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Therapeutic innovations in endocrine diseases – Part 5: Rituximab and graves' orbitopathy

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In this issue

Summary

The use of rituximab in Graves' orbitopathy is appealing but its exact role in the therapeutic arsenal remains to be clarified, and its safety profile also needs to be confirmed on a larger scale.

Graves' orbitopathy (GO), also known as thyroid eye disease or thyroid-associated orbitopathy, is the most common extrathyroidal manifestation of autoimmune thyroiditis. It has an estimated prevalence of 25% in patients with Graves' disease [1]. The majority of forms are mild and inactive; 5% of forms are moderate to severe and active; and 0.3% of forms are vision-threatening (optic neuropathy or serious corneal complications).

Pathophysiology

Pathophysiology of GO consists of an inflammatory and oedematous process that particularly affects the orbital fibroadipose tissue and the oculomotor muscles, resulting in an increase in intraorbital pressure. The course is characterised by an initial inflammatory phase described as "active", in which the disease worsens; a later "inactive" phase then occurs, which is marked by a partial decrease in symptoms, leaving subsequent sequelae of varying degrees of disability. The activity level of TAO is clinically evaluated using the clinical activity score (CAS).

The autoimmune reaction that occurs in the orbit involves antigens, cellular elements (inflammation cells and target cells) and humoral elements. The pathophysiology of GO is founded on the hypothesis of shared antigens between the thyroid and the orbit, with the main causal antigens being the TSH receptor (TSHR) and the IGF-1 receptor (IGF-1R). The cellular elements of this process are the inflammatory cells, T-lymphocytes, B-lymphocytes, macrophages and plasmocytes, which interact with the target cells (the orbital fibroblasts) either directly or through the intermediary of various cytokines [2]. The stimulation of fibroblasts by the anti-TSHR antibodies results in their differentiation into adipocytes, which then themselves overexpress the TSHR and IGF-1R. This phenomenon is the cause of adipogenesis. Cytokines secreted by the T-lymphocytes activate

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another group of fibroblasts to synthesise hyaluronic acid, a highly hydrophilic substance, which causes edema of the muscles. B-lymphocytes are involved in the presentation of antigens, the secretion of pro-inflammatory cytokines and the production of auto-antibodies, particularly directed against TSHR and IGF-1R.

Rituximab

Systemic corticosteroid therapy is considered as the reference for active moderate to severe GO, with a clearly demonstrated superiority of the intravenous (IV) route versus oral therapy [3–5]. It also has a better tolerability when the cumulative dose does not exceed 8 g of methylprednisolone. This is indicated as first-line treatment, although it is ineffective in 20 to 30% of patients, and recurrence upon discontinuation of corticosteroid therapy is observed in 10 to 20% of cases [6]. The development of therapeutic alternatives has proven to be necessary, and many teams are interested in using more specific immunomodulators. The most studied drug to date is rituximab, which targets a key element of the pathophysiology of GO, the B-lymphocyte.

Rituximab is an immunomodulator, widely used in the treatment of malignant non-Hodgkin's lymphoma, rheumatoid arthritis, chronic lymphocytic leukaemia and Wegener's granulomatosis. It is a mouse/human chimeric monoclonal antibody directed against CD20, a transmembrane protein expressed by 95% of B-lymphocytes during their differentiation, i.e. immature B-lymphocytes to mature B-lymphocytes [7]. It induces lymphocytic depletion via 3 main mechanisms:

- apoptosis per mitochondrial route;
- complement-dependent cytotoxicity;
- antibody-dependent cellular cytotoxicity through the intermediary of macrophages and NK (natural killer) cells [8].

The lymphocytic depletion therefore affects the mature and immature B-lymphocytes, the short-life plasmocytes but not the long-life plasmocytes or memory B-cells, which produce antibodies. Antibody production can therefore continue under the effects of rituximab despite the depletion of B-lymphocytes. The exact mechanism that underlies the beneficial effects of rituximab in GO described in some studies remains poorly defined. In fact, the response to treatment does not seem to be correlated to the level of B-lymphocyte depletion, and the decrease in anti-TSHR antibodies titre is not greater with the use of rituximab than with corticosteroid therapy or methimazole alone [9–12]. The beneficial effects therefore could mainly be related to the alteration in function of antigen presentation and cytokine production exerted by the B-lymphocytes. Studies have shown that B-lymphocyte-deficient mice were unable to generate the T-lymphocytic response induced by TSHR, suggesting that B-lymphocytes play a crucial role in initiating the autoimmune reaction [13,14]. Finally, part of the effect could be the result of a decrease in the proportion of T-lymphocytes expressing the IGF-1R, which occurs 4 to 6 weeks after the administration of rituximab and seems to be correlated with the improvement of GO clinical activity [15]. The quantification of the IGF-1R(+) T-lymphocytes could therefore be a biological marker of rituximab efficacy.

The first trials of rituximab use in GO were reported in 2006 in isolated patients. El Fassi et al. described a positive effect of rituximab on the activity and severity of GO in 2 patients who had not responded to a combination of IV corticosteroid therapy and orbital radiation therapy [16]. In the same year, Salvi et al. likewise described a significant effect of rituximab on the CAS and on ocular motility in a patient who was resistant to IV corticosteroid therapy [17]. Several teams then reported small series of patients in non-controlled studies. Most of these studies used dosages of rituximab usually given for rheumatoid arthritis, i.e. infusions of 500 to 1000 mg repeated from 2 to 4 times. The series from Salvi et al. and Silkiss et al. included 9 and 12 patients, respectively, who had improvement of GO on rituximab, both with regard to clinical activity and severity [10,18]. Khanna et al. described the positive effects of rituximab combined with corticosteroid therapy in 6 patients who had been resistant to previous IV corticosteroids used alone. Four of them presented with optic neuropathy that responded to rituximab, with recovery of their previous visual acuity 2 months after the treatment [19]. Madaschi et al. used rituximab in one patient with GO and diabetes who was positive for anti-GAD antibodies associated with stiff-person syndrome. They observed complete inactivation of the GO and simultaneous improvement of the neurological signs [20]. The team of Mitchell et al. reported a positive outcome of GO on rituximab in 9 patients resistant to IV corticosteroid therapy, as well as a significant reduction in the anti-TSHR antibodies titre [21]. This reduction was not correlated to the level of B-lymphocyte depletion or to the decrease in CAS, and it was not observed in any other series. The effects on CAS reduction seem to occur early, with inactivation of GO observed 4 to 6 weeks after the administration of the treatment [15,22]. Finally, these effects seem to be maintained over time, up to 5 years in the series that reported the longest follow-up, with no relapse or subsequent modification of the CAS in the 67 months of mean follow-up (58–81 months) [22]. More anecdotally, intraorbital injections of rituximab were tested by Savino et al. in 5 patients with successful results and no major adverse reactions [23].

Finally, two negative studies need to be pointed out. In one, by Krassas et al., the GO worsened and was complicated by optic neuropathy in one patient after treatment with rituximab [24]. In the other, by Gess and Silkiss, rituximab proved to be ineffective despite complete depletion of CD20+ B-lymphocytes in the patient's blood and orbit [25].

Smaller doses of rituximab have been tested and found to have comparable efficacy with the standard doses. In 3 patients, Salvi et al. showed that a low dose of rituximab, i.e. a single infusion