Clin Thyroidol 2013;25:56–57.

Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION
FOUNDED 1923

Are Anti-CD20 Antibodies Useful in the Management of Severe Graves' Orbitopathy?

Albert G. Burger

Mitchell AL, Gan EH, Morris M, Johnson K, Neoh C, Dickinson AJ, Perros P, Pearce SH. 2013. The effect of B cell depletion therapy on anti-TSH receptor antibodies and clinical outcome in glucocorticoid refractory Graves' orbitopathy. Clin Endocrinol. January 16, 2013 [Epub ahead of print].

SUMMARY

Background

Mild orbitopathy is seen in 25% to 50% of patients with Graves' disease; the orbitopathy mostly evolves favorably over a 2-year period. One rare but severe complication is optic-nerve involvement (dysthyroid optic neuropathy). In this situation, emergency interventions are necessary. The first choice is large doses of steroids, preferably intravenous methylprednisolone. This procedure induces a marked reduction of the lymphocyte population, particularly B lymphocytes. An even more efficient reduction of B lymphocytes may be achieved by specific B-cell antibodies. Rituximab (RTX) is an antibody against the cell-surface antigen CD20 and is capable of inducing a complete depletion of B lymphocytes. This treatment was first tested in Graves' orbitopathy in 2006, but the results were equivocal (1, 2). Several studies followed, since RTX could conceivably represent a valuable alternative to the orbital decompression that may be necessary in some cases after failure of intravenous methylprednisolone. The results provided positive results concerning the clinical activity score (CAS) (3), but none of the studies included an adequate control group.

Methods

Nine patients (one man, eight women; age range, 37 to 87 years) were treated. Four patients had sight-threatening optic-nerve involvement (No SPECS score, 6) (4), and the others had moderate to severe disease but did not respond to methylprednisolone treatment. Hyperthyroidism was under control at the time of treatment; the patients were either euthyroid or had hypothyroidism. The patients had received IV methylprednisolone at a high cumulative dose of 3 to 5 g over a median period of three months before treatment with RTX.

RTX treatment was given in combination with 500 mg of IV methylprednisolone and 10 mg of chlorpheniramine plus aspirin. This treatment was repeated at 2-week intervals. The cumulative doses of RTX were 1 g (2 x 0.5 g) in six cases and 2 g (2 x 1 g) in three cases. B-cell depletion, defined as <1 per 10,000 total lymphocytes, was achieved in all except one patient.

Results

No severe adverse effects were reported. Nine months after treatment, the number of B lymphocytes had returned to normal. The treatment had no effect on thyroid function or on peripheral thyroid hormone parameters. During the 8 months following treatment, the level of TSH-receptor binding inhibitory immunoglobulin (TBII) was markedly reduced in all cases, but the improvement of the CAS did not parallel the TBII pattern. Nevertheless, the CAS improved in all patients. The authors do not give detailed information as to the effect on orbital neuropathy. In one patient emergency orbital decompression was necessary.

Conclusions

RTX following methylprednisolone treatment was most successful in decreasing the TBII titer significantly in all patients. The CAS improved moderately, but the effects on optic neuropathy are not specified. Thyroid function was not affected by the treatment.

continued on next page

ANALYSIS AND COMMENTARY

The present study differs from earlier ones, since RTX was given together with methylprednisolone. The positive findings of the study are the reduction in the CAS score and the good tolerance of RTX treatment. We know, however, how variable the evolution of Graves' orbitopathy can be and agree with the authors that only prospective multicenter studies can definitely prove the effectiveness of the proposed treatment.

The striking decrease in TBII is remarkable and compatible with the depletion of B lymphocytes. The article does not describe in detail the thyroid status of the patients; for example, we are not informed whether they underwent thyroidectomy or had received radioactive iodine, which would explain the absence of any change of thyroid function following RTX treatment There is also no information on anti-TPO and antithyroglobulin antibodies.

It is therefore too early to recommend the described treatment protocol routinely in severe Graves' orbitopathy. Rather, it should be further evaluated in specialized centers and in a prospective way. Thyroidologists are advised to collaborate with eye surgeons experienced in the field of Graves' disease. In some cases, surgical decompression may be the only means to bring relief to the optic nerve.

References

1. Salvi M, Vannucchi G, Campi I, Rossi, S., Bonara P, Sbrozzi F, Guastella C, Avignone S, Pirola G, Ratiglia R, et al. Efficacy of rituximab treatment for thyroid-associated ophthalmopathy as a result of intraorbital B-cell depletion in one patient unresponsive to steroid immunosuppression. Eur J Endocrinol 2006;154:511-7.
2. Salvi M, Vannucchi G, Campi I, Curro N, Dazzi D, Simonetta S, Bonara P, Rossi S, Sina C, Guastella C, et al. Treatment of Graves' disease and associated ophthalmopathy with the anti-CD20 monoclonal antibody rituximab: an open study. Eur J Endocrinol 2007;156:33-40.
3. Bartalena L, Baldeschi L, Dickinson A, Eckstein A, Kendall-Taylor P, Marcocci C, Mourits M, Perros P, Boboridis K, Boschi A, et al. Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. Eur J Endocrinol 2008;158:273-85.
4. Werner SC. Modification of the classification of the eye changes of Graves' disease: recommendations of the Ad Hoc Committee of the American Thyroid Association. J Clin Endocrinol Metab 1977;44:203-4.