts are found in high concentrations in IgG4-RD, regardless of the serum IgG4 concentration (8). Both B cells and plasmablasts may play a variety of roles in IgG4-RD, the most important of which may be the presentation of antigen to T cells. The circulating plasmablasts in IgG4-RD demonstrate intense somatic hypermutation, a hallmark of interaction with T cells within the germinal centers of lymph nodes (9).

Recent evidence suggests that T-cells play a central role in IgG4-RD pathogenesis (10). CD4<sup>+</sup> T-cells, the most abundant cell within affected tissues, are dispersed throughout IgG4-RD lesions. Conflicting reports have implicated both Th1 cells and Th2 cells in IgG4-RD pathophysiology, but it appears that Th2 cells accumulate in the blood only in subjects with concomitant atopy (11). A clonally-expanded population of CD4<sup>+</sup> cytotoxic T lymphocytes in both the peripheral blood and fibrotic lesions of IgG4-RD patients suggest that these cells are central to the disease (10). These cells are described in further detail below.

The CD4<sup>+</sup> T-cells believed to orchestrate IgG4-RD may be sustained by continuous antigen-presentation by B-cells. The interaction of cells of both the B and T cell lineages in this manner offers a number of appealing therapeutic approaches.

### Traditional treatment approaches

Most patients with IgG4-RD respond at least partially to glucocorticoids, and the initial response is generally swift and convincing, much as the response of patients with giant cell arteritis or polymyalgia rheumatica to these agents (12-15). Treatment is indicated in all patients with symptomatic and active IgG4-RD, and is particularly important for patients with IgG4-related kidney disease, autoimmune pancreatitis, fibrotic lung disease, and aortitis. Patients at risk for irreversible damage in any organ should be treated urgently regardless of symptoms (12). Examples of manifestations requiring urgent treatment to prevent irreversible organ damage include TIN, AIP, biliary tract disease, RPF, and aortitis.

No randomized clinical trials have been performed in IgG4-RD. The majority of data pertaining to treatment come from retrospective studies of IgG4-related AIP. Prednisone is typically initiated at 40 mg/day for 2-4 weeks, then slowly tapered off over 2-6 months (12). In Japan, patients are often maintained on low-dose glucocorticoids (5-10 mg/day) for several years (16). As is true with many immune-mediated conditions, IgG4-RD has a propensity to flare when glucocorticoid doses are tapered, and many patients suffer disease exacerbations while still on glucocorticoids (14, 15). Because the IgG4-RD patient population tends to be middle-aged to elderly and frequently has pancreatic disease as part of the underlying condition, the morbidity of treatment with glucocorticoids is substantial.

### Conventional steroid-sparing drugs

Many experts use a "steroid-sparing agent" for relapsing disease in lieu of treating with repeated courses of prednisone (12). Furthermore, some clinicians opt to use a steroid-sparing agent in conjunction with glucocorticoids for severe disease or if relapse could lead to significant morbidity or mortality. However, there is no high-quality evidence to suggest that "steroid-sparing" agents such as methotrexate, azathioprine, mycophenolate mofetil, and other medications employed for this purpose actually work.

### B cell depletion

B cell depletion with rituximab appears effective (17-19). Treatment with rituximab often results in a sustained remission while allowing glucocorticoids to be tapered rapidly (18). In one open-label trial of 30 patients, 26 of whom received rituximab alone, 97% of patients demonstrated a treatment response and 47% were in complete remission at six months (20). Rituximab-induced remissions have variable duration, from occasionally as short as 3-4 months to periods lasting two years or more. Forty percent of the patients in one trial were in remission one year after treatment despite receiving only one course of rituximab.

### Lessons from mechanistic studies

The rapidity with which the serum IgG4 concentration declines following B cell depletion suggests that the cells making most of the serum IgG4 are short-lived plasmablasts and plasma cells. The fact that B-cell depletion does not lead to the complete normalization of serum IgG4 concentrations implies the presence of long-lived plasma cells that continue to make this immunoglobulin from niches within the bone marrow. The level of circulating plasmablasts is superior to IgG4 levels at gauging disease activity (8, 9).

B cell depletion may achieve its effects through interference with the function of a novel CD4<sup>+</sup> cytotoxic T lymphocyte (CTL)(10). These cytotoxic T cells were first identified in the blood of patients with IgG4-RD through next-generation sequencing and subsequently confirmed to be present in large quantities within the tissues of affected organs. These CD4<sup>+</sup> CTLs bear SLAMF7, previously described only on cells of the B cell lineage, on their surfaces. The CD4<sup>+</sup> CTLs elaborate interleukin-1, transforming growth factor beta, and interferon-gamma, all of which are potentially important mediators of the storiform fibrosis observed in IgG4-RD. The cells also make products such as granzyme B and perforin, more commonly associated with CD8<sup>+</sup> T cells.

Blood concentrations of the CD4<sup>+</sup> SLAMF7<sup>+</sup> CTL have been shown to decline slowly following B cell depletion in patients with IgG4-RD. Because these T cells do not have CD20 on their surfaces and are therefore not targeted directly by anti-CD20 treatment approaches, the hypothesis is that the CD4<sup>+</sup> CTLs are sustained by cells of the B cell lineage (*e.g.*, B cells themselves and plasmablasts), presumably through continuous antigen presentation. Supported by B cells and plasmablasts, these CD4<sup>+</sup> SLAMF7<sup>+</sup> CTLs likely serve as the principal driver of the fibrosis and tissue injury in IgG4-RD. To a certain degree, the fibrosis associated with IgG4-RD appears to be reversible with effective treatment (21). The precise mechanism of this improvement remains unclear.

### Alternative treatment approaches

The theoretical understanding in broad strokes of the interactions between cells of the B and T cell lineage in the pathophysiology of IgG4-RD leads to multiple possible treatments approaches targeting either lineage or the ways in which these lineages interact directly. On the B cell side, XmAb5871 is a humanized anti-CD19 antibody with an Fc portion that engineered for affinity (200- to 400-fold increase over native IgG) for Fc-gamma-RIIb. Fc-gamma-RIIb is the only Fc receptor on B cells. Co-ligation of CD19 and Fc-gamma-RIIb leads to downregulation and inhibition of B lineage cells bearing these targets. FcγRIIb inhibitory activity requires bridging to specific co-targets. Reversible inhibition of B cell function without B cell ablation is one potential advantage of this approach. On the T cell side, the CD4+ CTL also offers an appealing target. Few data on T cell-targeted approaches have been reported thus far. Because the fibrosis associated with IgG4-RD is presumed to result from the downstream effects of interactions between B and T cells, the elaboration of fibrogenic cytokines such as interferon-gamma, T-growth factor-beta, and interleukin-1, and the activation of fibroblasts, the impact of current and future therapies on fibrosis will be of keen interest.

### Conclusions

Advances in understanding the pathogenesis of IgG4-RD may translate eventually into improved efforts at diagnosing and treating this disease. Plasmablasts may become important in both diagnosing IgG4-RD and

monitoring disease activity. The CD4+ SLAMF7+ cytotoxic T cell, believed to be central to the disease process, offers an additional potential therapeutic target. Bedside-to-bench collaborations have been essential to progress in IgG4-RD thus far. The insights provided with regard to T and B cell interactions and the impact of disrupting these pathogenic processes in a variety of ways may have implications well beyond IgG4-RD.

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