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RESEARCH ARTICLE

Perspectives on Antibody-Based Thyroid-Associated Orbitopathy Treatments

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ABSTRACT:
Thyroid-associated orbitopathy (TAO) is a disfiguring and in severe cases debilitating autoimmune disease that has been the subject of much recent drug development and investigation. This condition is characterized by an acute inflammatory phase followed by a resolving, cicatricial phase. There has been a search to find an effective agent to address the acute inflammatory phase of this disease, which would hopefully minimize end stage disfigurement, overall morbidity, and the need for surgery. The advent of antibody-based immunologic therapies has shown promise in this regard. Herein we discuss the current biologic therapeutic landscape, including agents targeting the insulin-like growth factor-1 receptor (IGF-1R, teprotumumab) and the interleukin-6 receptor (IL-6R, tocilizumab), and provide additional insight and opinion from our group practice that is highly experienced in treating a large number of TAO patients. Notably, though teprotumumab is effective, and we regularly prescribe this agent with good success, we feel that tocilizumab should be regarded as another first-line therapy that may be a more appropriate choice for certain patients with active inflammatory TAO.

Introduction

Thyroid-associated orbitopathy (TAO) is a deforming and in severe cases blinding autoimmune disease that is the subject of much recent drug development and investigation. TAO is characterized by an acute inflammatory phase lasting 6-36 months, 18 months on average, followed by a resolving, cicatricial phase, during which relapses can occur.[1–6] The search to find an effective agent to address the acute inflammatory phase has accelerated with the advent of antibody-based immunologic therapy, and teprotumumab has quickly become nearly synonymous with antibody-based therapy for TAO. Though this agent is effective and plays a significant role in our group's treatment of TAO, the apparent shortcomings of teprotumumab and the utility of alternative antibody-based therapies merit greater discussion and broader consideration among treating providers. As such, we will review the current landscape of antibody-based therapies for TAO and our group's experience with and insights regarding treatment.

Clinical Parameters

Prior to discussing various therapies, it is helpful to set the stage regarding parameters of therapeutic success. Chief among these are changes in the clinical activity score (CAS) and proptosis. The CAS was first introduced by Mourits et al. in 1989 as a means of more reliably differentiating between patients with active, inflammatory TAO and those who had already entered the cicatricial phase in order to guide treatment decisions.[7] Ten categories are included, as noted in Table 1. Patients with a CAS of three or more were likely to respond to anti-inflammatory treatment in the original investigation, and a CAS of 4 or more has become a standard for defining clearly active, inflammatory TAO.[8] Alternatively, patients with a CAS less than 2 were not likely to improve with anti-inflammatory treatment,[7] and a CAS of 0 or 1 is now widely used to define "inactive" disease.[9]

Table 1. Clinical Activity Score Factors (One point per factor)

Spontaneous orbital pain
Pain with extraocular movements
Eyelid redness
Eyelid edema
Conjunctival injection
Conjunctival chemosis
Caruncle/plica inflammation
Proptosis - increase of 2 mm over 1-3 mo
Visual Acuity - decrease by one or more Snellen line over 1-3 mo
Decrease in extraocular movement by 5 or more degrees over 1-3 mo

Adapted from Mourits et al. 1989

Proptosis change is another common parameter used to assess improvement following novel drug administration. As noted in the CAS, a proptosis increase of at least 2 mm measured by exophthalmometer is considered significant, as the error of this device is generally regarded to be ±2 mm.[7] It is essential to view any decrease in proptosis associated with novel therapies in light of this margin of error. Furthermore, in our experience, East Asian patients are less likely to demonstrate severe levels of proptosis, even in the setting of otherwise severe inflammatory disease. This experience underlines the fact that although proptosis is common *overall* in thyroid eye disease, the extent to which proptosis affects patients differs widely. Despite these limitations surrounding proptosis and the subjectivity and low sensitivity of the CAS,[8] these parameters continue to perform a vital and reliable function in assessing disease

activity and therapeutic response in both the clinical and research settings.

Steroids - Historical and Current

Corticosteroids are the historic gold standard for treatment of TAO. Efficacy of this therapy is generally accepted for severe inflammatory TAO, especially when complicated by compressive optic neuropathy (CON). Systemic steroid therapy will usually decrease lid edema and conjunctival chemosis, decrease surface inflammation, possibly improve extraocular movements, and at least temporarily relieve CON. If a patient presents with CON, we usually begin treatment with oral prednisone 60-80 mg/day tapered over 6-8 weeks in moderately severe cases. Most patients respond adequately to this therapy, but if CON flares during the taper or recurs once tapering is complete, we restart steroids in preparation for orbital radiation or surgical orbital decompression. Steroids can be continued during orbital radiation therapy, as these treatments appear to have a synergistic effect when employed together.[10,11]

We reserve intravenous steroid treatment for more severe cases, in which this method of administration has proven effective with fewer systemic side effects.[12] Moderate dose IV steroids may be best for most of these cases, with higher doses reserved for only the most severe inflammation given potentially serious side effects.[13] Cumulative dosage should remain under 8 g of methylprednisolone, as patients can develop fatal hepatotoxicity at higher doses.[13,14] A myriad of well-known side effects make steroids inappropriate for use in poorly-controlled diabetics and in patients with pre-existing hepatic dysfunction, certain cardiovascular conditions, or steroid-responsive glaucoma.[10] Local, intraorbital injection of corticosteroids can allow treatment for some of these otherwise steroid-intolerant patients, but elevation of intraocular pressure remains a significant risk.[15] Mild gastrointestinal side effects like reflux can be minimized using a proton pump inhibitor or similar agent.

For ocular inflammatory disease, steroid therapy is only moderately effective long term, and relapse is common.[13] However, addition of steroid sparing agents may improve response to treatment, as Kahaly et al. demonstrated with the addition of mycophenolate mofetil to an intravenous steroid regimen.[16] Combining steroid therapy with other steroid-sparing agents may also be useful, but side effects are numerous.[10] Overall, steroid therapy has less than optimal effectiveness with numerous side effects, including those listed above as well as weight gain, psychosis, and acne. Thus, in the era of antibody-based biologic therapies, we find steroids to be most appropriate as bridging treatment prior to antibody therapy, radiation or surgical decompression or as treatment for CON, as other agents have not been recognized as effective at this time.

Anti-IGF-1R Therapy

As the first agent specifically approved by the FDA for thyroid associated orbitopathy, teprotumumab (Tepezza, Horizon Therapeutics plc, Deerfield, Illinois, USA) has already attained a prominent place in the treatment of TAO. This fully human anti-insulin-like growth factor-1 receptor (anti-IGF-1R) monoclonal antibody aims to selectively address the dysfunctional inflammatory cascade of TAO without broader systemic immunosuppression. The TAO orbit is infiltrated by CD34+ fibroblasts expressing both thyrotropin receptor (TR) and IGF-1R.[10] TAO patients have a greater level of IGF-1R expression in both systemic and orbital T and B cells, and B cells expressing IGF-1R appear to produce more anti-thyrotropin receptor (anti-TR) antibodies than non-expressing B cells.[17] The interactions of these anti-TR antibodies with the TR/IGF-1R complex in the orbit and the interactions of anti-IGF-1R immunoglobulins with the IGF-1R on orbital fibroblasts initiate the inflammatory process of TAO, which includes cytokine release, glycosaminoglycan generation, and tissue hypertrophy.[10,17,18] Noting the prominent place of IGF-1R in this mechanism of TAO, it is no wonder that this receptor is an attractive target for intervention.

Administered as eight intravenous infusions given once every three weeks, teprotumumab was shown by Smith et al. in the *NEJM* in 2017 to reduce CAS by at least two points and reduce proptosis by at least 2 mm in 69% of treated patients compared to 20% in the placebo group at 24 weeks ($p < 0.001$).[19] They also found a significant decrease in subjective diplopia and increase in quality of life score when compared to placebo. Subsequent investigations echoed these positive results. One such investigation, dubbed the OPTIC study,[20] was conducted at multiple sites in the United States and Europe among patients with a median TAO duration of 6.3 months. This study also demonstrated significantly greater improvement in proptosis, CAS, diplopia, and quality of life with teprotumumab compared to placebo. Extraocular muscle and/or orbital fat volume on imaging was also reduced with teprotumumab. Pooled analysis of the 2017 *NEJM* study and OPTIC demonstrated a mean proptosis change of -3.14 mm in the treatment groups versus -0.37 mm in placebo groups.[21]

To investigate whether a second course of treatment in non-responders or a first course of

treatment later in the disease would be effective, the OPTIC-X extension study was conducted.[22] A notable proportion of OPTIC responders (10/34 subjects) experienced a post-treatment flare, variably defined as worsening of CAS and/or proptosis after at least 6 months of disease inactivity. Among eight of these patients that were re-treated there was a 62.5% response rate. Previously placebo-treated subjects, now with median TAO duration of 12.9 months, were found to have similar response to treatment as the subjects treated in OPTIC. Most of these patients maintained their response through 48 weeks of follow up. Of note, a pooled analysis of OPTIC and OPTIC-X results indicated that tobacco users as a subgroup were among the least likely to have a proptosis or diplopia response to teprotumumab treatment, highlighting the absolute importance of interventions to assist TAO patients in tobacco cessation.[21]

Reported adverse events as pooled between the 2017 *NEJM* study and OPTIC included muscle spasms (18%), hyperglycemia (8%), and hearing loss (10%).[21] Any hearing impairment experienced by patients in the OPTIC trial was temporary. However, in OPTIC-X one of four first-time treatment patients who experienced hearing effects continued to have persistent tinnitus at the conclusion of the study, while two re-treatment patients with temporary hearing issues during OPTIC developed persistent hearing impairment by the end of OPTIC-X. Serious adverse reactions remained rare. Interestingly, though not reported in the aforementioned studies, the FDA's prescribing information for Tepezza notes menstrual irregularities in 23% of treated menstruating women versus only 4% of those given placebo (BLA 761143, Reference ID 4878418). The FDA also warns prescribers that use of teprotumumab may exacerbate pre-existing inflammatory bowel disease (IBD). New onset of IBD during teprotumumab treatment has also been documented.[23] As such, though teprotumumab does not induce systemic immunosuppression, our developing understanding of its suppression of end organ functions throughout the body should prompt careful consideration by prescribers.

Our experience with teprotumumab is consistent with the above results. We maintain particular concern regarding its relapse rate. Teprotumumab acts quite narrowly in the TAO-specific inflammatory cascade, influencing the IGF-1 receptor while not addressing the myriad of inflammatory cytokines and systemic immune overactivity also playing a role in this disease. Once the IGF-1 receptor is allowed to resume its activity after teprotumumab cessation, TAO patients are able to relapse and once again demonstrate the signs and symptoms of their underlying inflammatory autoimmune disease. Viewed from this perspective, other more systemically-active immunomodulating agents may be more effective in certain cases, especially those with more prominent extraorbital and extrathyroidal findings.

Furthermore, patients with the most severe disease, including those with recalcitrant corneal decompensation and those with pre-existing optic neuropathy, were excluded from teprotumumab studies.[19,20] Notably, one of the patients with disease flare excluded from OPTIC-X retreatment was excluded in the setting of CON requiring high dose steroid treatment,[22] highlighting the questions remaining about the efficacy teprotumumab could provide in CON. Despite these deficits in the randomized trials, case reports and case series have emerged documenting the efficacy of teprotumumab in CON, including three cases refractory to tolerable doses of steroids and/or surgical decompression.[24] Clearly much investigation is still needed to understand the extent to which teprotumumab can benefit the TAO patient. Encouragingly, an ongoing Phase 4 clinical trial (NCT04583735) is assessing the possible utility of teprotumumab to reduce proptosis in chronic, inactive TAO. Results are yet to come, and we await with interest such possible extensions to the indications for teprotumumab.

Given the success of teprotumumab, various other trials are ongoing, or are planned, to assess similar anti-IGF-1R inhibitory antibodies. Early data on VRDN-001 from Viridian Therapeutics suggests more complete blockage of IGF-1 binding and antagonism of signaling *in vitro* than with teprotumumab.[25] In a small Phase 1/2 proof of concept study in TAO patients, VRDN-001 led to improvement in diplopia, inflammation, and proptosis as compared to placebo, but more data is needed to fully understand what role this agent may play in TAO treatment.[26] A related agent, VRDN-002, can be administered subcutaneously and in non-human primates has demonstrated a longer half life and higher drug concentration than an equivalent dose of teprotumumab administered intravenously.[27] If VRDN-002 comes to market, it may remove the necessity for outpatient infusion appointments, a possible barrier to care. Other similar agents under investigation include Lonigutamab, a subcutaneously-administered anti-IGF-1R agent from ValenzaBio/Acelyrin (NCT05683496), and Linsitinib, a small molecule IGF-1R inhibitor from Sling Therapeutics, Inc. (NCT05276063).

IL-6 Directed Therapies

In addition to the recent strides made with teprotumumab, a number of groups have also demonstrated successful treatment of active TAO using tocilizumab (ACTEMRA, Genentech, South San Francisco, California, USA), an interleukin-6 (IL-6) receptor antibody already FDA approved for the treatment of other systemic inflammatory diseases, including rheumatoid arthritis. Studies employing tocilizumab demonstrate improvement in a broad range of patients with TAO, including those with keratopathy and optic neuropathy, though this comes at the expense of non-randomized, non-controlled studies in some cases.

Downstream from the thyrotropin receptor, activated mononuclear cells and orbital fibroblasts secrete various pro-inflammatory factors, including IL-6.[28] Among its various roles, IL-6 regulates immune and inflammatory processes. This cytokine promotes differentiation of T and B cells: influencing T cell development toward a predominantly Th17 rather than regulatory population and encouraging immunoglobulin production.[28] Additionally, IL-6 may increase expression of thyrotropin receptors in the orbit.[29] These various pro-inflammatory roles make IL-6 and its receptor another attractive target for the treatment of systemic autoimmune thyroid disease affecting the orbit.

Tocilizumab was first assessed in TAO via a prospective, nonrandomized study from Perez-Moreiras et al. in 2014, wherein monthly intravenous tocilizumab infusions were used to treat steroid-resistant active TAO.[30] Treated patients (median TAO duration 11 months) had a significant reduction in CAS of nearly 6 points on average. Proptosis decreased in 13/18 patients, with a mean reduction of nearly 4 mm. Extraocular movements improved in 83%, and more than half of patients with diplopia experienced resolution. Thyroid stimulating immunoglobulin (TSI) levels also dropped by an average of 76%--all with no severe side effects or relapses through nine months of follow up. Given these encouraging results, the same group in 2018 published a randomized, placebo-controlled study examining tocilizumab in moderate to severe steroid-resistant TAO.[31] Tocilizumab-treated patients were significantly more likely to have an improvement in CAS by at least 2 points by week 16 (93.3% vs 58.8% placebo) and to have a final CAS <3 (86.7% vs 35.2% placebo). CAS, soft tissue indicators, and interpalpebral distance were prominent areas of benefit over placebo in this study, while the group's results did not demonstrate significant robust improvement in diplopia or proptosis by week 40. However, it is important to note that this study included patients later in their disease course (median TAO duration just over 1 year) than the 2014 study, perhaps inherently limiting the potential effectiveness of anti-inflammatory therapy.

Perez-Moreiras et al. re-examined tocilizumab once again in 2021, looking back at their experience with this drug over a nine-year period among patients with a median TAO duration of 10.5 months prior to treatment.[32] Tocilizumab led to significant improvement from treatment baseline in CAS, TR antibody levels, exophthalmos (mostly for greater levels of exophthalmos), eyelid retraction, and diplopia. Their data demonstrated only a 7.4% relapse rate (defined as an increase in CAS of at least 2 points) in follow-up where nearly half of the subjects were followed for at least 2 years. Sánchez-Bilbao et al. in 2020 also presented retrospective data, though theirs was a broader sample collected from multiple centers in Spain.[33] Using the same treatment regimen, they noted improvement in best corrected visual acuity, CAS, and intraocular pressure among patients with a median of 0.9 years TAO duration prior to tocilizumab treatment. They encountered no relapses over a mean follow up of 16.1 +/- 2.1 months.

Most recently, Smith, Moscato, and Seiff from our group in 2022 reported retrospectively on a group of patients treated with tocilizumab in the setting of steroid-resistant TAO. In contrast to subjects in the prior studies, these patients had a mean duration of TAO prior to tocilizumab of only 2.89 months (range 1-6 months).[9] CAS, TSI, and thyroid-associated ophthalmopathy scale scores all demonstrated both statistically and clinically significant improvement after treatment. Significant improvement occurred after just the first infusion, which is consistent with the early improvement also seen by Perez Moreiras et al.[32] Over an average of 23.6 months of follow up, no relapses occurred in our cohort. Such robust results continue to be the experience of our group with tocilizumab, especially when this agent is initiated in patients who are less than six months into their TAO course. Indeed there may be some correlation between greater treatment success and earlier tocilizumab initiation, perhaps reflecting disease-modifying effects, but without meta-analysis no concrete conclusions can be drawn at this time.

As noted in the studies highlighted above, tocilizumab led to significant decrease in systemic inflammatory markers of TAO, namely TR antibodies[32] and TSI.[9] The significance of these reductions even after just one infusion suggests that tocilizumab is specifically acting to reduce the immunologic activity of TAO. Furthermore, by providing *systemic* immunosuppressive activity

through its effects on IL-6, as discussed above, tocilizumab may be especially useful in patients with prominent extra-orbital manifestations. These systemic immunosuppressive effects may be at least in part responsible for the lower relapse rate demonstrated so far in patients treated with tocilizumab versus teprotumumab. As such, we tend to favor tocilizumab in patients with significant systemic findings of autoimmune hyperthyroidism, for example pre-tibial myxedema or thyroid acropachy.

Use of tocilizumab incurs such risks as immunosuppression, elevated cholesterol, elevated hepatic transaminases, and cytopenias, but as used in the context of TAO, adverse events of these type are generally mild to moderate in severity.[9,31–33] Though one could argue that systemic immunosuppression is a significant downside to tocilizumab, given the relatively brief duration of therapy (4-5 monthly infusions) we feel this is a rather small risk as long as appropriate pre-treatment laboratory investigation is completed. Given the clear benefits of this agent, for which TAO is currently an off-label use, development of an IL-6/IL-6 receptor targeting agent *specifically FDA-approved* to address TAO would be a valuable addition to the therapeutic landscape.

Rituximab and Other Therapies

Various other targets have been or are being explored for the treatment of TAO. Rituximab, a B-cell-targeting anti-CD-20 agent primarily used to treat lymphoproliferative disease, has demonstrated variable success. When used in patients with a somewhat longer duration of disease, rituximab demonstrated no additional benefit over placebo.[34] When compared to IV steroids in shorter duration disease, though, rituximab produced a larger CAS decrease and allowed a greater number of patients to reach disease inactivation than did steroids.[35] Interestingly, these rituximab-treated patients had superior ocular motility and fewer relapses than those patients given steroids, possibly indicating an overall disease-modifying effect of rituximab. A newer, multi-center retrospective study involving patients with a moderate pre-study TAO duration demonstrated some benefit from rituximab, though not as much as the previous shorter disease duration study, suggesting that any role rituximab has in treating TAO is best played early in the orbital disease course.[36]

Further targeted therapies under investigation include Secukimumab (NCT04737330) and Vunakizumab (also known as SHR-1314, NCT05394857), which are both subcutaneously-administered anti-IL-17a monoclonal antibodies. IL-17, similar to IL-6, plays a pro-inflammatory role in TAO pathogenesis, and IL-17 targeting drugs are already known to be effective in treating other systemic inflammatory conditions such as psoriasis.[37] Alternatively, Batoclimab (also referred to as RVT-1401 or IMVT-1401), a fully human monoclonal antibody directed against the neonatal immunoglobulin Fc receptor (FcRn), proposes a different mechanism that may help control inflammation in TAO. The FcRn recycles and, therefore, prolongs the half-life of IgG antibodies--including those directed against the thyrotropin receptor in TAO.[38] As such, blocking FcRn could allow for greater clearance of IgG antibodies from the blood, ultimately reducing auto-inflammatory signaling in TAO. A Phase 2a study employing this subcutaneously-administered agent demonstrated a modest decrease in proptosis in patients with moderate to severe TAO, as well as decreases in immunoglobulin levels (NCT03922321). The subsequent Phase 2b randomized controlled study demonstrated no change in proptosis response between placebo and any of the treatment arms, though the study was stopped before completion because of premature unblinding in the setting of a safety finding of hypercholesterolemia (NCT03938545). A phase 3 randomized, placebo-controlled study is currently recruiting (NCT05517421), while an open label extension study for participants of this and another Batoclimab study is planned but not yet recruiting (NCT05517447). However, our group does not feel particularly optimistic regarding this agent given its lack of encouraging results and its failure to address the underlying issue of auto-inflammatory IgG production, theoretically providing a greater chance for relapse upon discontinuation.

Conclusion

Overall, the landscape of non-surgical, antibody-based TAO treatment is dominated at this time by teprotumumab, the only agent described above with a specific FDA approval for use in TAO. We agree that teprotumumab is an appropriate and effective choice for many patients. However, given the success that we and others have had with tocilizumab and its apparently lower relapse rate, this agent is another excellent first-line therapy. Despite a thoughtful and evidence-based consideration and choice of tocilizumab for a subgroup of our patients, we repeatedly face barriers to patient care when seeking approval from insurers. An IL-6 targeted therapy *specifically FDA approved for TAO* would help improve access to appropriate and effective treatment for these patients. Ultimately, the treatment of TAO, once defined by steroids, radiotherapy, and surgical

intervention, has been forever altered by the advent of biologic therapies. At this time in our practice, we will continue to select between tocilizumab and teprotumumab based on specific patient needs and comorbidities, and we remain poised to embrace promising new therapies to come.

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