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Autoimmunity and Graves Disease

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Abstract

Current treatment options for Graves' hyperthyroidism and the related ophthalmopathy (GO) are not uniformly effective and carry with them potentially serious side effects. As a result, efforts have been focused on the development of novel therapies. Progress has been made, particularly in the production of thyroid-stimulating hormone receptor (TSHR) antagonists, as either monoclonal blocking antibodies or small-molecule ligands. In addition, rituximab (RTX) is the first targeted biological therapy to be studied as treatment for these conditions.

Current treatment options for Graves' hyperthyroidism and GO are inadequate because they are often invasive and generally target the signs and symptoms of the disease rather than the pathophysiology (Table 1). Patients with Graves' hyperthyroidism are offered thyroidectomy, radioactive iodine (RAI) therapy, antithyroid medication (methimazole), or a combination of these approaches.[1] The therapeutic goal of both surgery and RAI is to make the patient hypothyroid, necessitating lifelong thyroid hormone replacement, whereas methimazole generally produces euthyroidism with appropriate dosing and may induce remission. However, this medication is generally given for only a limited period of time because of potentially serious side effects including agranulocytosis and hepatotoxicity. Once methimazole has been discontinued, the majority of patients experience recurrent hyperthyroidism and require definitive treatment with either thyroidectomy or RAI. The available treatments for GO, including corticosteroids, orbital irradiation, and orbital decompression surgery, are not uniformly effective and carry with them significant potential side effects. Therefore, these treatments are generally reserved for disease that has progressed beyond the milder ocular manifestations.

The search for optimal treatment for Graves' disease (GD) and GO has focused on both antagonizing excessive TSHR signaling and dampening the immune system dysregulation directed against this receptor central to the initiation and propagation of the disease. Patients with hyperthyroidism produce autoantibodies that activate the TSHR on thyroid follicular cells, resulting in unregulated and excessive production of thyroid hormones. This receptor is a 764–amino acid membrane protein member of the glycoprotein hormone receptor family. It is composed of a large extracellular domain of approximately 414 amino acids, a 269–amino acid transmembrane domain that crosses the membrane seven times, and an 81–amino acid C-terminal domain. Binding of TSH or antibodies directed against TSHR (TRAbs) to the receptor activates G-proteins, primarily those containing $G\alpha_s$ subunits. As a result, transmembrane adenylyl cyclases are activated, levels of intracellular cyclic adenosine monophosphate (cAMP) are elevated, and thyroid function is increased. Some TRAbs also activate cAMP-independent cascades, including the phosphoinositide 3-kinase

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CONFLICT OF INTEREST
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pathway with subsequent phosphorylation of Akt (protein kinase B) and activation of downstream effectors. Evidence suggests that the pathogenesis of GO involves the targeting by TRAbs of TSHR expressed on orbital fibroblasts.[2] This stimulates the cells, perhaps partially via pathways not dependent on cAMP, to augment hyaluronic acid production and increase adipogenesis. These cellular changes, together with an infiltration of immune cells producing proinflammatory cytokines, lead to the orbital tissue changes characteristic of GO.

Patients with GD produce a variable mixture of polyclonal TRAbs with differing relative quantities, affinities, potencies, and actions at the receptor. TRAbs that activate TSHR and increase cAMP production are termed “stimulatory,” and those reducing TSH action are “blocking” and may themselves be weak agonists. TRAbs having no influence on TSH binding or cAMP induction are termed “neutral.” Some TRAbs also inhibit agonist-independent (“constitutive”) signaling and are therefore termed “inverse agonists.” To characterize and better understand the complex interactions between these polyclonal antibodies and their impact on thyroid function, investigators have developed monoclonal TRAbs using plasma cells from several species. The first human monoclonal TRAb with the ability to block both TSH and stimulatory TRAbs was produced by the group of Sanders and Rees Smith using B cells from a patient with a rare form of autoimmune hypothyroidism caused by blocking TRAbs.[3] This monoclonal antibody (termed 5C9) is also an inverse agonist and has high affinity for the TSHR. It recognizes an epitope consisting of noncontiguous amino acids that are closely opposed owing to the three-dimensional structure of the receptor. Of great importance is that 5C9 acts as a powerful antagonist of either stimulatory or blocking polyclonal TRAbs in GD patient sera, and it also blocks other monoclonal TRAbs.

This same group recently obtained another human monoclonal blocking TRAb (K1–70) with similar properties and was able to determine the crystal structure of TSHR bound to this antibody. The ability of these monoclonal TRAbs to act as powerful antagonists of stimulatory TRAbs suggests that similar preparations could be used as specific inhibitors of thyroid stimulation in patients with GD, including those with GO. The inverse agonist properties of 5C9 suggest other clinical uses, including treatment of a rare form of hyperthyroidism due to TSHR-activating mutations and suppressing constitutive TSHR activity in thyroid remnants after surgery for thyroid cancer or in thyroid cancer metastases.

Recently developed small-molecule ligands (SMLs) that antagonize protein–protein interactions in members of the glycoprotein hormone receptor subfamily hold great promise as therapeutic agents. Unlike antibodies, SMLs can be administered orally, as they are absorbed and not degraded in the gastrointestinal tract. Because they are synthesized chemically, they can be produced in large quantities with reliable quality and modest cost. The group of Susanne Neumann and Marvin Gershengorn (Clinical Endocrinology Branch, National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health) used molecular modeling of SML antagonists of the luteinizing hormone/chorionic gonadotropin receptor (LHCGR), chemical modification, and functional experiments to introduce the first SML antagonists of TSHR. Functioning as allosteric modulators of the receptor, these SMLs act without direct competition for extracellular TSH or TRAb binding sites. They sit within the transmembrane helices binding pocket, near the extracellular region, and prevent contact with deeper residues that are important for agonist activity. These compounds also exhibit inverse agonist properties at the receptor. Whereas the initial studies of these compounds were done in cells stably expressing wild-type TSHR, later studies in primary cultures of human thyroid cells using an SML of higher affinity and potency (termed “compound 1”) showed significant inhibition of cAMP stimulated by all of 30 GD sera tested.[4] Compound 1 and related preparations are therefore of great interest as

potential novel therapeutics for GD and GO. Efficacy testing of these compounds in humans awaits animal studies regarding toxicology, metabolism and excretion, absorption, and distribution.

RTX is a targeted biological agent approved by the US Food and Drug Administration (FDA) for use in polyarteritis nodosa (in microscopic disease, combined with glucocorticoids) and rheumatoid arthritis (in moderate to severe disease, in combination with methotrexate in disease resistant to tumor necrosis factor antagonist). Off-label indications (i.e., not approved by the FDA) include primary Sjögren syndrome, autoimmune hemolytic anemia, and rheumatoid arthritis (in combination with methotrexate in methotrexate-resistant disease), and systemic lupus erythematosus (in disease refractory to immunosuppressive therapy). Because of its success relative to these conditions and the clinical experience gained, interest has grown regarding its potential efficacy in GD and GO. RTX is a humanized chimeric monoclonal antibody that targets CD20, an antigen expressed on the surface membrane of pre-B lymphocytes and mature B lymphocytes. Because hematopoietic stem cells, pro-B lymphocytes, and plasma cells do not express this antigen, RTX blocks the activation and differentiation of B cells without preventing the regeneration of B cells from stem cells and pro-B lymphocytes. RTX is thought to lyse targeted cells either by activating complement or by permitting antibody-dependent, cell-mediated cytotoxicity. The antibody also alters the ability of B cells to respond to antigen or other stimuli and may initiate programmed B-cell death. As a result, the antigen-presenting role of B cells is inhibited. In addition, because T-cell activation is dependent on the presence of B cells, the levels of T and B cell–derived cytokines and direct T-cell effects are diminished.

The rationale for the use of RTX in GD and GO includes its potentially beneficial effects on TRAb production, antigen presentation by B cells, and proinflammatory cytokine production.[5] Three variably controlled studies involving only a handful of patients in total have suggested that RTX may prolong remission in patients with GD, particularly those with mild hyperthyroidism. A moderate decrease in TRAb levels was found in all three studies (29–52%), showing perhaps a more pronounced effect on stimulatory than on other varieties of TRAbs. Although several case reports of RTX treatment in GO have shown promise, to date no randomized control trials have been completed, although two are under way.[2] Until these and future studies in patients with GD or GO have been completed, no valid conclusions concerning rituximab's efficacy or side effects in these patients can be drawn.

Because current treatment options for Graves' hyperthyroidism and GO are inadequate, recent effort has focused on the development of novel therapies (Table 2). Progress has been made, particularly in the production of TSHR antagonists, either as monoclonal blocking TRAbs or as SML compounds. In addition, RTX has been introduced as the first targeted biological therapy to be studied as treatment for these conditions. Although each of these therapies has significant advantages over currently available modalities, much work is needed before these or other novel therapies are available for use in patients with Graves' hyperthyroidism or GO.

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Table 1

Currently available treatments for Graves' hyperthyroidism

Treatment	Advantages and preferences	Disadvantages
Radioactive iodine ablation	Definitive treatment May be preferred for patients with increased surgical risk or necks previously operated upon Simplifies management of future pregnancy	Requires lifelong thyroid hormone replacement Risk of worsening Graves' ophthalmopathy in patients with active disease
Thyroidectomy (when performed by high-volume thyroid surgeon)	Definitive treatment and rapid resolution of hyperthyroidism Preferred in patients with documented or suspected thyroid malignancy or coexisting hyperparathyroidism requiring surgery Simplifies management of future pregnancy Preferred in patients with moderate to severe active Graves' ophthalmopathy	Inherent surgical risks Requires lifelong thyroid hormone replacement
Antithyroid medication (methimazole)	May induce remission May be preferred for patients with increased surgical risk, or necks previously operated upon, or limited life expectancy Preferred in patients with moderate to severe active Graves' ophthalmopathy	Potential serious side effects of hepatic dysfunction and agranulocytosis Need for continued monitoring of thyroid hormone levels Possibility of disease recurrence

Table 2

Potential novel therapies for Graves' disease and Graves' ophthalmopathy

Potential therapy	Theoretical advantages	Disadvantages and unknowns
Monoclonal thyrotropin receptor–blocking antibodies[3]	Control of hyperthyroidism until disease is in remission	Parenteral administration Expensive Difficult to produce in large quantities with uniform quality Pharmacodynamics and toxicity not yet defined Unknown impact on Graves' ophthalmopathy
Small-molecule-ligand antagonists of thyrotropin receptor[4]	Control of hyperthyroidism until disease is in remission Oral administration Relatively inexpensive to produce in large quantity with reliable quality	Short half-life Pharmacodynamics and toxicity not yet defined Unknown impact on Graves' ophthalmopathy
Rituximab[5]	Long half-life May induce remission in mild hyperthyroidism	Parenteral administration Expensive Potentially serious side effects Unlikely to control hyperthyroidism Unknown impact on Graves' ophthalmopathy