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Emerging pharmacotherapy for treatment of Graves' disease

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“The ideal therapy for Graves' disease would be relatively safe, would normalize thyroid hormone levels without harming the hormone synthetic capacity of the thyroid gland and would also improve the ocular component of the disease.”

The clinical triad of Graves' disease (GD) includes hyperthyroidism, diffuse goiter and the associated ocular condition, Graves' ophthalmopathy (GO). Hyperthyroidism can cause not only significant weight loss, osteoporosis and sarcopenia, but also embolic events such as atrial fibrillation and cardiovascular collapse. In addition, approximately 50% of patients with Graves' hyperthyroidism experience at least mild GO manifest by ocular erythema and discomfort, and 20% display more significant eye disease that may variably include pain, forward protrusion of the eyes (proptosis), periorbital soft tissue swelling and double vision. Some 3–5% of GD patients suffer quite severe eye disease with corneal ulceration or compressive optic neuropathy that may threaten vision [1].

The treatments currently offered to patients with Graves' hyperthyroidism include surgical removal of the thyroid gland, the administration of radioactive iodine (RAI) targeting the hormone synthetic capacity of thyroid follicular cells, or antithyroid drugs that decrease thyroid hormone production levels [2]. While each of these modalities is efficacious, which is best for a particular patient generally requires considerable discussion between patient and physician. While antithyroid drug therapy does not permanently impact thyroid hormone production, it carries the risk of serious hepatic and hematologic complications and the relapse rate upon discontinuation is high [3]. Relapse is rare following surgery or RAI treatment. The goal of both of these treatments is to render the patient hypothyroid, which necessitates life-long thyroid hormone replacement. Furthermore, there is strong evidence that RAI administration increases the risk of development or worsening of GO in the year following treatment [4,5]. The available treatment options for GO also carry risk and are not uniformly successful. Treatment of GO is therefore generally reserved for patients with severe eye disease and includes oral or intravenous corticosteroids, a course of orbital radiotherapy or orbital decompression surgery, frequently followed by extraocular muscle repair [6].

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The ideal therapy for GD would be relatively safe, would normalize thyroid hormone levels without harming the hormone synthetic capacity of the thyroid gland and would also improve the ocular component of the disease [7]. This therapy might target autoantibodies directed against the thyrotropin receptor (TSHR), or their effects, as there is mounting evidence that these antibodies play a significant role in the development of both conditions [1,8]. TSHR is a member of the G-protein-coupled glycoprotein hormone receptor family. It consists of a large ligand-binding extracellular domain (~414 amino acids), a serpentine transmembrane domain (269 amino acids) and an intracellular signaling domain (81 amino acids) [9]. The hyperthyroidism of GD is caused by circulating TSHR antibodies (TR Ab) that target this receptor on thyroid follicular cells and stimulate excessive production of thyroid hormones. TSHR is also expressed on fibroblasts residing within the orbital connective tissue [1]. *In vitro* studies have shown that monoclonal stimulatory TRAb can target TSHR on these cells, resulting in increased hyaluronic acid production and differentiation of a subset into mature adipocytes. It is thought that circulating TRAb in GD also target this receptor on fibroblasts residing within the orbit. The resulting soft tissue remodeling would expand the orbital tissues, leading to increased local pressure, impairment of venous drainage and varying degrees of proptosis. Inflammatory cytokines produced by infiltrating immune cells accumulate within these tissues and contribute to the inflammatory signs and symptoms of the disease. Clinical observation also implicates TRAb in GO pathogenesis as levels of these antibodies correlate with both the degree of proptosis and the inflammatory activity of the disease [10].

The potential use of targeted biological agents in general, and rituximab (RTX) in particular, in the treatment of GD is based on the central role of circulating TRAb in pathogenesis. Production of these antibodies follows the internalization and degradation by antigen-presenting cells of thyroidal or orbital TSHR. Peptides are subsequently relayed to helper T cells in association with major histocompatibility antigens [11]. These activated T cells interact with B cells through CD154-CD40 bridges and secrete IL-2 and IFN- γ , cytokines that induce the differentiation of B cells into the plasma cells producing TRAb. RTX is a humanized chimeric monoclonal antibody that targets CD20, an antigen expressed on pre-B and mature lymphocytes. It causes lysis of these cells either by activating complement or by permitting antibody-dependent cell-mediated cytotoxicity [12]. As a result, the activation and differentiation of B cells is diminished without preventing the regeneration of B cells from stem cells and pro-B lymphocytes. RTX also inhibits the ability of B cells to act as antigen-presenting cells and impairs T-cell activation, thereby decreasing levels of both T- and B-cell-derived cytokines. Early studies of RTX in patients with GD demonstrated a decrease in TRAb levels of only 30–50% without significant impact on the hyperthyroidism, except perhaps in the prolongation of remission in patients with mild disease [12]. By contrast, several promising case reports in the literature suggest that RTX may be effective as treatment for GO. However, as the natural history of the condition is one of spontaneous improvement over time, whether this agent is indeed beneficial in these patients awaits completion of two randomized control trials currently underway [1]. If found to be effective, the use of RTX in GO would probably be limited to patients with severe disease owing to the potentially serious side effects of this agent. However, newer generation CD20-targeted agents with a more favorable side effect profile and increased efficacy are currently in clinical or preclinical development. The rationale is also strong for the study of other immunomodulatory agents in GO, including those targeting receptors for IL-1, IL-6 and TNF, modulating costimulatory pathways or decreasing leukocyte recruitment into the orbit [1].

Other potential therapy for both hyperthyroidism and GO might involve blocking TRAb that would compete with stimulatory TRAb for receptor binding. The first human monoclonal blocking TRAb was produced from the B cells of a patient with autoimmune

hypothyroidism caused by these autoantibodies [13]. This high affinity antibody (termed 5C9) has the ability to block the effect of not only monoclonal stimulatory TRAb and thyroid stimulating hormone, but also the polyclonal TRAb found in the sera of GD patients. Such antibodies have not yet been studied for toxicity or pharmacodynamics in humans. Limitations to monoclonal antibody therapy include the risk of immune reactions such as serum sickness, acute anaphylaxis and the generation of other antibodies. In addition, the need for parenteral administration increases the cost and decreases ease of administration.

Recently developed drug-like small-molecule ligands (SMLs) that antagonize TSHR signaling hold particular theoretical promise in GD treatment. Binding of stimulatory TRAb to thyroid follicular cells results in activation of adenylyl cyclase, increased intracellular cyclic adenosine monophosphate (cAMP) levels, and excessive thyroid hormone production. In some instances, cAMP-independent signaling cascades are also involved, including phosphoinositide 3-kinase with phosphorylation of Akt and activation of downstream effectors [14]. Similar signaling cascades are involved in the stimulation by TRAb of hyaluronic acid production and adipocyte differentiation in GO orbital fibroblasts [15,16]. Two different groups of investigators have developed SML TSHR antagonists using molecular modeling of other G-protein-coupled receptor antagonists, high-throughput studies and functional studies [17,18]. These high affinity and potency molecules sit within transmembrane pockets and act as allosteric modulators of TSHR signaling without competing for extracellular ligand-binding sites. They have been shown to inhibit TSHR signaling in primary thyroid follicular cell cultures, as well as in cultures of GO orbital fibroblasts [19,20]. Because these compounds are small, they would not be degraded by the GI tract, and could therefore be orally administered. If future toxicity studies are favorable, these or similar TSHR antagonists might be attractive agents to study not only as treatment for hyperthyroidism and GO, but also in the prevention of GO in high-risk individuals.

Conclusion

At present, treatment modalities available for the hyperthyroidism of GD are generally efficacious, but both carry with them potentially serious side effects or necessitate life-long thyroid hormone-replacement therapy. Treatment of GO is also not optimal and is generally reserved for patients with severe disease as the current approaches are not without risk. Recent developments in the understanding of GO pathogenesis suggest that therapies targeting TRAb, or its effects, on thyroid follicular cells or orbital fibroblasts might favorably impact both hyperthyroidism and GO. To date, novel therapies being studied aim to modulate the autoimmune process directed against TSHR (RTX), compete with stimulatory TRAb for receptor binding (blocking TRAb), or inhibit TSHR signaling (SML TSHR antagonists). While promising, each approach represents but an early iteration of what may in future prove to be of benefit to patients with GD.

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