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

IgG4-related disease (IgG4-RD) is a rare fibroinflammatory, multisystemic condition with a relapsing-remitting progression.[1] The level of serum IgG4 correlates with inflammatory activity and organ involvement.[1] Glucocorticoids are first line for IgG4-RD, but there are numerous adverse effects with chronic use.[2] Dupilumab is a monoclonal antibody that acts on the interleukin 4 (IL-4) receptor alpha, shared by the IL-4 and IL-13 receptors.[1] IL-4 causes isotype switching from IgM to IgG4 and IL-13 is implicated in fibrosis.[3] Thus, it was postulated by the authors to investigate dupilumab as a novel steroid-sparing treatment for IgG4-RD.

A 67-year-old man with no known allergies and a history of sensory neural hearing loss, recurrent bronchitis, spinal stenosis, moderate positional obstructive sleep apnoea, asthma, atopic dermatitis (which caused swelling around his eyes) and allergic rhinoconjunctivitis underwent extensive investigations over the past 2 years due to suspected IgG4-RD.

The patient's initial complaint was pruritic erythematous lesions on the legs, arms, chest and palms. Further investigations revealed parotitis, sinusitis, normocytic anaemia and eosinophilia. An MRI showed retroperitoneal and genitourinary fibrosis (figure 1A). Total IgG and IgG_4 levels were found to be 32.40 g/L and 20.60 g/L, respectively. The patient had a prostate biopsy which revealed 50 IgG4 cells per high power field and an IgG4+/IgG+ cell ratio of 40%. This result is exactly borderline as per the IgG4-RD comprehensive diagnostic criteria,[4] making the result of the biopsy probable for IgG4-RD. Interventional radiologists determined the retroperitoneal fibrosis to be inaccessible for biopsy and the patient declined a repeat prostate biopsy. Although the biopsy was borderline, given that the imaging, clinical features and laboratory investigations fulfilled the remainder of the comprehensive diagnostic criteria (1 to 3a), IgG4-RD was the consensus diagnosis.[4]

A treatment plan of a 40 mg daily dose of prednisone was suggested by rheumatology, with the option of adding the adjuvant immunosuppressant azathioprine. The patient was on 40 mg prednisone daily but declined other agents due to the risk of adverse effects.

Laboratory investigations revealed haemoglobin counts of 131 g/L (normal range 135–175 g/L), haematocrit levels of 0.391 L/L (normal range 0.4–0.5 L/L), eosinophil levels of 1.4×10^9 cells/L (normal range $0.0–0.5\times10^9$/L) and alkaline phosphatase serum levels of 34 U/L (normal range 40–129 U/L). On examination, atopic dermatitis was present with 50% body surface area (BSA) involvement with an Investigator Global Assessment (IGA) score of 4, indicating severe disease. An initial 600 mg subcutaneous injection of dupilumab, followed by a 300 mg subcutaneous injection every other week for 12 months was given to treat atopic dermatitis, asthma and potentially IgG4-RD.

After 3 months on dupilumab, the patient's eye swelling resolved, and his skin and asthma noticeably improved to IGA1 and <10% BSA. Both total IgG and IgG4 levels reduced substantially to 19.41 g/L and 11.43 g/L, respectively. After 12 months on dupilumab, the patient's retroperitoneal fibrosis improved dramatically corresponding with the decreased IgG4 levels (figure 1B). It is noted that dupilumab is in itself an IgG4 monoclonal antibody.

Current treatments for IgG4-RD are associated with many long-term adverse effects. The first-line treatments are glucocorticoids, second-line treatments are chemotherapeutic immunosuppressants and the third-line treatment is B-cell depleting rituximab, an anti-CD20 monoclonal antibody. The adverse effects associated with these therapies include increased risks of infection and potentially lasting immune deficiency.[5]

Dupilumab has been observed to be safe with long-term use across multiple indications.[6] In this patient, IgG4-RD was

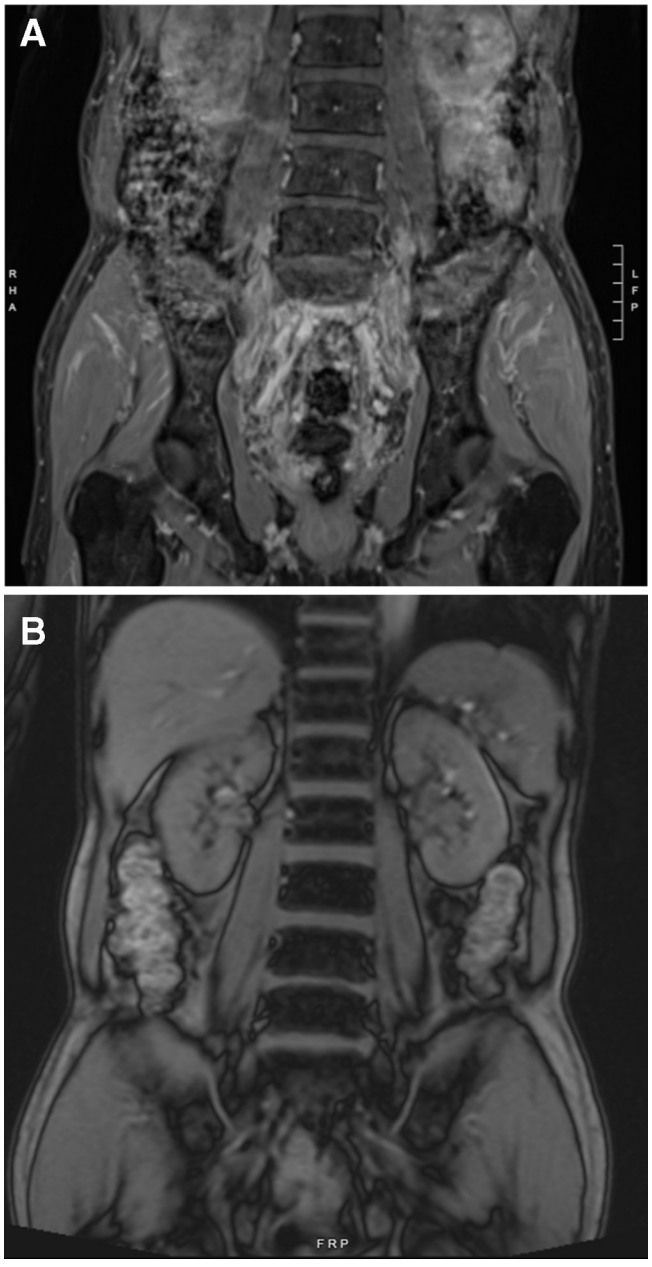

Figure 1 (A) Patient's initial MRI findings before dupilumab treatment showed extensive retroperitoneal and extraperitoneal fibrosis. (B) MRI taken approximately 1 year after dupilumab treatment showed dramatic resolution of fibrosis.

controlled with no further relapses across all affected organ systems with no significant long-term adverse events and prednisone withdrawal within 2 months. Dupilumab's efficacy in the treatment of IgG4-RD also highlights the importance of IL-4 and IL-13 in the pathological mechanisms of this condition.

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