

The Role of Biological Agents and Immunomodulators in Treatment Strategies for Thyroid Eye Disease: An Evidence-based Review

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ABSTRACT

Graves' Disease is an autoimmune disease where circulating antibodies bind to the thyrotropin receptors on the thyroid gland. These bound antibodies mimic thyroid stimulating hormone without the normal feedback from the anterior pituitary, causing hyperthyroidism and thyrotoxicosis. These antibodies also interact with orbital tissues and cause the characteristic orbital findings of thyroid eye disease (TED). It is not clearly understood why anatomically and physiologically distinct tissues like the thyroid gland and orbit are affected selectively, or why the orbital disease tends to be self-limited. Identifying and understanding these processes is critical to targeting therapy.

In the active phase of the disease patients may experience orbital inflammation, eyelid and conjunctiva edema (chemosis), eyelid retraction, proptosis, ocular motility restriction, and optic nerve compression. Current treatment strategies for the ocular symptoms have been predominantly directed at symptomatic relief. More recently, investigators have concentrated their efforts to better understanding the underlying pathophysiologic processes to direct therapy at these processes. This review examines the current literature exploring a variety of newer therapeutic alternatives, including immunomodulative and suppressive agents, targeted at strategic points of the active-phase TED pathophysiological pathways. Specifically, biological agents including rituximab, adalimumab, intravenous immunoglobulin and others are reviewed with considerations for pathophysiology, extent of literature support, and adverse effects.

KEYWORDS: Grave's Disease, thyroid eye disease, TED, TED treatment options

INTRODUCTION

Thyroid Eye Disease (TED) is the most common extra-thyroid manifestation of Grave's Disease. (1) The annual incidence of TED has been estimated at 16 cases per 100,000 population for women, and 3 per 100,000 for men. (2) It is an immune-mediated disease and is most often associated with the immune thyroid diseases Graves' disease and Hashimoto's thyroiditis, but it can also occur with thyroid carcinoma,

primary hyperthyroidism and neck irradiation. Up to 50% of patients with immune thyroid diseases develop TED, and of those, as many as 10% may develop severe inflammation, orbital congestion, impaired ocular motility, or compressive optic neuropathy. (3)

The range of TED treatment options varies depending upon severity, from topically palliative treatments including artificial tears, ointments, or prisms, to immunosuppressive agents such as steroids or cyclosporine, radiotherapy, and surgical decompression in more severe cases. Novel approaches to treatment have included anti-oxidant solutions containing selenium (4) and biological agents like rituximab and anti-tumor-necrosis-factor, among others. (5-7) This review considers the latter category of biological agents, examining briefly the agent, mechanism of action, existing evidence supporting their use, efficacy, and adverse effects. Some consideration will be also given to the role of biological agents in the context of overall TED treatment options, but a detailed consideration of all treatment options is beyond the scope of this biological agent-focused review.

RATIONALE FOR USE OF BIOLOGICAL AGENTS AND IMMUNOMODULATORS

Hyperthyroidism and TED, though temporally concomitant in many cases, may occur over 18 months apart, and even in the absence of one another. (8) Smoking (9) and poor control of the underlying thyroid disease have also been associated with more severe TED. (10) TED typically starts with an active inflammatory progression over 6 to 24 months (**Fig. 1**), with expansion of extraocular muscles (EOMs) and surrounding fat (**Fig. 2**), often causing proptosis, impaired extraocular muscle movement, and in severe cases compressive optic neuropathy (**Fig. 4**). (11) Ultimately fibrosis and infiltration of glycosaminoglycans into the extraocular muscles result in the permanent changes seen in the chronic phase of the disease (**Fig. 4**).

Orbital fibroblasts are now considered the primary immunologic target in TED. Fibroblasts from patients with TED have been shown to express inflammatory cytokines, CD 34 and CD40. Pathophysiological studies in TED have also shown increased expression of thyrotropin receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-R1) on these fibroblasts. (12-14) Strategies, in turn, have been targeted at different components of the presumed pathophysiology.

Figure 1. Active phase of TED with eyelid and orbital edema



Figure 2. CT scan showing asymmetric extraocular muscle enlargement in TED

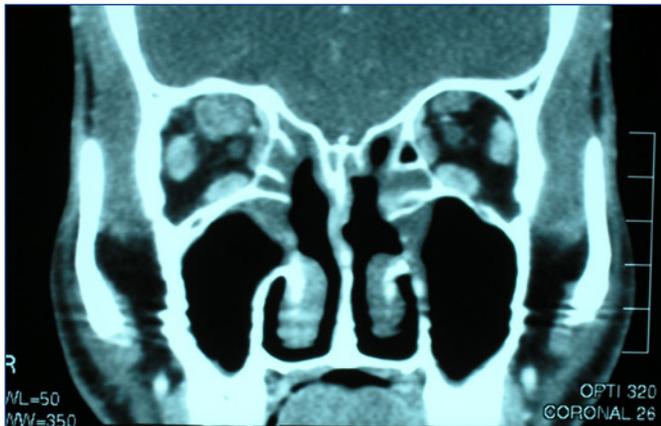


Figure 3. Optic nerve compression from enlarged extraocular muscles



Figure 4. Chronic phase of TED with proptosis and lid retraction



Interestingly, only about one-third of moderate-severe TED sufferers are helped by traditional anti-inflammatory treatment options such as corticosteroids. (1,15) Hence, with the limitations of presently existing therapies and observed inconsistent associations between TED, thyroid disease, traditional anti-inflammatory treatment response, and smoking, the need for other therapeutic strategies is evident. Several such strategies, all at best incomplete and with varying efficacy, are discussed in the following sections on biological agents in TED, along with mechanisms of action and effects.

SPECIFIC AGENTS AND THEIR MECHANISMS OF ACTION

While few or no biological agents are exactly specific for a given target, a few have a thus far recognized preferential target (e.g. rituximab for B-lymphocytes). Hence, for purposes of our discussion below, we consider specific agents with specific targets. This discussion is caveated with the following points: (1) a "pure target" and "pure agent" have not presently been discovered, so some additional effects may occur; (2) no single strategy has shown complete efficacy or "cure"; (3) some of these agents' efficacy is extrapolated from analogous autoimmune diseases but actual human studies are either scarce or non-existent.

Broad-spectrum anti-inflammatory and immunosuppressive agents

Corticosteroids, the mainstay of TED therapy, can be administered orally or systemically as intravenous (IV) infusions. However, current literature favors high dose systemic administration for severe active TED as reported by Kahaly, with greater positive clinical response in 77% of patient receiving IV methylprednisolone treatment vs. 51% of patients treated with oral prednisolone. (16) Similar response results were also reported for treatment of moderate active TED (17) by Aktaran et al with 72% responding to IV steroids vs. 49% responding to oral steroids.

Intraorbital injection of steroids are occasionally used to alleviate the acute orbital inflammation in TED.(18) In a prospective, single-blind randomized study (19) Marocci et al evaluated cobalt radiation combined with steroid treatment, either administered systemically or locally by retrobulbar injection. Clinical improvement was noted in both groups, but there was significantly greater efficacy of systemic steroids compared to retrobulbar injection (60% vs. 30%) in severe active TED.

Antimetabolites form a group a potent immunomodulators. Azathioprine has not been shown to be of benefit as a single agent (20) but exhibits effectiveness when combined with radiation therapy or steroids. (21, 22) Methotrexate, although not commonly used, is effective as a sole treatment

in patients who failed steroids. (23) Another member of the antimetabolite family, mycophenolate mofetil, was noted to be not only effective but exhibited more effectiveness as a sole treatment than cyclosporine (24); however, the literature regarding this agent remains sparse. Moreover, no comparison of this agent to standard steroid treatment is found in the presently available literature.

The anti-oxidant agent selenium was evaluated against the anti-inflammatory agent pentoxifylline in 159 patients with mild Graves' orbitopathy. The authors noted decreased clinical activity scores of TED in both treatment groups, with significant improvement in quality of life, reduced ocular involvement, and slowed disease progression in the selenium treatment group at the 12-month follow-up. (4) This data suggests selenium oral supplements at a dose of 100ug, twice per day, appears a harmless adjunct to conservative management in early mild stages of TED.

Anti-B-cell agents

Rituximab (RTX), a monoclonal chimeric antibody against the transmembrane protein CD20 on B cells (but not plasma cells), has resulted in improved clinical activity score and efficacy over 18 months in several studies. (25-27) A recent randomized, prospective study evaluating intraorbital injection of rituximab versus high dose of systemic glucocorticoids in the treatment of thyroid-associated orbitopathy demonstrated a therapeutic efficacy of RTX in active disease, even in low doses and locally administered, with the efficacy on the inflammatory component of the disease comparable to that of steroids and seemingly related with the reduction of peripheral CD20+ lymphocytes. (28) Further studies are needed to fully evaluate efficacy and safety of rituximab.

Anti-T-cell agents

T-cells expressing IGF-1 receptors are thought to play an important role in mediating the autoimmune process in TED. Teprotumumab is a human monoclonal antibody that blocks the IGF-1 receptor, initially designed for treatment of solid and hematologic tumors; it is presently also undergoing phase 2 clinical trials in patients with active TED. A recent retrospective, limited sample-study (5) showed that RTX also had an effect on reduction of IGF-1R(+) T cells, coinciding with clinical improvement at 4 to 6 weeks post-treatment.

Meanwhile, a study involving a 12-week treatment period with 11 patients treated with prednisone and 4 using cyclosporine found that combination therapy was better tolerated than prednisone treatment alone, while single-drug therapy with prednisone was found more effective than cyclosporine in patients with severe Graves' ophthalmopathy. (29) A separate study of 40 patients noted some role for cyclosporin with improvement of all signs of endocrine ophthalmopathy while administering cyclosporin-prednisone combination therapy. (30)

Anti-auto-antigen and intravenous immunoglobulin

The hypothesis of an anti-auto-antigen targeting strategy may be supported by a recently published study (31) which showed that thyroid stimulating but not blocking autoantibodies are highly prevalent in severe and active thyroid-associated orbitopathy. Therapeutic measures targeting the autoantibodies may be effective, though such consideration must be cautioned in determining whether the presence of such autoantibodies is truly causal or an epiphenomenon.

A randomized, controlled trial of 19 patients treated with 20 weeks of oral prednisolone vs. 21 receiving 1 g IVIG/kg body weight for two consecutive days every 3 weeks (repeated 6 times) noted a comparable successful outcome between the two groups (at 62-63%), with responders noted to have improved proptosis, visual acuity, intraocular pressure, lid aperture, and eye muscle area. In addition, thyroid antibody titers were reduced markedly in the IVIG group. However, the incidence of side effects was noted to be more severe in the steroid group, for which the authors suggested IVIG may be preferable to steroids for TED. (32)

Plasma Filtration

A separate randomized study of 20 patients comparing IV methylprednisolone alone or in conjunction with plasma filtration(33) found that while both groups improved their clinical activity scores, the change occurred more rapidly in patients treated with plasma filtration.

Biologic response modifiers

Various anti-cytokine-specific strategies have been evaluated in patients with different severity of TED. For example, in a small (10 consecutive patients) study, the TNF receptor blocker etanercept was found to improve the clinical activity score significantly for those suffering from mild-to-moderate TED. (7) One case showed infliximab (monoclonal antibody against TNF) being successfully used in a sight-threatening TED resistant to oral steroids. (34) Anti-TNF medication adalimumab (a fully human monoclonal antibody against TNF) may have a limited role in TED with prominent inflammatory symptoms, as noted in a small sample observer-blinded. (35)

Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, mainly used in treatment of severe rheumatoid arthritis and juvenile idiopathic arthritis, proved to be effective when used in steroid-resistant active, severe TED in a small study of 18 patients, with improvement in proptosis in 72% of patients, extraocular motility in 83% of patients, and diplopia in 54% patients. (36) However, this is a novel drug, and hence minimal data is available.

Anti-Cell-Adhesion

A prospective, randomized, controlled trial of colchicine (1.5 mg/day) vs. prednisone (0.75 mg/kg/day) in 22 patients during the inflammatory phase of Graves' ophthalmopathy found improved clinical activity scores in 68% of the colchicine

treated patients, with signal intensity on MRI also noted to be improved; side effects were prevalent in the steroid group but absent in the colchicine group. (37) It has been proposed that colchicine is specific to neutrophil and endothelial cell adhesion, modulating chemokine and prostanoid production. (38)

Future Considerations

Not all novel treatments have shown promise. Somatostatin analogs, which may play a role in the development and regulation of T cells, have been shown to offer no improvement in TED patients in randomized controlled trials. (39-42) An interesting side effect of prostaglandin F₂-alpha eye drops (bimatoprost), an agent used to treat glaucoma, is the development of orbital fat atrophy, termed Prostaglandin Associated Periorbitopathy. (43) This eye drop is undergoing a randomized, controlled, double-blind crossover trial in thyroid eye disease to assess its effect on the orbital fat of TED patients.

Animal models for auto-immune thyroid eye disease are limited, but some success has been achieved and described. (44) Though beyond the scope for detailed consideration in this review, such models, if they can accurately be extrapolated to human disease, could be very valuable in creating effective treatment modalities.

CONCLUSIONS

The data considered above suggests a role for different, newer agents, exemplified by wide-ranging predecessors such as selenium's anti-oxidant properties (for milder TED) to anti-inflammatory and generally immunosuppressive properties of steroids or cyclosporin. Specific biological agents such as RTX have shown improvement, with IVIG and even anti-TNF medications having potential roles in specified symptoms. Patient selection for specific therapy, as well as a broader understanding of pathophysiology will likely lead to creation of more targeted therapies. These, in turn, must be evaluated in properly designed prospective, double-blinded, randomized, controlled trials.

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