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Strapline: Thyroid disease

Restoring 20:20 vision in thyroid eye

Marian Ludgate

Effective medical treatment for thyroid eye disease, a debilitating condition which may cause sight-loss, has been lacking. A recent phase III trial of Teprotumumab, an IGF1R antagonist, reports most encouraging results – may be a game-changer? The trial is put in the context of current management strategies to address this question.

Refers to Douglas, R. S. et al. Teprotumumab for the treatment of active thyroid eye disease. *N. Engl. J. Med.* **382**, 341–352 (2020).

Graves orbitopathy also known as thyroid eye disease (TED) and thyroid associated ophthalmopathy (TAO), remains one of the last great challenges in endocrinology¹, but that might be about to change. A study published in January 2020, in the *New England Journal of Medicine*, reports a phase III clinical trial of teprotumumab for the treatment of active TED. The randomized, multicentre trial recruited 41 and 42 patients who received infusions, at 3 week intervals for 21 weeks, of teprotumumab (10 mg/kg then 20 mg/kg bodyweight) or placebo, respectively². The primary outcome was a reduction of >2mm in proptosis. At week 24, 83% of the patients who had been treated with teprotumumab had achieved the primary outcome, compared with 10% of the placebo group. More encouragingly, teprotumumab treatment was free of serious adverse effects and also statistically significantly improved all secondary outcomes, including overall response rate, clinical activity score, diplopia response rate and improvements in the Graves orbitopathy-specific quality of life questionnaire.

Teprotumumab is a human monoclonal antibody to insulin-like growth factor 1 receptor (IGF1R) that was originally developed for the treatment of solid tumours. It is highly selective and blocks receptor activation directly, by inhibiting binding of ligands such as IGF1, and indirectly by receptor internalization³. Ray Douglas and Terry Smith, the lead and senior authors of the study, have described the central role of the IGF1R in TED pathogenesis⁴, in which expansion of the orbital tissues in the confines of a bony orbit, by excess adipogenesis (generation of new adipocytes by differentiation) and over-production of glycosaminoglycans (especially hyaluronan), leads to proptosis. Smith and colleagues demonstrated that IGF1 and Graves immunoglobulins (which are distinct from the thyroid stimulating antibodies (TSAB) that cause hyperthyroid Graves disease) were

able to increase production of inflammatory cytokines and hyaluronan by orbital fibroblasts and also to enhance orbital fibroblast proliferation. However, it must be noted that evidence for autoantibodies to the IGF1R being more abundant in people with TED than healthy controls is controversial, as is the ability of autoantibodies to activate the receptor by phosphorylation⁵.

The phase III trial confirmed and extended the phase II results; however, in the latter trial proptosis was a component of the primary outcome rather than being the sole primary outcome⁶. More than 80 patients with TED have been treated with teprotumumab and the longer-term follow-up of outcomes, particularly relapse rate, is eagerly awaited.

TED is a rare autoimmune condition that predominantly affects women, in whom the cosmetic effects have at least the same negative effect on quality of life as vision disturbance¹. A major strength of the study is that recruitment at 13 sites enabled the required number of patients to be randomized in less than a year. The inclusion and exclusion criteria were appropriately rigid but the cohort investigated showed some anomalies; for example, a lower than usual percentage of smokers in both treatment groups (smoking is a major risk factor for TED⁷ but strategies to encourage quitting meet with measured success) and several individuals who might have been overweight (the BMI was not provided) and experienced substantial weight loss following treatment with teprotumumab.

The majority of patients with TED (>90%) have Graves disease yet neither the phase II nor phase III trials have reported TSAB levels, whether their titre at baseline correlates with response to teprotumumab or whether TSAB levels are affected by the treatment. TSAB are highly relevant, as illustrated by the fact that patients with Graves disease who have the highest levels of TSAB, or who relapse following anti-thyroid drug therapy, are most likely to develop TED¹. Some of the trial's authors and other groups⁸ have reported on possible cross-talk between the IGF1R and the target of TSAB, the thyrotropin receptor (TSHR) in TED pathogenesis. Indeed, TSHR antagonism, using a monoclonal antibody (lacking stimulating activity) derived from a patient with Graves disease, ameliorated both Graves disease and TED in an unusual patient who also had follicular thyroid cancer⁹. This approach will need to be tested in large scale controlled trials but it further illustrates the importance of the TSHR in TED. It also hints at how teprotumumab might function — my money is on the ability of the IGF1R antagonist to inactivate by receptor internalization rather than by interfering with ligand binding. In all honesty, its' mode of action is academic; the important thing is that it works!

Current TED treatment depends on whether the disease is mild, moderate to severe or sight threatening. Sight-threatening TED is due to compression of the optic nerve, occurs in <5% of patients and requires immediate surgical decompression¹. In all patients with TED, restoring and maintaining euthyroidism should be a priority and smokers should be advised to stop smoking. Furthermore, disease management is greatly enhanced by joint clinics with an endocrinologist and an ophthalmologist¹⁰. In most patients (>70%), TED is mild and requires only local measures such as synthetic tears and selenium. In moderate to severe disease the anti-inflammatory actions of intravenous glucocorticoids improve most of the signs and symptoms; however, relapse upon withdrawal is common but can be mitigated by the addition of an anti-proliferative such as mycophenolate¹⁰. Immunologics, such as tocilizumab (an anti-IL6 receptor) and rituximab (an anti-CD20 that depletes B cells) and orbital radiotherapy have all been trialled with varying success¹. Even when a stable inactive disease phase is reached, most people with TED require rehabilitative surgery, for example to improve cosmetic appearance and correct squint, the whole process requiring several years to complete.

Throughout my career I have written that most of the signs and symptoms of TED, which have dramatic negative effects on vision, appearance and quality of life, can be attributed to proptosis. The fact that a medical treatment, mainly free of adverse effects and able to reduce proptosis as efficiently as orbital decompression surgery — but without the agonising wait — is now available is indeed cause for optimism. Teprotumumab was approved by the FDA in 2020; but people with TED outside the USA might have to wait for the drug to be compared with glucocorticoid treatment, which has been the mainstay for active TED, before it is available elsewhere.

Marian Ludgate^{1†}

¹Thyroid Research Group, Division of Infection & Immunity, Cardiff University School of Medicine, Heath Park, Cardiff, UK.

[†]ludgate@cardiff.ac.uk

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Competing interests

The author declares no competing interests.

Pullquotes

At week 24, 83% of the patients who had been treated with teprotumumab had achieved the primary outcome

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Images



<https://www.gettyimages.co.uk/detail/photo/cropped-image-of-woman-eye-royalty-free-image/598327849> I find this image the most appropriate of those provided, 'shining a light' on the eye.