# Interleukin-4 as an emerging therapeutic target for IgG4-related disease

We read the manuscript reported by Simpson *et al* with great interest.[1] They showed remarkable effectiveness of dupilumab, a monoclonal antibody targeting the interleukin-4 (IL-4) receptor alpha, in immunoglobulin G4-related disease (IgG4-RD) complicated with retroperitoneal fibrosis for the first time. Considering the frequent relapse in patients with IgG4-RD during glucocorticoid tapering and the difficulty in glucocorticoid withdrawal,[2] it is of great value that their patient could discontinue prednisone within 2 months after starting dupilumab and even remain stable without any relapse for 12 months.[1] They also showed no significant adverse effects of dupilumab for the duration. We have previously revealed that IL-4 plays an important role in the pathogenesis of IgG4-RD.[3–5] In particular, IL-4-producing follicular helper T cells contribute to IgG4 class-switching and plasmablast differentiation in the disease.[3–5] The case reported by Simpson *et al* connects the basic research findings with the translational application and sheds light on the possibility of dupilumab as a glucocorticoid-sparing and relapse-suppressing agent in patients with IgG4-RD. We are pleased to read their great report and would like to ask several questions for clarification.

The first is regarding the diagnosis of IgG4-RD. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis can mimick IgG4-RD as patients with ANCA-associated vasculitis frequently show elevated levels of serum IgG4 and IgG4-positive B-cell infiltration along with fibrosis in the inflamed tissues, whereas neutrophilic inflammation, granulomatous changes, necrotising lesions and multinucleated giant cells are not usual findings in IgG4-RD.[6] Therefore, the findings of serum IgG4 levels and pathological IgG4-positive B-cell infiltration might not be sufficient for differentiating the two diseases. And, while retroperitoneal fibrosis is one of the major organ involvements in patients with IgG4-RD, ANCA-positive retroperitoneal fibrosis has also been reported.[6] Clinical characteristics of ANCA-positive retroperitoneal fibrosis are very similar to those of IgG4-RD in terms of elderly and male predominance. Collectively, careful exclusion of ANCA-associated vasculitis is needed before the final diagnosis with IgG4-RD. In the context, we would like to ask if the patient had any indication of ANCA-associated vasculitis rather than IgG4-RD such as fever, elevated blood neutrophil counts and serum C reactive protein levels, and ANCA positivity as well as neutrophilic infiltration, granulomatous formation, necrotising vasculitis and multinucleated giant cells in the prostate tissues. Of note, the similar case of granulomatosis with polyangiitis complicated with rhinitis, retroperitoneal fibrosis and pathologically confirmed granulomatous prostatitis along with PR3-ANCA positivity was reported.[7] Furthermore, prostatitis is the most common extrarenal urogenital manifestation of granulomatosis with polyangiitis.[8]

Second, the authors noted that the patient also had the eye swelling and parotitis at initial presentation, however, it is unclear whether those manifestations were derived from IgG4-RD. We are curious about the laterality of his lacrimal and parotid gland enlargement and the improvement in those organs after dupilumab therapy.

Third, why did the patient get a prostate biopsy for pathological confirmation of IgG4-RD? Was the enlargement of prostate symptomatic or just found by images? In addition, the information about whether tertiary lymphoid organs (also known as 'ectopic lymphoid organs', 'ectopic germinal centres' or 'lymphoid aggregates') were observed in the prostate biopsy specimen is important as those lymphoid organ-like structures frequently observed in the lesions of IgG4-RD are associated with IL-4-producing follicular helper T-cell infiltration.[6 9]

We believe that answers to our questions can further confirm the promising prospects of dupilumab as the treatment of IgG4-RD. Further randomised studies are warranted to determine the benefits of dupilumab in terms of its glucocorticoid-sparing effect and reduction of relapse or even remission induction in patients with IgG4-RD.

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