Rituximab Is Better Than Corticosteroids for Active Graves’ Orbitopathy

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SUMMARY

Background
Graves’ orbitopathy (GO) occurs in about one fourth of patients with Graves’ disease and is a significant problem in about 5% to 10% of these patients. Glucocorticoids are the principal medical therapy for active moderate-to-severe GO (1) but are not very effective in many patients. Rituximab, a monoclonal antibody targeted against the CD20 antigen on B lymphocytes, destroys the B lymphocytes and is used for treatment of hematologic and autoimmune disorders. Rituximab has also been reported to be effective in the treatment of GO (2). The current study is a randomized, double-blind, controlled trial of rituximab (RTX) versus IV methylprednisolone (MP) in patients with moderate-to-severe GO.

Methods
The study included patients with Graves’ disease who were euthyroid for 6 to 8 weeks and were affected by active GO based on a clinical activity score of 4 or greater or a NOSPECS classification score of 3 or greater. Patients who had been treated previously with steroids were included as long as the steroid had been discontinued for at least 3 months.

The study was designed to include 60 patients but was stopped based on interim analyses of 32 patients. In the RTX group, the first 6 patients received 1000 mg twice separated by 2 weeks. Subsequent patients in the RTX group received a single 500 mg infusion after it was reported that a single infusion of 100 mg caused complete depletion of CD20 cells (3). Patients in the MP group received 830 mg of MP IV weekly for 6 weeks followed by 415 mg weekly for another 6 weeks based on the schedule of the European Group on Graves Orbitopathy (4). Patients in the MP group were also treated with proton-pump inhibitors, bisphosphonates, and calcium and vitamin B supplements.

The primary end point was a decrease in the clinical activity score by 2 or more points. Additional end points included a decrease in proptosis, improvement of eye motility, disease reactivation, requirement for surgical procedures after 12 months, and quality of life as assessed by a specific questionnaire for GO. Measurements also included lymphocyte subpopulations and TSH receptor antibody (TRAb).

Results
Thirty-two patients were randomly assigned, 16 in each group, including 26 women and 6 men; 19 were smokers. One woman receiving RTX withdrew without completing the study. Three patients in each study group had received corticosteroids previously. The duration of GO had been 4.5 months for patients in each group.

Impressive decreases in clinical activity score (CAS) were similar in the two groups up to 12 weeks; after that, the CAS continued to improve with RTX but plateaued with MP, and the differences between the scores was significant at 16, 20, and 24 weeks, favoring RTX. There was no difference in the CAS responses with regard to the RTX dose (2000 mg vs. 500 mg).
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Mean proptosis values did not decrease significantly in either group. There was no improvement in diplopia scores in either group, but ocular motility was slightly improved in the RTX group. Five of 16 patients in the MP group had reactivation of GO within 1 year, but none of the patients in the RTX group had reactivation. Ten patients in the MP group and 3 in the RTX group underwent a surgical procedure for GO. Based on the GO quality-of-life scale, RTX caused much greater improvement than did MP.

During the 24 weeks of observation, TRAb antibodies declined in the patients in the RTX group but not in the patients in the MP group.

Adverse reactions occurred in 10 of 16 patients in the MP group, mainly hyperglycemia and liver-function abnormalities. Adverse events occurred in 13 of 15 patients in the RTX group, mainly infusion reactions with throat itching and nasal stuffiness.

Conclusions
Treatment with rituximab results in a better therapeutic outcome for active moderate-to-severe Graves’ orbitopathy than treatment with methylprednisolone.

ANALYSIS AND COMMENTARY

This interesting, carefully performed randomized trial provides convincing evidence that rituximab is preferable to intravenous corticosteroid therapy for moderate-to-severe GO. The authors believe that rituximab has a disease-modifying effect because it results in better eye motility, better quality of life, and reduces the need for surgical procedures as compared with the steroid group. Although the improvement in the RTX group justified stopping the study before recruiting the target of 60 patients, 30 in each group, results from a larger number of patients would be more convincing with regard to the benefit of RTX.

In the same issue of JCEM (and at the same session of the ATA meeting last year), there is a paper comparing RTX against placebo in a randomized study performed at the Mayo Clinic (5). This study evaluated 11 patients who received 1000 mg of RTX twice separated by 2 weeks and 10 who received infusions of saline as controls at 24 weeks, with loss of one from each group in evaluations at 52 weeks. Forty percent of the patients had received prior steroid therapy. The Mayo study showed significant but similar improvements in clinical activity score in each group at 24 and 52 weeks. By 52 weeks, the disease was inactive in 4 of 10 patients in the placebo group and in 6 of 10 patients in the RTX group (P not significant). CT-measured orbital muscle and fat volume did not change significantly in either group. There was improvement in proptosis by >2 mm in 25% of patients in the placebo group and in 15% of those in the RTX group at 24 weeks (P not significant). Diplopia did not improve in either group.

What is the basis for the difference between the two studies? Both rituximab and steroids modify the inflammatory aspect of the disease. The mean duration of the GO in the Mayo Clinic study was 11.2 months (range, 8 to 36) while the mean duration of GO in the Italian study was 4.5 months. This suggests that the inflammatory component of GO was probably more active in the Italian study and the disease was less likely to have plateaued; antiinflammatory therapy is more likely to be beneficial when administered in the early phase of the disease. Of course, this explanation is speculative.

The lack of benefit of the active therapy for diplopia is reinforced by the recent report from Denmark that is reviewed in this issue showing that diplopia correlates negatively with inflammatory signs of GO (6).
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References


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