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TEPROTUMUMAB, A NEW TREATMENT FOR GRAVES' ORBITOPATHY

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Introduction

Graves' orbitopathy (GO), a complication of Graves's disease (GD), may cause orbital inflammation, exophthalmos, diplopia and, in most severe cases, optic nerve compression. While topical symptomatic treatment and oral selenium may suffice in some, patients more severely affected require different combinations of intravenous (IV) steroids, radiotherapy and surgery. Optic neuropathy mandates rapid implementation of high-dose IV steroids and often, decompressive surgery, in order to safeguard vision (1). Response to standard treatment in moderate-severe GO may be disappointing, which has prompted research on molecules, like Rituximab (2), able to affect the immune-pathogenesis of the disorder. Teprotumumab is a monoclonal antibody capable of binding the IGF-1 receptor (IGF1-R). The results of an international, multicenter, randomized controlled trial on the role of Teprotumumab in GO were recently published (3).

THE STUDY

Rational: Use of Teprotumumab is based on the observation that in patients with GD

- IGF-1 synergistically enhances the actions of thyrotropin.
- Immunoglobulins activating IGF1-R may be detected.
- IGF1-R is overexpressed by orbital fibroblasts and by T cells and B cells.

Protocol: Randomized double blind allocation to placebo or Teprotumumab (an IV infusion every 3 weeks for a total of 8 infusions).

Inclusion Criteria: Moderate-severe GO diagnosed no more than 9 months after the onset of symptoms, with a Clinical Activity Score (CAS) ≥4 on a 7-point scale.

Patients: Among the 88 eligible patients undergoing randomization, 39 patients in the placebo group and 37 patients in the Teprotumumab group completed the intervention. Despite stratified randomization, there was a higher percentage of smokers in the placebo group (41% vs. 26%).

Evaluations: CAS, measurement of proptosis, quality of life (QOL) evaluated with the use of a GO-specific questionnaire (GO-QOL).

Primary end-point: A composite of reduction ≥2 points in CAS and a reduction of ≥2 mm in proptosis at week 24.

Secondary end points: Previous end-points (assessed individually) and GO-QOL measured as continuous variables.

Analysis: All randomly assigned patients who received at least one infusion were included in the intention to treat (ITT) population, used for primary and secondary efficacy outcomes (45 in the placebo group and 42 in the Teprotumumab group).

Results

Primary End-Point: In the ITT population, 20% of patients who received placebo and 69% of patients who received Teprotumumab had a response at week 24 ($p < 0.001$). Among patients who took the drug according to protocol, the response was 22% and 79%, in the placebo and Teprotumumab group, respectively ($p < 0.001$). Time to first response was shorter in the Teprotumumab group than in the placebo group at weeks 6, 12, and 18 ($p < 0.001$).

CAS: A higher number of patients had a reduction >3 points in the Teprotumumab group. A post-hoc analysis showed that 69% of the patients who received Teprotumumab had a CAS of 0 to 1 at week 24, as compared with 21% of the patients who received placebo ($p < 0.001$).

Proptosis: At weeks 6,12, 18, and 24, the reduction in proptosis from baseline, measured as a continuous variable, was significantly greater in patients who received Teprotumumab than in those who received placebo ($p < 0.001$). At week 24, a total of 17 of 42 patients (40%) who received Teprotumumab had a reduction of ≥4 mm in proptosis, as compared with 0% of patients who received placebo.

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GO-QOL Score: The GO-QOL visual-functioning score increased significantly in the Teprotumumab group compared to placebo (p <0.009 at 24 weeks). Response rates with respect to subjective diplopia were also significantly higher in the Teprotumumab group than in the placebo group (p <0.001 at 24 weeks).
Post-treatment follow-up: Assessment of efficacy at week 28 (7 weeks after the final dose was administered), showed no evidence of diminution (i.e. no "rebound" phenomenon).
Safety: Most adverse events were mild, and resolved while patients continued to receive the intervention. The most common adverse event was a worsening of glycemic control in patients with pre-existing diabetes. Hyperglycemia in patients who did not have diabetes was uniformly mild, intermittent, and occurred at similar rates in the two groups. No deaths occurred during the trial.

Conclusions
A 24-week course of Teprotumumab therapy provided clinical benefit in patients with active, moderate-to-severe GO, by reducing proptosis and the CAS, and by improving the patients' QOL. No significant safety issues have emerged in the course of the study.

DISCUSSION

The study shows that Teprotumumab may induce a regression of the exophthalmos comparable to that achievable by decompressive surgery, a result not reported with the use of steroids (2) and rituximab (3). Of interest, the significant improvement in the CAS was not followed by a rebound, which has been reported in some trials of steroids (but not with Rituximab). In analogy with other medications, precocity of intervention seems to improve results in patients with moderate-severe GO.
The study has however some limitations. Only patients with recent-onset moderate-severe GO (CAS ≥4) were enrolled, which limits the extrapolation of results to patients with milder, less active or stable disease. Although patients were stratified according to smoking status, there was an imbalance between placebo and active treatment group with respect to this variable, which may affect results. Longer-term observation is necessary for assessing the durability of the response, and the results need to be validated in a confirmatory trial. Finally, even though no medication has previously been shown to induce a significant reduction in proptosis, it would help define the efficacy of Teprotumumab if it were tested against an active comparator rather than placebo.
In the study, the majority of adverse events was mild, involved no treatment and resolved while the patients continued to receive the intervention. It must be taken into account that worsening of glycemic control in diabetic patients, the most common unwanted event, is a side-effect shared by steroids, a standard first-line intervention in patients with moderate-severe GO.
The results of the study have prompted a «*breakthrough therapy*» designation from the Food and Drug Administration. Due to its apparent «*disease-modifying*» role, Teprotumumab might perhaps be envisaged as a first-line treatment in moderate-severe GO. Cost of treatment is certainly going to be superior to steroids but probably less than Rituximab, which has however the advantage of a single-dose administration. It is perhaps possible to envisage a use in parallel or in series with other medications already in use, to act on several points of the immune-pathogenic cascade.

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