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# A Potential Breakthrough in the Treatment of Graves' Disease

A new day in the treatment of inflammatory Graves' disease may be approaching.

Since the early 20th century, the search for the pathogenesis and targeted treatment for ophthalmic Graves' disease has been elusive. Candidates for pathogenesis initially included the beta subunit of thyroid stimulating hormone (B-TSH). In the 1960's and 70's, enthusiasm for long-acting thyroid stimulating antibodies (LATS), and LATS-Protector (LATS-P) antibodies, as well as thyroglobulin-anti thyroglobulin antibody complexes were thought to play a role. In the 1990's and 2000's, the role of T and/or B lymphocytes was debated. T helper 1 cytokines (TH1) were speculated to play a role in the inflammatory manifestations of the disease, while T helper 2 cytokines (TH2) were suggested as playing a role in the more fat-proliferative cases. Along the way, 64 kilo-Dalton surface protein, mitochondrial succinate dehydrogenase protein, and calcequestrin all came and went as potential key pathogenic mediators.

Without the understanding of the underlying pathogenesis, treatment has remained in the realm of the non-specific anti-inflammatory, and surgical mechanical treatment of the orbit and eyelids. Pulsed steroids systemically, followed by surgical decompression of the orbit with eyelid retraction repair, has become the most effective and most commonly practiced treatment. Radiation has, by and large, faded into the background as a second tier modality. Initial enthusiasm for rituximab, adalimumab, etanercept, and tocilizumab, as targeted biologic mono-clonal antibody treatments in ophthalmic Graves' disease has waned (1).

We believe that ophthalmic Graves' disease presents as two distinct and clinically recognizable entities, classified as Type I, and Type II (2,3). Type I disease is primarily a proliferative disease of orbital fat, combined with non-cicatrizing extraocular muscle (EOM) enlargement. These patients may present at any age, but the median onset is in the mid thirties. Women are more commonly effected by a ratio of 8:1 to 11:1 in our studies. Inflammatory presentation is not generally a component of Type I disease, progression is rare, compressive optic neuropathy has not been observed to occur despite extreme proptosis in some cases. Diplopia within 20 degrees of primary position does not occur, by definition of type I disease.

Type II disease, however, is primarily an inflammatory and cicatrizing disease which focuses on the extraocular muscles. Restrictive diplopia, orbital inflammation, and high risk for compressive neuropathy (36%), regardless of amount of proptosis, make this a more virulent syndrome compared to Type I disease.

A recent study in the New England Journal of Medicine may add significant new information regarding the pathogenesis of the inflammatory type II syndrome, as well as an exciting new treatment option for those patients (4).

A new drug (teprotumumab) was tested on "moderate to severe" ophthalmic Graves' disease patients. The drug was administered intravenously weekly, once every three weeks for a total of eight infusions. The patients were randomly divided into placebo and teprotumumab groups in a double blinded manner. Sixty-nine per cent of the teprotumumab group vs. 20% of the placebo group responded well, as defined as a decrease of 2 out of 7 clinical activity score points, combined with a decrease of 2 mm in proptosis. Adverse effects of the drug were minimal and consisted primarily of increased blood sugar, especially among diabetic patients.

Teprotumumab is a human monoclonal antibody to the Insulin-like growth factor 1 receptor (IGF-IR). Immunoglobulins which activate IGF-I receptor have been found in patients with Graves' disease (5). IGF-I enhances the actions of thyroid stimulating hormone, and the IGF-IR is overexpressed in orbital fibroblasts (6), as well as in T cells and B cells in persons with Graves' disease (7,8). IGF-IR forms a signaling complex with TSH receptors, and is transactivated with the TSH receptor (6). In vitro studies have demonstrated IGF-IR inhibitory antibodies can attenuate the actions of IGF-I, TSH, TSI, and immunoblobulins from patients with Graves' disease (6,9).

The in vivo results of the NEJM study, therefore, are quite promising, and a second phase clinical trial is now underway. Indications are that teprotumumab may become available for wide-spread clinical use sometime later this year. If acute, inflammatory patients continue to respond well to teprotumumab, it likely will point to IGF-1R receptor activation as a key element in the pathogenesis of type II ophthalmic Graves' disease.

The weakness, however, in the NEJM study, in our opinion, is the failure of the trial to segregate ophthalmic Graves' disease patients into the clinical subtypes I and II. The lack of inflammatory signs in type I patients, along with a lack of convincing history of prior inflammatory signs in these patients, suggests a different pathogenic pathway than those who present primarily with clear inflammatory orbital signs, and are associated with early cicatrization of the extra ocular muscles. These Type II patients are those who are at risk for compressive neuropathy and diplopia, and who, we believe, are most likely to respond to teprotumumab.

We will look forward to planning and participating in trials which do segregate types I and II, as soon as teprotumumab becomes available for clinical use. In the meantime, teprotumumab appears to be an exciting addition to the therapeutic armamentarium for acute, inflammatory, type II ophthalmic Graves' disease patients. We believe teprotumumab may be less effective for the proliferative orbitopathy (type I) patients, perhaps suggesting a different pathogenic pathway for these patients.

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