CLINICAL VIGNETTE

Concurrent Thyroid Eye Disease and Ankylosing Spondylitis

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Case

A 31-year-old male presented to rheumatology to establish care for ankylosing spondylitis (AS), and for assistance in management of thyroid eye disease (TED). He had been diagnosed with AS, ulcerative colitis (UC), and asthma 13 years prior to presentation. He was on chronic prednisone 5 mg/day, primarily for management of asthma. He had tried biologic therapies for his AS and UC, including adalimumab, with modest short-term benefit, and infliximab with significant prolonged benefit. Unfortunately, he developed colon dysplasia and underwent colectomy 14 months prior to presentation. His back pain improved moderately after colectomy, and infliximab was stopped five months later. He developed hyperthyroidism and was diagnosed with Graves disease, and underwent total thyroidectomy four months prior to presentation. He developed exophthalmos two months after thyroidectomy and was diagnosed with TED. He was started on prednisone 60 mg/day, starting two weeks prior to presentation, tapering by 10 mg per week. At presentation he described recent worsening of his inflammatory arthritis, including pain and stiffness in his neck, shoulders, low back, and hips. These symptoms were mostly controlled by the high dose prednisone.

His TED worsened with prednisone taper, particularly below 15-20 mg/day. His ophthalmologist recommended a trial of tocilizumab, a monoclonal antibody to the interleukin-6 receptor, for steroid-sparing effect. However, due to concurrent worsening of his AS he was instead started on certolizumab pegol, a tumor necrosis alpha (TNF) inhibitor (TNFi), to treat both conditions. Tocilizumab has not been found effective in AS.

He received one dose of certolizumab pegol and noted some improvement in his eye disease, but unfortunately developed angioedema and hives. He was switched back to adalimumab, with improvement in his eye disease enabling reduction in prednisone to 5 mg/day. However, after three months of treatment, he had minimal improvement in his arthritic symptoms. He then switched to golimumab which led to significant improvement in his back pain and other arthritic symptoms over four months, but only modest benefit for the TED. He developed a significant flare in his eye disease during treatment with golimumab requiring increase of his prednisone to 60 mg/day. At this point, azathioprine was added for further steroid sparing effect, and golimumab was continued. After starting azathioprine, he noted improvement in his eye disease and was able to taper prednisone to 10 mg/day. Unfortunately, at this time he relocated to the East Coast and was lost to follow up.

Discussion

Thyroid eye disease, also known as Graves orbitopathy or ophthalmopathy, is an autoimmune inflammatory condition of the retro-ocular tissues in patients with Graves disease. There is a temporal relationship between the onset of Graves disease and that of TED. In one study of 120 patients with TED, the onset occurred in the six months prior to the onset of thyroid dysfunction in 19%, concurrently in 20%, in the six months following onset of thyroid dysfunction in 22%, and six months or more following thyroid dysfunction onset in 35%. Only 4% of Graves patients had onset of TED more than six months prior to the onset of hyperthyroidism.[1]

The primary autoantigen involved in the development of Graves disease is the thyroid stimulating hormone (TSH) receptor (TSHR), which has a close association with the insulin-like growth factor 1 (IGF-1) receptor. The TSHR is expressed primarily in thyroid tissue, but also in other tissues including fibroblasts and adipocytes. Auto-antibodies to the TSHR, in addition to activated T cells with resulting cytokines such as interferon gamma and TNF-alpha, can activate retro-ocular fibroblasts and adipocytes to create an inflammatory environment.[2] This implies that TED is both a B- and T-cell mediated process.[3]

The volume of the retro-ocular tissues is also increased due to fibroblast proliferation. The fibroblasts secrete hydrophilic glycosaminoglycans (GAG), primarily hyaluronic acid, which leads to fluid accumulation and increased pressure within the orbit, in addition to muscle swelling. This process, in addition to increased retro-ocular adipogenesis, pushes the orbit forward and leads to ocular muscle dysfunction and decreased venous drainage.[2]

The natural history of TED is variable.[4] Many patients have stable disease for years, whereas others improve or worsen over time, and some have exacerbations and remissions. This variability in clinical course makes it challenging to assess treatment effectiveness.

Fortunately, TED is relatively uncommon, and when present is often mild and self-limited. In one study of 237 patients with newly diagnosed Graves disease, 74% had no ocular involvement, 20% had mild involvement, 6% had moderate to severe involvement, and 0.3% had sight-threatening disease.[4] At 18 months follow up, 58% of patients with mild disease at baseline were in complete remission.

Treatment of TED is tailored to severity. However, general measures include smoking cessation, correction of hyperthyroidism, treatment of ocular irritation, and treatment of periorbital inflammation and swelling. Mild symptoms can often be treated with topical measures only. Moderate to severe disease typically requires immunomodulatory therapy, while sight-threatening disease can necessitate surgical intervention.[5]

The mainstay of treatment of moderate to severe orbitopathy is glucocorticoids. Moderate symptoms are often treated with oral glucocorticoids, with typical starting dose of prednisone around 30 mg/day for four weeks.[5] However, intravenous (IV) glucocorticoids are felt to be more effective and better tolerated. A typical IV regimen is methylprednisolone 500 mg IV weekly for six weeks, followed by 250 mg IV weekly for another six weeks. In severe disease, initial IV therapy is appropriate.[6]

In the setting of refractory disease, or contraindication or intolerance to steroids, it is appropriate to use a secondary immunomodulatory agent. Unfortunately, there are few trials that directly compare these agents.[5] There is some evidence for efficacy of TNF inhibitors in small case series.[7,8] Likewise, a post-hoc analysis of a randomized, double blind, placebo controlled trial of azathioprine suggested improved clinical outcome at 48 weeks with azathioprine treatment, although the primary analysis did not find added benefit.[9]

Agents with the strongest evidence of benefit in moderate to severe TED include mycophenolate mofetil, tocilizumab, rituximab, and particularly teprotumumab, which was recently approved by the Food and Drug Administration in January 2020. A randomized trial found Mycophenolate mofetil superior to glucocorticoid taper at 24 weeks, with overall response rates of 91% vs 68%.[10] Another randomized trial of steroid resistant patients found that Tocilizumab demonstrated benefit versus placebo at 16 weeks, 93% vs 59%, where primary outcome was a 2 point or greater improvement from baseline in a 10 point clinical activity score (CAS).[11] Rituximab, a B cell depleting agent, has shown mixed results in two randomized controlled trials, with benefit in one trial but not the other.[12,13] These different outcomes were perhaps due to variability in patient populations, as the study involving patients with earlier and more severe disease demonstrated efficacy.[5]

Teprotumumab, an inhibitor of the IGF-1 receptor, is the first medication approved by the FDA for TED. A therapeutic response was demonstrated in two 24-week randomized, placebo controlled trials involving a total of 171 patients with moderate to severe eye disease.[14,15] Therapeutic response was defined as improvement in proptosis by 2 mm or more and improvement in CAS by 2 or more points. Both studies showed a high response rate versus placebo, 69% vs 20% in one and 78% vs 7% in the other. These studies included patients with onset of eye disease within nine months of trial start date, so it is not clear if patients with more chronic disease will have similar results. There was also no comparison to glucocorticoid therapy, which is the current standard of care for TED.[5]

REFERENCES

1. **Bartley GB, Fatourechi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, Gorman CA**. Chronology of Graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol*. 1996 Apr;121(4):426-34. PubMed PMID: 8604736.
2. **Shan SJ, Douglas RS**. The pathophysiology of thyroid eye disease. *J Neuroophthalmol*. 2014 Jun;34(2):177-85. doi: 10.1097/WNO.0000000000000132. Review. PubMed PMID: 24821101.
3. **Davies T, Burch H**. Clinical features and diagnosis of Graves' orbitopathy (ophthalmopathy) Post TW, ed. *UpToDate*. Waltham, MA, 2020.
4. **Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, Pariani N, Gallo D, Azzolini C, Ferrario M, Bartalena L**. Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. *J Clin Endocrinol Metab*. 2013 Apr;98(4):1443-9. doi: 10.1210/jc.2012-3873. Epub 2013 Feb 13. PubMed PMID: 23408569.
5. **Davies T, Burch H**. Treatment of Graves' orbitopathy (ophthalmopathy) Post TW, ed. *UpToDate*. Waltham, MA, 2020.
6. **Wiersinga WM**. Advances in treatment of active, moderate-to-severe Graves' ophthalmopathy. *Lancet Diabetes Endocrinol*. 2017 Feb;5(2):134-142. doi: 10.1016/S2213-8587(16)30046-8. Epub 2016 Jun 23. Review. PubMed PMID: 27346786.
7. **Durrani OM, Reuser TQ, Murray PI**. Infliximab: a novel treatment for sight-threatening thyroid associated ophthalmopathy. *Orbit*. 2005 Jun;24(2):117-9. PubMed PMID: 16191800.
8. **Ayabe R, Rootman DB, Hwang CJ, Ben-Artzi A, Goldberg R**. Adalimumab as steroid-sparing treatment of inflammatory-stage thyroid eye disease. *Ophthalmic Plast Reconstr Surg*. 2014 Sep-Oct;30(5):415-9. doi: 10.1097/IOP.0000000000000211. PubMed PMID: 24978425.
9. **Rajendram R, Taylor PN, Wilson VJ, Harris N, Morris OC, Tomlinson M, Yarrow S, Garrott H, Herbert HM, Dick AD, Cook A, Gattamaneni R, Jain R, Olver J, Hurel SJ, Bremner F, Drummond SR, Kemp E, Ritchie DM, Rumsey N, Morris D, Lane C, Palaniappan N, Li C, Pell J, Hills R, Ezra DG, Potts MJ, Jackson S, Rose GE, Plowman N, Bunce C, Uddin JM, Lee RWJ, Dayan CM**. Combined immunosuppression and radiotherapy in thyroid eye disease (CIRTED): a multicentre, 2×2 factorial, double-blind, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2018 Apr;6(4):299-309. doi: 10.1016/S2213-8587(18)30021-4. Epub 2018 Jan 31. PubMed PMID: 29396245.
10. **Ye X, Bo X, Hu X, Cui H, Lu B, Shao J, Wang J**. Efficacy and safety of mycophenolate mofetil in patients with active moderate-to-severe Graves' orbitopathy. *Clin Endocrinol (Oxf)*. 2017 Feb;86(2):247-255. doi: 10.1111/cen.13170. Epub 2016 Sep 7. PubMed PMID: 27484048.

11. **Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Romo Lopez A, Rodríguez Alvarez FM, Castillo Laguarta JM, Del Estad Cabello A, Gessa Sorroche M, España Gregori E, Sales-Sanz M; Tocilizumab in Graves Orbitopathy Study Group**. Efficacy of Tocilizumab in Patients With Moderate-to-Severe Corticosteroid-Resistant Graves Orbitopathy: A Randomized Clinical Trial. *Am J Ophthalmol*. 2018 Nov;195:181-190. doi: 10.1016/j.ajo.2018.07.038. Epub 2018 Aug 4. PubMed PMID: 30081019.
12. **Salvi M, Vannucchi G, Currò N, Campi I, Covelli D, Dazzi D, Simonetta S, Guastella C, Pignataro L, Avignone S, Beck-Peccoz P**. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. *J Clin Endocrinol Metab*. 2015 Feb;100(2):422-31. doi: 10.1210/jc.2014-3014. Epub 2014 Dec 15. PubMed PMID: 25494967; PubMed Central PMCID: PMC4318899.
13. **Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA, Bahn RS**. Randomized controlled trial of rituximab in patients with Graves' orbitopathy. *J Clin Endocrinol Metab*. 2015 Feb;100(2):432-41. doi: 10.1210/jc.2014-2572. Epub 2014 Oct 24. PubMed PMID: 25343233; PubMed Central PMCID: PMC4318907.
14. **Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, Harris GJ, Antonelli A, Salvi M, Goldberg RA, Gigantelli JW, Couch SM, Shriver EM, Hayek BR, Hink EM, Woodward RM, Gabriel K, Magni G, Douglas RS**. Teprotumumab for Thyroid-Associated Ophthalmopathy. *N Engl J Med*. 2017 May 4;376(18):1748-1761. doi: 10.1056/NEJMoa1614949. PubMed PMID: 28467880; PubMed Central PMCID: PMC5718164.
15. **Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EHZ, Perdok R, Fleming JC, Fowler BT, Marcocci C, Marinò M, Antonelli A, Dailey R, Harris GJ, Eckstein A, Schiffman J, Tang R, Nelson C, Salvi M, Wester S, Sherman JW, Vescio T, Holt RJ, Smith TJ**. Teprotumumab for the Treatment of Active Thyroid Eye Disease. *N Engl J Med*. 2020 Jan 23;382(4):341-352. doi: 10.1056/NEJMoa1910434. PubMed PMID: 31971679.