Dupilumab as a potential steroid-sparing treatment for IgG4-related disease

We read with interest the article from Simpson et al on the efficacy of dupilumab—an anti-IL-4 receptor alpha monoclonal antibody—in a patient with multi-organ IgG4-related disease (IgG4-RD) involving the retroperitoneum and, apparently, the prostate and the parotid glands. According to the case presentation, the patient refused immunosuppressive agents due to the risk of adverse events, and treating physicians decided to start him on 40 mg oral prednisone. Subcutaneous dupilumab was added based on multiple concomitant poorly controlled atopic manifestations including asthma, dermatitis and peri-orbital angioedema. Prednisone was tapered over 2 months and then withdrawn. Dupilumab was administered subcutaneously at initial dose of 600 mg, followed by 300 mg injections every other week for 12 months. Three months later, amelioration of all manifestations was observed, and after 12 months on dupilumab, retroperitoneal fibrosis was dramatically improved. Sensible decrease in serum IgG4 was also reported after 3 months of treatment. Based on these findings the authors conclude that dupilumab is effective in IgG4-RD and represents a novel steroid sparing treatment for this multifaceted condition.

Although we strongly support the idea that, by interfering with IL-4 and IL-13 pathways, dupilumab might represent a promising biologic therapy for IgG4-RD, we would like to share with the authors our perplexities about the conclusions drawn from this case report.

First and foremost, we think that concomitant use of glucocorticoids in the first months prevents from claiming that dupilumab is effective in IgG4-RD. Prompt response to corticosteroids is, indeed, a hallmark of IgG4-RD. As such, the rapid improvement of the retroperitoneal fibrosis as well as the reduction of serum IgG4 levels were expected after induction of remission therapy with glucocorticoids. Indeed, failure to respond to an appropriate dose of glucocorticoids is considered an exclusion criterion by the recently released American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for IgG4-RD.

Second, the authors provide a follow-up abdominal magnetic resonance after 12 months of treatment with dupilumab showing marked improvement compared with baseline. A comparison with the evolution of the retroperitoneal fibrosis at 3 months, after corticosteroid treatment, would have been more useful to provide definitive proof of the additional benefit of dupilumab over steroid therapy. Response of IgG4-RD to glucocorticoids, in fact, can last for up to 2–3 years before disease relapses, and a 12-month follow-up is, to our mind, too short to conclude that dupilumab alone maintains remission.

Finally, magnetic resonance findings appear difficult to compare because the images captured before and after treatment are not representative of the same anatomical structures, and the contrast enhanced sequences used are different. In addition, while different organs affected by IgG4-RD can respond differently to immunosuppressive treatments, the authors do not provide evidence of disease response in the prostate and salivary glands.

All together, although we think that no clear conclusions can be drawn on the efficacy of dupilumab in IgG4-RD from this case, we also believe that the experience reported by Simpson and colleagues is of value to highlight the importance of exploring novel therapeutic targets for IgG4-RD. Current available treatments for IgG4-RD including glucocorticoids and B-cell depleting agents, in fact, are associated with many potential side effects, and their long-term use can become problematic in a disease that frequently affects middle-aged to elderly individuals. Given the central role of IL-4 and IL-13 in IgG4 class switch and tissue fibrosis, targeting these pathways has strong rationale in IgG4-RD.

Whether dupilumab might find ideal application in disease phenotypes characterised by peripheral eosinophilia, elevation of serum IgG4 or IgE levels, or atomic manifestations remains speculative and deserves confirmation in randomised clinical trials.

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