

Response to: 'Dupilumab as a *potential* steroid-sparing treatment for IgG4-related disease' by Della-Torre *et al*

We thank Della-Torre *et al* for their interest in our paper and for providing their thoughts through correspondence.^{1,2} As they have summarised, our case described a patient whom was prescribed a 40 mg daily dose of prednisone to treat his IgG4-related disease (IgG4-RD); however, the patient declined to pursue additional adjunct immunosuppressants due to the concern of adverse effects.¹ To hopefully mitigate such concerns and control his disease, we proposed that dupilumab, a monoclonal anti-interleukin 4 (IL-4) and IL-13 antibody, would be able to treat the patient's condition mechanistically through two pathways. First, because IL-4 is the signal which plays a pivotal role in class switching from IgM to IgG, we theorised that dupilumab would be able to reduce the amount of serum IgG and IgG4, which is a hallmark of IgG4-RD pathology. Second, because dupilumab inhibits IL-13, which is implicated in the activation of fibroblasts causing fibrosis,³ we believed dupilumab would also be able to address this component of the IgG4-RD mechanism of disease. Upon initiation of dupilumab treatment, we observed remission of the patient's condition with improvements starting as soon as 3 months post-dupilumab treatment.¹ As such, our theory is that IgG4-RD is an example of type 2 inflammation, similar to other conditions such as chronic spontaneous urticaria (CSU) that have been misclassified as non-type 2 inflammation in the past.⁴ This is what we believe allows dupilumab to be an effective treatment.⁴

To address Della-Torre *et al*'s first point with respect to their concern that the remission in the patient's IgG4-RD was actually due to a delayed response to glucocorticoids, at the time of publication, his records from rheumatology stated that the patient was on 40 mg prednisone daily prior to initiating dupilumab treatment. However, from a recent correspondence with the patient post-publication (on 29 December 2019), it has actually come to light that the patient was non-compliant and did not take a single dose of the prednisone that was prescribed. This oversight was due to discordance of clinical report and patient compliance. The absence of any corticosteroids however, greatly strengthens the role of dupilumab in reversing IgG4-RD. As such, we conclude that the improvements in the patient's condition can actually be fully attributed to effectiveness of dupilumab therapy alone.

Second, Della-Torre *et al* expressed concerns with respect to the timelines of the MRI provided.² Although it would have been ideal to implement MRI more frequently over the course of treatment, there is no current accepted consensus on how frequently imaging should take place to monitor IgG4-RD progression and such factors such as availability and cost should be taken into consideration as limiting factors.⁵ Specifically, in our jurisdiction of Ontario, Canada, MRI booking is triaged based on priority and wait times can vary greatly based on this necessity.

With regards to Della-Torre *et al*'s point that 12 months post-treatment is too soon to pronounce disease remission in our case, we recognise that because IgG4-RD has a relapsing-remitting disease progression, it is inherently difficult to determine if a patient will remain in remission. We can state his manifestations both externally and internally are controlled and from the patient's complete resolution of IgG4-RD-related symptoms including fibrosis, atopic dermatitis, asthma, parotitis, prostatitis and sinusitis, along with his decrease in serum IgG and IgG4 levels, we believe we have sufficient evidence to conclude that there is remission and/or control. Moreover, there is no consensus guideline to assess IgG4-RD

remission.⁵ The IgG4-RD responder index, which is a tool that can help in assessing IgG4-RD remission, was not done over the course of treatment as we did not have publication in mind at the time, but when done retrospectively for the 12 months post-treatment time-point, the patient's organ site activity score was 0 and his serum IgG4 concentration was 11.43 g/L. This is significantly improved from his previous multiple organ involvement pretreatment and his serum IgG4 concentration of 20.60 g/L showing compelling evidence of remission. Due to the fact that IgG4-RD does exhibit a remitting-relapsing disease progression, we continue to monitor the patient's successful improvements on dupilumab and report that we have not observed any relapses or adverse effects since the initiation of treatment or since the time of publication.

Finally, we thank Della-Torre *et al* for pointing out the discrepancies in figure 1. Unfortunately, an error occurred in which the lower section of figure 1B was omitted during the publication process of our paper. We have thus included in this response to show the respective anatomical structures such as the prostate for comparison against figure 1A (figure 1). The imaging slices were selected as they show a similar region and were recommended by our radiologist. The same procedure and contrast (gadolinium) were used for both images. The initial findings pretreatment that revealed parotitis were found through a CT of the neck, chest, abdomen and pelvis. However, the 12-month postdupilumab treatment MRI was only done of the lumbar plexus region to prioritise the most pressing symptoms and reduce healthcare burden as the patient was asymptomatic with regards to parotitis at 12 months postdupilumab treatment and showed no further signs of parotitis on physical examination. As can be seen in the 12-month post-treatment lumbar plexus MRI (figure 1), prostatitis improved significantly and this was noted in the report from radiology.

Due to the fact that Della-Torre *et al*'s concerns lie predominantly around the belief that a delayed response to glucocorticoids confounds our result of dupilumab being an effective treatment for IgG4-RD, we believe that such issues are no longer applicable to our case considering it has recently been brought to our attention that the patient never commenced prednisone



Figure 1 MRI taken approximately 1-year postdupilumab treatment showed dramatic resolution of fibrosis.

treatment out of fear of side effects and failed to disclose this to their healthcare provider. However, we recognise the fact that we have observed the remission of IgG4-RD in only a single patient and that larger randomised control trials would ideally provide the most robust evidence to conclude the safety and efficacy of dupilumab for IgG4-RD. Due to the fact that IgG4-RD is a rare condition in which the prevalence is actually unknown because it is commonly misdiagnosed or unrecognised,⁶ this can be a profound limiting factor to recruitment in such trials. We advocate for these randomised control trials to be done and believe that our case provides strong rationale to further explore the uses of dupilumab for IgG4-RD.

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REFERENCES

- 1 Simpson RS, Lau SKC, Lee JK. Dupilumab as a novel steroid-sparing treatment for IgG4-related disease. *Ann Rheum Dis* 2019;annrheumdis-2019-216368.
- 2 Della-Torre E, Lanzillotta M, Yacoub M-R. Dupilumab as a potential steroid-sparing treatment for IgG4-related disease. *Ann Rheum Dis*:annrheumdis-2020-216945.
- 3 Chiamonte Met al. Studies of murine schistosomiasis reveal interleukin-13 blockade as a treatment for established and progressive liver fibrosis. *Hepatology* 2001;34:273–82.
- 4 Lee JK, Simpson RS. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticaria. *J Allergy Clin Immunol Pract* 2019;7:1659–61.
- 5 Khosroshahi A, Wallace ZS, Crowe JL, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheumatol* 2015;67:1688–99.
- 6 Kamisawa T, Zen Y, Pillai S, et al. Igg4-Related disease. *The Lancet* 2015;385:1460–71.