ORIGINAL RESEARCH

Effects of Rituximab on Graves' orbitopathy

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Abstract
Background: Graves' orbitopathy (GO) is a potentially sight-threatening and disfiguring, extrathyroidal manifestation of Graves' disease. It often impairs patients' quality of life, causing severe social and psychological sequelae. To study the effects of rituximab on graves orbitopathy. **Materials & Methods:** A total of 10 subjects were enrolled. The Wilcoxon rank sum test for paired samples was employed to compare the Clinical Activity Score (CAS) between baseline and 12 weeks, as well as between baseline and 24 weeks. The p- value less than 0.05 were considered statistically significant. The results were analysed using SPSS software. **Results:** A total of 10 subjects were enrolled. The average age group was 50-70 years. The number of male subjects was 3(30%). A modest enhancement in the clinical activity score was noted, with a median improvement of 1 point at 24 weeks (p=0.001) conjunctival injection depicted in 50%. **Conclusion:** Rituximab, known for its favorable tolerance and safety record, showed only modest and incomplete efficacy in treating active moderate-to-severe Graves' ophthalmopathy with a prolonged disease duration.

Keywords: Graves' disease, Rituximab, Graves' orbitopathy.

INTRODUCTION

Graves' orbitopathy (GO), otherwise referred to as Graves' eye disease or thyroid eye disease, is an autoimmune, inflammatory disorder of the retroocular tissue occurring in patients with autoimmune thyroid disease (ATD). It is mainly associated with Graves' disease (GD) but may also be seen in patients with chronic lymphocytic thyroiditis. Most commonly, it accompanies hyperthyroidism, but it may also occur in euthyroid patients, preceding the diagnosis of ATD by months or even years. The onset of GO may also be observed many years after the diagnosis of ATD. [1] Recent research suggests that as many as 70% of patients with GD have evidence of GO in MRI. [2] The incidence of clinically relevant cases was 16 per 100,000 in females and 2.9 per 100,000 in males. [2-4] The symptoms of GO include excessive tearing, foreign body sensation, photophobia, and/or pain in the orbit, either resting or gaze evoked. Diplopia, blurring, and desaturation of colors may also be present. Patients commonly present with swelling or redness of upper or lower eyelids and conjunctivae or proptosis. It is not rare that these symptoms are asymmetrical or even unilateral.[5]

The role of genetic factors conferring predisposition to Graves' disease has long been proposed, based on twin and family studies, and family clustering of thyroid autoimmune disorders. [6,7] Several candidate genes have been indicated, but the differentiation of the genetic profile of Graves' patients with or without GO is uncertain. [8,9] Additionally, in twin studies the concordance rate is only about 30%, suggesting a low penetrance of involved genes. [10] Epigenetic factors—including abnormal DNA methylation, histone modification, and noncoding RNAs—may contribute to GO pathogenesis, but their role is not clear. Preliminary studies reporting differences in gut microbiota composition in Graves' patients with or without GO —as well as animal studies suggesting a pivotal role of gut microbiota in TSHR-induced disease —opened an interesting field of research.[11-13] Hence, this study was conducted to analyse the effects of rituximab on graves orbitopathy.

MATERIALS & METHODS

A total of 10 subjects were enrolled. Rituximab was given through an intravenous route, with a dosage of 1000mg twice, spaced two weeks apart. Evaluating the reduction in clinical activity scores at 24 weeks,

defined as an improvement of ⩾2 points or disease inactivation (clinical activity score<3). The Wilcoxon rank sum test for paired samples was employed to compare the Clinical Activity Score (CAS) between baseline and 12 weeks, as well as between baseline and 24 weeks. Additionally, Spearman's rank correlation analysis was conducted to assess the univariate correlation between various parameters. The p- value less than 0.05 were considered statistically significant. The results were analysed using SPSS software.

RESULTS

A total of 10 subjects were enrolled. The average age group was 50-70 years. The number of male subjects was 3(30%). A modest enhancement in the clinical activity score was noted, with a median improvement of 1 point at 24 weeks (p=0.001) conjunctival injection depicted in 50%. Eyelid edema can be seen in 10%. In diplopia, 60% cases were seen at baseline. At 12 and 24 weeks, diplopia was present in 14.2%, respectively.

Table 1: Clinical and ophthalmological characteristics of subjects treated with RTX at baseline (N=10 patients)

Parameters	Number (%)	Median
Age (year)		50-70 (Range)
Gender Male	3 (30)	
Female	7 (70)	
GO duration (months)		15-45 (Range)
CAS (baseline)		2-4 (Range)
GO finings before GD	2(20)	
GO findings after GD	7(70)	
Decompression prior RTX	2 (20)	

RTX: rituximab, GO: graves orbitopathy, CAS: clinical activity score, GD: graves disease

Table 2: CAS score at baseline, at 12weeks and at 24weeks

CAS	Baseline	12 weeks	24 weeks
Conjunctival injection, n (%)	10 (100%)	7 (70)	5 (50)
Eyelid oedema	4 (40)	1 (10)	1 (10)
Decrease of eye movement>8^0	0	1 (10)	0
Eyelid erythema	1 (10)	0	1 (10)
Chemosis	8 (80)	7 (70)	6 (60)

Table 3: Assessment of diplopia at baseline and at 24weeks according to Gorman score

Diplopia	N (%)
Present at baseline (n=10)	6 (60)
12 weeks (n=7)	1 (14.2)
24 weeks (n=7)	1 (14.2)
Gorman score	
At baseline (n=9)	
Absent	3 (33.4)
Intermittent	1 (11.2)
Inconstant	1 (11.2)
Constant	2 (22.3)

DISCUSSION

The Graves' orbitopathy (GO) is an autoimmune inflammation of the orbital tissues and the most common extra-thyroid symptom of Graves' disease (GD). GO occurs in 25–50% of patients with GD, although the literature shows that subclinical ocular lesions can be observed in the majority of patients with GD when high-quality imaging techniques are used. [14-16] Mild cases of GO are often misdiagnosed as conjunctivitis or allergic symptoms, which prolongs the diagnostic and therapeutic process, in some cases leading to exacerbation of the disease. [17] Symptoms typical of GO—ocular pain, excessive tearing, photophobia, visual disturbances, including double vision—significantly reduce the quality of life of patients. [18] The inflammatory state in the orbit manifests itself mainly as redness and swelling of conjunctivas and eyelids, exophthalmos, and retrobulbar pain. A severe course of GO with the occurrence of dysthyroid optic neuropathy (DON) or corneal ulceration may lead to permanent vision loss. [19] The current treatment of active GO consists predominantly in intravenous administration of glucocorticoids (GCs); however, according to the literature, the results of such treatment are unsatisfactory in 35% of cases. Immunosuppressive

treatment is not effective in patients in whom a chronic inflammatory process has caused fibrous changes in the orbits. [20] Hence, this study was conducted to analyse the effects of rituximab on graves orbitopathy.

In the present study, a total of 10 subjects were enrolled. The average age group was 50-70 years. The number of male subjects was 3(30%). A modest enhancement in the clinical activity score was noted, with a median improvement of 1 point at 24 weeks (p=0.001) conjunctival injection depicted in 50%. A study by Deltour JB et al, Forty patients were included (65% smokers, 38% dysthyroidism). Thirty-two patients were treated with RTX alone (one patient excluded owing to side effects): 64.5% had favorable responses at week 24 and significant reduction in baseline CAS (3.29 ± 1.6) at 12 weeks (1.93 ± 1.1; P < 0.001) and at week 24 (1.59 ± 1.1; P < 0.001); reduction in anti-TSH receptor antibodies at week 24 (P < 0.01); and significant improvement of visual acuity (P = 0.04) and ocular hypertonia (P = 0.04) at week 12, but no improvement in oculomotor dysfunction. Eight patients needed emergency treatment with concomitant RTX and orbital decompression, with favorable outcome for 5 patients. Predictive factors for a poor response to RTX were low baseline CAS, smoker, and baseline ocular hypertonia. All patients reported good tolerance except one serious side effect (a cytokine release syndrome). The efficiency results of RTX in reducing CAS in this cohort are just between those of Stan and Salvi. This could be explained by delay before treatment initiation, quicker than Stan but longer than Salvi. RTX appears to be effective as a second-line treatment for the inflammatory component of GO, especially if the disease is highly active and recent. [21]

In the present study, eyelid edema can be seen in 10%. In diplopia, 60% cases were seen at baseline. At 12 and 24 weeks, diplopia was present in 14.2%, respectively. Another study by Salvi M et al, RTX has been used in 43 patients with active Graves' orbitopathy (GO). Disease has become inactive in as many as 39 (91%), has not changed in three, and worsened in one patient. In most patients, proptosis and eye motility have been shown to improve. Side effects have been reported in about one-third of patients, usually infusion-related reactions. Because RTX does not seem to modify circulating TSH receptor antibodies, its effect may result from the blockade of antigen presentation by B cells after anti-CD20-induced lysis. Although evidence from controlled trials is needed before proposing RTX as a novel therapeutic tool in this disease, collected data suggest that RTX does significantly affect the activity and severity of GO. Controlled studies will also help decide whether RTX is to be used in any patients with active GO or only in those with otherwise unresponsive disease of a severe degree. The data reported on RTX therapy in GO suggest that B-cell depletion may be pursued shortly after diagnosis, and not only as a therapeutic option when standard immunosuppression has failed. [22] Rituximab is a monoclonal antibody against the CD20 protein present on the surface of immune B cells. Its potential efficacy in GO is most likely associated with the inhibition of antigen presentation by B lymphocytes, what inhibits the production of autoantibodies and pro-inflammatory cytokines. [23] On the other hand, in a prospective, randomized, double-blind, placebo-controlled study Marius et al. did not observe RTX superiority over placebo in patients with active moderate-to-severe GO of long duration. [24] According to the literature, there are some reports of DON occurrence after RTX, therefore it should not be used in patients at high risk of DON development. In view of the presented data further large and adequately designed studies have to be undertaken to assess the use of RTX both as a first and second-line treatment of GO. Moreover, investigations to evaluate the relationship between the duration of the disease and the efficacy of RTX therapy as well as the association between RTX and DON should be performed. Active moderate-to-severe forms of GO affect a minority of patients but are a major challenge and dilemma because established medical treatments often achieve incomplete results. [25] GCs still constitute the mainstay in the management of active moderate-to-severe and sight-threatening GO, but recent advances using either old drugs with new applications or novel biological agents have expanded the armamentarium available for treatment. [26]

CONCLUSION

Rituximab, known for its favorable tolerance and safety record, showed only modest and incomplete efficacy in treating active moderate-to-severe Graves' ophthalmopathy with a prolonged disease duration.

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