Supplementary Material:

In our supplementary material we will further discuss the recommended treatment strategy of IgG4-RD that pertains to our cases. We also added brief remarks in relation to COVID-19 infection and vaccination in IgG4-RD patients.

For all patients with active IgG4-RD, glucocorticoids are the first-line agent to induce remission. The aim of inducing remission is to resolve symptoms and biochemical and radiological abnormalities. The improvement is typically observed within days to several weeks, depending on the organs involved (Lanzillotta, 2020). Steroid therapy was given as 0.5-1.0 mg/Kg body weight/day in some cases, whereas some responded to replacement dose of hydrocortisone (Iseda, 2014). Many experts agree that the initial dosage should be tapered gradually after 2–4 weeks, induction therapy to be discontinued in 3–6 months after starting treatment, then a low-dose maintenance therapy to be given for up to 3 years (Floreani, 2021). This tapering strategy was followed in case 1, leaving him with a minimum dose of maintenance prednisone. Nevertheless, in case 2 the initial dose of prednisone was tapered over 2 months followed by discontinuation. A year later prednisone was transiently restarted given the appearance of symptomatic pulmonary infiltrates, it was discontinued when rituximab was started. We

occasionally restarted prednisone, tapering it over 6-8 weeks, between the rituximab treatments, these were led by the relapse of symptoms. Of note, in case 2 the relapses were mostly pulmonary. We noticed that relapses were better controlled when prednisone was tapered slowly, over 3 months, only after the second dose of every rituximab treatment round.

Prolonged course of steroid therapy might be needed when other organs are involved and if relapse occur after steroid tapering (Iseda, 2014). No differences were found in terms of remission rate between high dose (0.8-1 mg/kg) and medium dose (0.5-0.6 mg/kg) corticosteroids in patients with IgG4-RD, however, a higher frequency of relapse was observed in the latter group. In addition, high dose intravenous glucocorticoids (e.g., 1 g methylprednisolone for three consecutive days) might be warranted as an urgent treatment to avoid organ damage, such as cases with cranial or spinal nerve involvement. Additional evaluations, including repeated biopsy procedures, to confirm the diagnosis should be performed in case of delayed or unsatisfactory response to steroids (Lanzillotta, 2020). Azathioprine is thought to be an alternative therapy, resulting in marked improvement in IgG4-RD cases (Iseda, 2014). Universal consensus does not exist regarding glucocorticoids treatment duration and tapering regimens. Some experts suggest that the initial steroid dose should be kept for at least two to four weeks, tapered gradually by 5 mg every two weeks over three to six months. In one clinical trial 93% of patients clinically responded to an initial dose of 0.6 mg/kg/day that was reduced by 10% every two weeks. Higher relapse rate is associated with faster lowering and early discontinuation of steroids. Forty-six to ninety percent of patients relapse within three years of diagnosis in the same organ or at a different organ, both during the taper (26-40% of patients) and the post-withdrawal of steroids (46-54% of patients). Nevertheless, in a case of relapse, typically cases respond well to the same dose of glucocorticoids used for induction of remission. Addition of other immunosuppressive agents or rituximab and slower tapering of the corticosteroid therapy are also indicated such cases (Lanzillotta, 2020). This was evident in case 2.

The dramatic response to steroids was evident in all of our cases, patients improved clinically, radiologically, and IgG4 levels dropped significantly. However, for the ophthalmic case, there was clear recurrence of the mass with absent clinical correlate, this is quite common in the literature. In general, steroids reduce remarkably enlarged pituitary gland and hormonal insufficiency could also abate (Cheuk, 2010), however it has been shown that some pituitary enlargement cases did not respond size-wise to glucocorticoids even though glucocorticoids administration resulted in IgG4 reduction (Iseda, 2014). Moreover, although cases of hypopituitirism were found to respond to treatment, diabetes insipidus was found not to resolve with glucocorticoid administration in most patients (Iseda, 2014).

Disease modifying anti-rheumatic drugs (DMARDs) addition to first line steroid therapy is thought to improve the likelihood of obtaining disease remission. Therefore, when predictors of relapse emerge (such as multi-organ involvement, elevation of serum IgG4 and IgE at baseline, and peripheral blood eosinophilia) azathioprine, mycophenolate mofetil, methotrexate, leflunomide, tacrolimus, ciclosporin A, iguratimod, and cyclophosphamide could be combined with glucocorticoids. The efficacy of such approach is based on little evidence and is mostly derived from retrospective studies. To date, four prospective studies (all uncontrolled and only one randomized), looked into DMARDs combination with steroid therapy concluding higher remission rate (93%) in comparison to glucocorticoids alone (79%) at six months. Mycophenolate mofetil (1-1.5 g/day), cyclophosphamide, and iguratimod appear to be particularly effective in this regard. Nevertheless, the latter has been tested only in localized sialadenitis with no internal organ involvement. Meta-analysis of 15 observational, uncontrolled, non-randomized clinical trials confirmed these observations and concluded that patients treated with combination therapy had a higher remission rate than those given only monotherapy of DMARD (55.31, 13.73 to 222.73) or glucocorticoid (odds ratio 3.36, 95% confidence interval 1.44 to 7.83). Adding immunosuppressive agents could also reduce the cumulative toxicity of chronic glucocorticoids use, especially in patients prone to relapse needing repeated courses of corticosteroids. Patients with IgG4-RD are typically older people with comorbidities representing major contraindications to corticosteroids, such as osteoporosis, diabetes, glaucoma, and hypertension (Lanzillotta, 2020).

While randomized controlled trials are still lacking, recent published papers are repeatedly discussing the role of the biological agent, rituximab, in resistant cases (Gange, 2019; Comai, 2019; Lanzillotta, 2020). Data from uncontrolled non-randomized prospective and retrospective studies indicate that disease remission using rituximab was seen in 67-83% of cases, allowing early tapering of glucocorticoid therapy (Lanzillotta, 2020). For instance, studies of ophthalmic IgG4-RD have shown an excellent treatment response with rituximab (Gange, 2019). In addition, rituximab was found to be a useful treatment in cases of diagnostic dilemma between ophthalmic IgG4-RD and ocular lymphoma, being effective against indolent lymphomas as well (Gange, 2019). A prospective open-label trial studying rituximab on 30 participants with IgG4-RD in different organs; has shown its effectiveness for IgG4-RD, even without concomitant steroid therapy (Carruthers, 2015). This could be explained by the absence of CD20 receptor on plasma blasts, interfering with the principal B-cell/T-cell cross-talk process (Comai, 2019). Furthermore, B cell depletion could improve tissue fibrosis in IgG4-RD by directly targeting a subset of B lymphocytes with pro-fibrotic properties involved in fibroblast activation and recruitment of inflammatory cells (Lanzillotta, 2020).

One study showed that patients experiencing active disease, needing urgent treatment, that were put on rituximab alone, maintained favorable response at 6 months. These favorable results were obtained even in those with multiorgan involvement, prior relapse, and failure of previous response to DMARD indicating high risk for relapsing or refractory disease (Carruthers, 2015).

The effective dose of rituximab administration needs to be determined. Some suggested using two 1 g infusions 15 days apart (rheumatological protocol) or in four weekly 375 mg/m2 infusions (hematological protocol), as well as at lower doses (single 1 g infusion) in few other reports. The best dosage and timing of administration remain to be defined, and some drawbacks are emerging that are similar to those observed in hematological settings and other autoimmune disorders. However, one French nationwide study showed that 43% of IgG4-RD patients that were treated with rituximab developed relapse, it also revealed that one third of the patients experienced serious infections or hypogammaglobulinemia (Lanzillotta, 2020). In addition, allergic reactions or reduced response to rituximab are increasingly reported in the literature, highlighting the need for alternative treatment approaches (Lanzillotta, 2020). In case 2, rituximab was given in the form of two 1g infusion, 15 days apart. There was an excellent response of the neurological symptoms to treatment. He received a total of eight rituximab treatment since his diagnosis. The intervals between the first three treatments were every1-2 years, however, the recurrent pulmonary relapses urged us to shorten these intervals to every 6 months. Eventually, the pulmonary symptoms responded dramatically to bi-yearly rituximab treatments.

As for case 3, the patient did not receive further maintenance of remission therapy. This decision was made after the clinical improvement post-resection, based on patient’s preference. The commencement of therapy was re-entertained when radiological progression was first noted, however, due to absence of symptoms the patient insisted not to be started on therapy. For that reason, she is being followed closely and yearly brain MRI is being performed.

Based on anecdotal case reports, the use of some other targeted therapies seemed successful, yet remained limited. For example, infliximab, a chimeric anti-tumor necrosis factor α antibody, was successfully used in refractory orbital pseudotumor to multiple immunosuppressive agents. Infliximab appears to reduce serum IgG4 concentrations and induce marked clinical responses (Lanzillotta, 2020).

Maintenance of remission therapy should be considered in patients with signs indicating high risk for relapse including multi-organ disease, elevation of serum IgG4 and IgE, and peripheral eosinophilia. Also, it should be offered for patients with organ threatening manifestations in an effort to minimize disease morbidity related to a potential relapse. Maintenance may consist of either low dose glucocorticoids or any of the steroid sparing agents mentioned above. One retrospective study compared the addition of different DMARDs to glucocorticoid monotherapy. It showed no differences in terms of relapse-free survival at two years. Furthermore, according to some retrospective studies and a single meta-analysis, rituximab appears to perform better than DMARD therapies in reducing the rate of relapses (odds ratio 0.10, 0.01 to 1.63). Some experts suggest discontinuing maintenance therapy in three years of persistent serological and radiological improvement. However, the biochemical and radiological follow-up after discontinuation of therapy need to be maintained (Lanzillotta, 2020).

It is worth mentioning that in case 2, after the patient’s fifth, sixth, seventh, and eighth rituximab treatments he respectively received four doses of the Pfizer COVID-19 vaccine. There was no change in his disease activity or response to treatment after the vaccination. He also contracted COVID-19 infection between dose six and seven of rituximab treatment, for which he received sotrovimab, with no complications or effect on disease control. The literature is still lacking when it comes to COVID-19 infection and vaccination in patients with IgG4-RD. In one paper, there was a mention of pleural effusion following vaccination with Pfizer vaccine. This was the first reported case of IgG4-related pulmonary and pleural disease following Pfizer COVID-19 vaccine (Tasnim, 2022). The second paper was the first to report the susceptibility of COVID-19 in IgG4-RD patients (Chen, 2020). Of the 91 cases of IgG4-RD that responded, two of which developed COVID-19. Both patients had a moderate-severity COVID-19 disease, the severity was attributed to the early detection and prompt treatment of the infection. The study concluded that IgG4-RD patients should be considered a susceptible population to COVID-19 infection and its complications. It also mentioned that the disease activity of IgG4-RD could affect the recovery process of COVID-19. Therefore, patients with IgG4-RD need more careful personal protection, early detection, and proper treatment. This was thought to be related to the immune-related disease itself and the treatments they take. High-dose steroids might increase the risk of long-term complications, secondary infections, and prolonged virus shedding in patients with COVID-19 (Chen, 2020).

References of Supplementary Material:

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