Response to: 'Is rituximab effective for IgG4-related disease in the long term? Experience of cases treated with rituximab for 4 years' by Yamamoto *et al*

We thank Yamamoto and colleagues[1] for their response to our paper[2] and their description of their experience with rituximab (RTX) in IgG4-related disease (IgG4-RD) in three patients. Their letter raises a number of important points pertaining to the management of IgG4-RD, in general, and to the use of B-cell-depletion strategies, specifically.

First, their patients are exemplary of the fact a sizeable subset of IgG4-RD patients has a propensity to disease relapse over time. This point has been underappreciated from early reports of the use of glucocorticoids to treat IgG4-RD because those reports were characterised by short follow-up periods. Although the great majority of patients respond to glucocorticoids initially, repeated disease flares are the rule for many.

Second, patients with IgG4-RD endure substantial morbidity from the requirement for repeated courses (or continuous on treatment) with glucocorticoids. The three patients described by Yamamoto and colleagues are reported to have experienced bilateral avascular necrosis of the hips and glucose intolerance (severe diabetes mellitus in one case). Our general sense is that the toxicities of prolonged glucocorticoid use in this and other diseases are underestimated. Moreover, patients who are middle-aged or elderly, that is, who fit the classic profile of a patient with IgG4-RD, are at high risk for steroid-induced complications than are younger patients. We are therefore curious about why Yamamoto *et al* propose to limit B cell depletion to young patients. Elderly patients are also likely to tolerate RTX well, and the judicious use of RTX in this high-risk population would avoid the all-too-certain morbidities associated with glucocorticoids. More detailed assessments of damage from both the disease and standard treatment approaches are an important part of the research agenda for IgG4-RD.

Third, traditional 'steroid-sparing' therapies are often ineffective in IgG4-RD. These three patients received, in addition to glucocorticoids, a total of five conventional immunosuppressive agents, including cyclophosphamide, azathioprine, methotrexate, cyclosporine and mizoribin. The lack of efficacy of these agents, often used in efforts to spare patients the adverse effects of glucocorticoids, is consistent with our own experience, that of the medical literature in general, and an international consensus of IgG4-RD experts.[3] We note that none of these 'steroid-sparing' agents has been studied in a rigorous fashion to date.

Fourth, the correlation between serum IgG4 concentrations was inconsistent in the three patients described by Yamamoto *et al*. These patients' experience support substantial accumulating data that serum IgG4 concentrations have serious shortcomings as biomarkers for the disease. We have reported that blood plasmablast concentrations, detectable by flow cytometry gated on $CD19^{+}CD27^{+}CD20^{-}CD38^{hi}$ plasmablasts, appear to correlate much better with visit-to-visit disease activity than does the serum IgG4 level.[4 5] On the other hand, extremely elevated serum concentrations of IgG4 at baseline appear to mark patients who are at high risk of disease relapse compared with those with normal serum levels (unpublished data).

The efficacy of RTX observed by Yamamoto and colleagues[1] is highly congruent with our own reported experience.[2] The great majority of patients appear to respond swiftly and impressively to B cell depletion. It is interesting that Yamamoto *et al* observed this same phenomenon despite the relatively low RTX dose employed: 500 mg times one dose, rather than the 1000 mg times two doses employed in our trial. Their experience echoes that of the French Vasculitis Study Group, which demonstrated recently that only 500 mg of RTX every six months was highly effective in preventing disease flares in patients with antineutrophil cytoplasm antibody (ANCA)-associated vasculitis.[6]

It is also not surprising that the patients treated by Yamamoto *et al* ultimately experienced disease relapses following their good initial treatment responses. The illusion that B cell depletion might 'cure' immune-mediated diseases, leading to the restoration of immune tolerance and the permanent abolition of recurrent inflammation, was discarded some years ago. Following RTX therapy in IgG4-RD, patients' B cells undergo reconstitution at variable rates. After B cell reconstitution—or even in some cases before B cells are once again detectable in the blood—disease recurs in a significant subset of patients. In our experience, however, the time to disease flare following B cell reconstitution is highly variable. Some patients achieve normal B cell concentrations approximately six months following RTX, yet maintain their clinical remissions for many months beyond this time. The absence of a linear relationship between B cell concentrations and disease activity underscores the fact that the precise mechanisms through which B-cell-depletion strategies achieve their clinical effects remain unknown. It is likely that a symphony of other cells and other disease mediators, affected indirectly by treatments directed at CD20, also contribute in important ways to the pathophysiology of IgG4-RD. These other cells might also make appealing targets for therapy.

Finally, the notion that some patients with IgG4-RD become 'refractory' to B cell depletion over time has not been our general experience with this treatment, nor is it consistent with publications of repeated use of this treatment strategy in diseases such as ANCA-associated vasculitis and rheumatoid arthritis.[6–8] B cell depletion is less likely to have a meaningful clinical impact on organs that have reached a fibrotic stage of the disease. Perhaps this is what Yamamoto and colleagues have observed. Appropriate aggressive treatment at a time when the disease is at an 'inflammatory' as opposed to a 'fibrotic' stage is crucial to preventing long-term damage and to preserving organ function. More longitudinal data about the efficacy of B-cell-depletion strategies and other novel treatment approaches are needed in IgG4-RD.

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