Teprotumumab for the treatment of active thyroid eye disease.
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This is a phase 3 randomized, double-masked, placebo-controlled trial (called the OPTIC trial) of the efficacy and safety of teprotumumab, an insulin-like growth factor 1 receptor inhibiator, in patients with clinically active thyroid eye disease. Thyroid-associated ophthalmology (or Graves' orbitopathy) is a rare debilitating autoimmune disease which prior to this had no FDA-approved medical therapy available.

This trial was conducted at 13 sites in the United States and Europe. Eligible patients had to be between age 18-80 years, have received a diagnosis of Graves' disease, had active moderate-to-severe thyroid eye disease, had ocular symptoms that began within 9 months before the baseline assessment with an eligible Clinical Activity Score (see description in the paper) in the more proptotic (study) eye, and had to be euthyroid. Patients were excluded if they had prior orbital irradiation or surgery for thyroid eye disease, decreasing vision defect from optic nerve involvement within the prior 6 months, glucocorticoid use greater than 1g equivalent of methylprednisolone, and any prior treatment with rituximab or tocilizumab. Patients who were eligible were randomly assigned to receive either IV teprotumumab (10mg/kg for first infusion and then 20mg/kg for subsequent infusions) or placebo once every 3 weeks for 21 weeks for a total of 8 infusions (last infusion at 24 weeks). The primary outcome was the proptosis reduction response at week 24. Secondary outcomes included overall response (reduction of proptosis and reduction in the Clinical Activity Score), mean change in proptosis across visits, diplopia response, and mean change of score in a quality of life questionnaire at week 24. Patients, investigators, and trial-site personnel (except for the pharmacists) were unaware of the trial-group assignments throughout completion of the study. Intention-to-treat analysis was performed.

A total of 83 patients were eligible for randomization. Baseline characteristics between the teprotumumab group (N=41) and placebo group (N=42) were similar. For the primary outcome, patients in the teprotumumab group had a significantly greater proptosis reduction response compared to placebo (83% of teprotumumab patients compared to 10% in placebo patients). An initial response to teprotumumab was seen at around 6 weeks in most patients (56%). The proptosis response, including mean change from baseline in proptosis, were all consistently significantly greater throughout the visits in the teprotumumab group compared to placebo (see Figure 2). For the secondary outcomes, a higher percentage of teprotumumab patients had a Clinical Activity Score of 0 or 1 (signifying absence of disease activity) compared to placebo patients throughout the treatment period. Out of the patients who had diplopia (28 in each group), a diplopia reduction response was seen in a higher percentage of teprotumumab patients compared to placebo throughout the treatment period (regardless of the severity of diplopia at baseline). In addition, the overall score in the quality-of-life questionnaire was better in the teprotumumab group than the placebo group. An analysis of orbital imaging performed in 6 patients in the teprotumumab group found that the reduction in proptosis was associated with a reduction in extraocular muscle volume and/or orbital fat volume. Adverse events were usually mild or moderate and most frequently included muscle spasm, alopecia, and nausea, among others.

In conclusion, this phase 3 trial showed a remarkable meaningful benefit of teprotumumab over placebo in reducing symptoms associated with active thyroid eye disease. The clinical benefit was most evident starting at around week 6, with continued improvement in outcomes over the 24 week treatment period. They did not study its effects beyond 24 weeks. In addition, it is important to note that teprotumumab is absolutely contraindicated in pregnancy, which is worth keeping in mind as Graves' disease preferentially affects women of reproductive age.

Summary by Amy Li Safadi, MD