Efficacy of dupilumab reveals therapeutic target for IgG4-related disease: simultaneous control of inflammation and fibrosis

We read with great interest the article from Simpson *et al* on the clinical efficacy of dupilumab in a patient with IgG4-related disease (IgG4-RD).[1] Glucocorticoid is currently the first-line induction therapy for IgG4-RD.[2] Since it generally suppresses acquired immune cells, we could not know the therapeutic targets in IgG4-RD. So far, the efficacy of rituximab, targeting B cells, has been discussed,[3] but we reconfirm that type 2 helper T (Th2) cells can be one of the therapeutic targets in IgG4-RD by this article. Tanaka *et al* previously disclosed that the expression of Th2 cytokine mRNA was elevated in the labial glands from patients with IgG4-RD, compared with the patients with Sjögren's syndrome and healthy controls.[4] We have shown that the levels of serum interleukin (IL)-5 were elevated according to the disease progression,[5] and the ST2$^+$ memory T produced large amount of IL-5.[6] Because ST2 is the receptor of IL-33, which could lead to differentiation from naïve T to Th2, we had considered that IL-5 would be a therapeutic target for IgG4-RD. Based on the hypothesis, we treated with mepolizumab—a humanised anti-IL-5 monoclonal antibody—for several IgG4-related dacryoadenitis and sialadenitis (IgG4-DS) patients with bronchial asthma. They experienced several relapses or presented with difficult for tapering glucocorticoid. As a result, bronchial asthma was improved, and the peripheral counts of eosinophils promptly led to 0 in all patients. However, the enlargement of lacrimal and salivary glands was not changed, and the serum IgG4 concentration also unchanged or slightly decreased. The steroid tapering effect was limited and mepolizumab could not lead to overall control in IgG4-DS.

For this reason, it was presumed that IL-4, among the Th2 cytokines, was more involved in the pathogenesis of IgG4-RD. IL-4 is indispensable cytokine for the formation of germinal centres, and in especially IgG4-RD, it is also important in humoral immune reactions including IgG4 production by the contact between follicular helper T cells and B cells.[7] So, in the long term, we want to focus not only on clinical improvement but also on changes in immunological findings including globulin levels in the case presented by Simpson. In addition, dupilumab can also inhibit IL-13 signal because IL-13 receptor uses IL-4Rα. Clinical efficacy of dupilumab was initially confirmed in atopic dermatitis.[8] In atopic dermatitis, IL-13 leads to self-proliferation of fibroblasts via periostin.[9] Ohta *et al* reported that the production of both IL-13 and periostin was detected in the involved organs of IgG4-RD.[10] It is possible that IL-13 is one of the key player cytokines in the mechanism of the fibrosis in IgG4-RD. For this reason, dupilumab has a potential to suppress the progression of the fibrosis in IgG4-RD. It is necessary to perform large-scale clinical trials for the evidence of long-term efficacy and safety.

In 2016, we reported the IgG4-RD case that abatacept was effective in this journal.[11] The patient has been treated safely with abatacept for more than 5 years without the relapse. Although the number of patients treated with abatacept has increased since then, no patient experienced secondary non-response. If it can be proved the long-term maintenance and safety in dupilumab administration, it is probably regarded as one of the T cell-targeted biologics for IgG4-RD. Abatacept regulates T cells as a whole, and dupilumab suppresses only Th2 cells. We will confirm that the regulation of T cells is important in IgG4-RD. In the future, we expect to compare the efficacy and safety in abatacept and dupilumab for IgG4-RD.

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