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OCULOPLASTICS UPDATE

Thyroid-associated orbitopathy: Current insights into the pathophysiology, immunology and management

Rina Bhatt, MS (India), FRCS (I), FRCS (Ed) [1], Christine C. Nelson, MD, FACS, Raymond S. Douglas, MD, PhD *

Ophthalmology and Visual Sciences, Kellogg Eye Center, University of Michigan, Ann Arbor, MI 48105, USA

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Abstract Half the patients suffering from Graves' disease develop thyroid-associated orbitopathy (TAO). The severity of TAO varies considerably with a mild form characterized by dry eyes and discomfort to the severe form with sight-threatening exposure keratopathy and optic neuropathy. The pathogenesis and immunologic mechanisms underlying Graves' disease and TAO is unknown, however, advances toward this understanding have indicated a prominent role of orbital fibroblasts, T cells and B cells. These advances have led to novel strategies for clinical treatment using immunomodulatory modalities. Initial results included use of infliximab and etanercept (anti-TNF agents), but currently there is an increasing interest in anti-B cell (Rituximab) therapy. Rituximab has shown promising results in progressive, sight-threatening TAO. It has also shown encouraging results in halting or slowing the disease process in patients unresponsive to corticosteroids. The primary advantage of these immunomodulatory agents is based upon targeting the molecular mediators of the disease and avoiding the potential side effects of non-specific therapies.

* Corresponding author. Tel.: +1 734 936 0946.
E-mail addresses: rina@cbhatt.freeserve.co.uk (R. Bhatt), cnelson@med.umich.edu (C.C. Nelson), raydougl@med.umich.edu (R.S. Douglas).
[1] Present address: Shrewsbury and Telford Hospitals, NHS Trust, Shrewsbury, United Kingdom.

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Contents

1. Introduction

Clinically relevant thyroid-associated orbitopathy (TAO) occurs in approximately 50% of patients with the systemic autoimmune condition, Graves' disease (GD) (Wiersinga and Bartalena, 2002). Thyroid-associated orbitopathy is more common in women as compared to men; however, the clinical course is typically more severe in men (Bartley et al., 1995). The majority of patients develop a mild form of disease characterized by dry eyes and ocular or periorbital discomfort. A minority of patients present with disabling proptosis and/or diplopia secondary to restrictive strabismus. Severe sight-threatening orbitopathy due to exposure keratopathy or compressive optic neuropathy occurs in approximately 3–5% of cases (Wiersinga and Bartalena, 2002). Most commonly, TAO has an active, inflammatory clinical phase which lasts for 18–24 months followed by a plateau and a fibrotic stage. The stable phase is marked by stability of clinical symptoms although signs and symptoms of congestive orbitopathy can persist. The natural history of the disease is more severe in smokers and these patients are refractory to current treatment modalities (Eckstein et al., 2003; Mann, 1999). There is evidence that cessation of smoking leads to disease stabilization and a better response to treatment (Eckstein et al., 2003).

The pathogenesis of GD and TAO is elusive but research in the past 5 years has broadened our understanding of the immunologic pathogenesis. However, many unanswered questions remain, including the causes of disease heterogeneity, site-specificity and interplay among pro-inflammatory and pro-fibrotic mediators and the pathogenic mechanism of smoking.

Current non-specific treatment modalities such as corticosteroids target the inflammatory symptoms and signs of the process while investigations continue to identify the specific molecular mediators. Since TAO is highly heterogeneous, randomized controlled treatment trials for specific or novel modalities have been slow to evolve. However, further insights into the mechanism of orbital fibroblasts, such as T cells and B cells, have enabled the undertaking of limited trials of immunotherapies (Leandro et al., 2002; Hasselbalch, 2003; Wang and Baker, 2006). We will review the pathophysiology of TAO and its management with biologic agents.

2. Pathophysiology and immunology in TAO

In TAO, lymphocytes, monocytes, and mast cells infiltrate orbital tissues including the orbital fat and the intercellular space between extraocular muscle cells. These tissues become extensively remodelled with fibrosis and extracellular matrix material including glycosaminoglycans such as hyaluronan (Hufnagel et al., 1984). The active phase of TAO is characterized by increased production of hyaluronan, which is highly hydrophilic, contributing to the increase in orbital volume. The extraocular muscles increase in size and volume which manifests clinically as painful eye movements and restrictive strabismus. One paramount goal of this paper is to understand the underlying mechanisms that result in inflammatory infiltration, tissue expansion, and fibrosis.

B cells have a multifaceted role in initiating and propelling the pathologic process in TAO. They are highly efficient antigen-presenting cells and they produce potent chemokines including IL-6, lymphotoxin, TNF-α, and IL-10 (Lanzavecchia, 1985; Paul, 2003; Smeland et al., 1989). Activated B cells contribute to cytokine production by stimulating T cells through CD40–CD154 interaction. T cells can differentiate into different types of effector cells such as cytotoxic T cells and helper T cells with varied functional properties (Th1, Th2, Th17, and Treg subsets) (Pritchard et al., 2003). T helper 1 (Th1)-type cytokine production has been identified in the active phase of TAO (Wakelkamp et al., 2000; Yang et al., 1999), while a Th2 immune response characterized by expression of IL-4, IL-5 and IL-10 is identified in patients with stable TAO (McLachlan et al., 1994). The relative proportion or activation of these T cell subtypes is of intense interest since altering the cytokine production may provide potential for treatment.

Orbital fibroblasts are considered to be the target cells in TAO based upon immune infiltration, cytokine production and antigen expression (Prabhakar et al., 2003; Bahn, 2003). Orbital fibroblasts from TAO patients exhibit many unique pro-inflammatory and pro-fibrotic properties that distinguish them from their normal counterparts. Additionally, orbital fibroblasts are capable of differentiating into either myofibroblasts (scar-forming cells) or lipofibroblasts (adipocytes) (Smith et al., 2002). There is an increase in orbital fat in active TAO. Adipogenesis is induced by peroxisome-proliferator-activated receptor γ (PPAR-γ), which is produced by activated T cells (Bahn, 2010). PPAR-γ activation triggers orbital fibroblasts to differentiate to adipocytes and hence an increase in orbital fat (Lehmann et al., 2008).

Two major subsets of orbital fibroblasts exist with distinct phenotypic and functional roles. Expression or absence of the surface protein Thy-1 (CD90) distinguishes two populations of fibroblasts that can either differentiate toward adipogenic or myofibroblast characteristics. The balance between

the two subsets could contribute to disease expression by influencing inflammation, fibrosis and fat expansion (Koumas et al., 2002, 2003). Recently, Thy-1 was found to be overexpressed in orbital tissues of TAO patients.

Orbital fibroblasts from TAO patients also overexpress the CD40 receptor relative to control orbital fibroblasts (Hwang et al., 2009). The activation of CD40 by its ligand CD154 displayed on T lymphocytes leads to expression of several cytokines and chemokines (Hwang et al., 2009; Khoo et al., 2008). This may be particularly relevant to patients with TAO since orbital fibroblasts from these patients overexpress CD40 and express abundant IL-6, IL-8, and MCP-1 (Hwang et al., 2009). These cytokines have also been implicated in the accumulation of glycosaminoglycans (Smith et al., 1989).

3. Management and current insights

Up to this point there has been a lack of understanding of the mechanistic regulators of TAO. Thus the clinical management has focused on symptom relief. The majority of patients have a mild form of disease with dry eyes and mild periorbital swelling. Conservative measures such as tear supplements, punctal cauterization, head elevation when asleep and oral anti-inflammatory medications (ibuprofen) may provide relief from these symptoms. The mainstay of management is identifying and treating patients who have progressive disease that may lead to debilitating strabismus and sight-threatening optic neuropathy and exposure keratopathy. An ideal treatment would be the one that can be given at an early stage of this progressive disease in order to slow the disease progression.

Intravenous, oral and periocular steroids have been used to treat moderate to severe and extreme thyroid-associated orbitopathy. Steroids are fast acting and cost effective, however, they do not effect a cure and there is conflicting evidence as to whether treatment improves the manifestations of long-term diseases. Glucocorticoid therapy imposes substantial side effects in the form of cushingoid syndrome, hyperglycemia, hypertension, steroid-induced psychosis, susceptibility to infections and electrolyte imbalance. Furthermore, there is a substantial relapse rate once steroids are discontinued, and up to 30–35% of patients have no response whatsoever. Steroid-sparing agents have been proposed to minimize the side effect profile. Immunosuppressants such as methotrexate, azathioprine, and cyclosporin have been used with moderate success (Bartalena, 2010; Smith and Rosenbaum, 2001). Orbital irradiation offers an adjunct to steroids in active thyroid-associated orbitopathy, though several studies bear conflicting data regarding its efficacy (Bradley et al., 2008; Claridge et al., 1997; Prummel et al., 1993). Due to local and systemic side effects these treatment modalities are not ideal options and for these reasons there has been a drive for immunomodulatory therapy in recent years.

The most substantial impact of immune-based therapies has come from therapies utilized in the treatment of other autoimmune disorders, especially rheumatoid arthritis. Infliximab, a chimeric human-mouse anti-TNF-α antibody, has been effectively used in the treatment of rheumatoid arthritis, Crohn's disease, psoriasis, ankylosing spondylitis and juvenile idiopathic arthritis and uveitis (El-Shabrawi and Hermann, 2002; Reimold, 2002; Winterhalter and Niehues, 2008). In a case report, Durrani et al. showed infliximab being successfully used in a sight-threatening TAO that was resistant to oral steroids (Durrani et al., 2005). The clinical activity score in this case improved from 10/10 before treatment to 2/10 seven days after treatment. Similarly, etanarcept, an anti-TNF agent, has shown beneficial effects in rheumatoid arthritis and uveitis (Moreland et al., 1997; Weinblatt et al., 1999). In a pilot study by Paridaens et al., etanarcept was used in 10 consecutive patients with recent onset of active, mild-moderate TAO. The authors found that 12 weeks after treatment, the mean clinical activity score had decreased by 60% and the ophthalmopathy index, based on the NOSPECS classification, had improved by 24% (Paridaens et al., 2005). The authors found improvement mainly in soft tissues; with no change in visual acuity and no average change in proptosis.

More recently, the impact of anti-B cell therapy has created great interest. B cells produce antibodies, including those autoantibodies that underlie the hyperthyroid manifestations of GD. However, probably more important, B cells are excellent antigen-presenting cells and potent participants in T cell activation (Lanzavecchia, 1985; Paul, 2003). Rituximab is a human/murine chimeric monoclonal antibody that targets CD20, a transmembrane protein present on immature and mature B cells, but is absent on most pro-B cells or plasma cells (Reff et al., 1994). It was first introduced for treating patients with relapsed low-grade non-Hodgkins lymphoma (Maloney et al., 1997; Sacchi et al., 2001). Since then, it has been used increasingly to treat several B-cell malignancies. It has also been added into the armamentarium of management of various autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, and dermatomyositis (Dorner, 2006; Martinez-Gamboa et al., 2006).

B cells are highly efficient antigen-presenting cells. Animal models of rheumatoid arthritis and type 1 diabetes mellitus have shown that B cells play a pivotal role in its pathogenesis (Falcone et al., 1998; Serreze et al., 1998). Rituximab has been shown to be beneficial in treating classic T-cell-mediated autoimmune diseases such as multiple sclerosis and type 1 diabetes mellitus (Hauser et al., 2008; Pescovitz et al., 2009).

Rituximab is thought to disrupt the pathogenic autoantibody generation through B-cell depletion and hence promote possible long-term remission (Edwards et al., 1999). Graves' disease and the associated orbitopathy are autoantibody-mediated diseases and Hasselbalch, and Wang and Baker were the first to suggest the likely benefit of Rituximab in Graves' disease (Hasselbalch, 2003; Wang and Baker, 2006). Salvi et al. and El Fassi et al. first tried Rituximab in patients with TAO in 2006. The B cell depletion in these cases was associated with improvement in the severity of TAO (Salvi et al., 2006; El Fassi et al., 2006).

Further evidence has been emerging regarding the efficacy of Rituximab in TAO patients. In an open study, Salvi et al. compared the results of Rituximab used in nine patients with intravenous glucocorticoids used in 20 patients (Salvi et al., 2007). After two infusions of Rituximab, all patients attained B-cell depletion that lasted for at least 4 months. The effect on clinical TAO severity was encouraging, with improvement of the clinical activity score (4.7 ± 0.5 pre-treatment level to 1.8 ± 0.8 post-treatment) while the complications were mild, in the form of a mild fever and itching in the nose and throat. The improvement in the clinical course of TAO

was not associated with similar improvement in thyroid function or levels of thyroid antibodies. The authors hypothesized that treatment with Rituximab leads to specific elimination of mature B cells without affecting regeneration of B cells from stem cells or production of immunoglobulins from plasma cells. A possible mechanism of therapeutic action in TAO may be through depletion of antigen-presenting B cells.

In 2007, El Fassi et al. also reported their experience with Rituximab in newly diagnosed untreated Graves' patients (El Fassi et al., 2007) without TAO. In a prospective, controlled non-randomized study they reported four of ten patients receiving Rituximab remained in remission at a median follow-up of 705 days, whereas all patients who did not receive Rituximab relapsed by day 393. Subsequently, Heemstra et al. assessed the efficacy of B cell depletion therapy in 13 patients with relapsing Graves' disease (Heemstra et al., 2008). They reported that nine of thirteen patients responded to treatment and demonstrated FT4 and TSH levels in the normal range. Thus, they concluded that this treatment may have a beneficial role in mild relapsing Graves' disease.

Rituximab has been utilized in patients with severe, progressive TAO that is unresponsive to corticosteroids (Khanna et al., 2010). In this study, all six patients were euthyroid and had previously received corticosteroids for 7.5 ± 6.4 months without clinical response. However, clinical improvement (improved vision and inflammatory signs) was noted as early as 4 weeks after RTX infusion. The clinical activity score of all patients improved (mean 5.3 ± 1.0 to 1.3 ± 0.5) 8 weeks following treatment. Improvement in visual acuity was seen in all four patients with dysthyroid optic neuropathy. There was no improvement in proptosis or extraocular motility in any of the patients. None experienced relapse in the follow-up period.

In addition to antibody production and antigen presentation, B cells are potent cytokine producers. Pro-inflammatory cytokine production by B cells includes IL-6, TNF-α, and lymphotoxin (Skok et al., 1999; Smeland et al., 1989), and anti-inflammatory cytokines including IL-10 and TGF-β (Fillatreau et al., 2002; Skok et al., 1999). Clinical B cell depletion may block the cascade of immunological interactions that lead to the clinical presentation of TAO. Recently, Wilk et al. suggested that in addition to B cells, there is a small proportion of T cells coexpressing CD20 in all individuals (Wilk et al., 2009). In patients with rheumatoid arthritis, the CD20 T cells and CD20 B cells were eliminated from the peripheral blood after Rituximab therapy. The CD20 T cells were functionally active in cytokine production and thus, their depletion might be an additional mechanism by which Rituximab therapy works in rheumatoid arthritis patients.

The efficacy of B cell depletion in active TAO patients is limited, but it offers advantages compared to glucocorticoids as patients demonstrate a high response rate with minimal relapses. Timing and patient selection will be of critical importance to minimize the side effects while maximizing the benefits.

4. Future

Our current understanding is that TAO is at least in part, a T cell-mediated disease. Hence, an ideal biologic treatment would include T cell modification. Type 1 diabetes mellitus is also a T cell-mediated autoimmune condition and has generated considerable research interest toward immunomodulatory therapies. Two humanized anti-CD3 antibodies; hOKT3γ1 (ala-ala or Teplizumab), a humanized mouse monoclonal antibody and ChAglyCD3 or otelixizumab, a humanized rat monoclonal antibody have been studied for treatment of type 1 diabetes mellitus. Preliminary results of phase 1 and 2 studies have shown promise (Herold et al., 2005; Keymeulen et al., 2005). Anti-CD3 treatment has also been tried in animal models of collagen-induced arthritis and has shown therapeutic potential (Notley et al., 2010). Researchers and clinicians are hoping for similar results for other autoimmune conditions including TAO.

5. Summary

Progressive thyroid-associated orbitopathy continues to be a challenge to manage. But we are now in an exciting period due to considerable advances in our understanding of the role of specific immunomodulating agents that enable us to target the basis of the disease rather than just addressing the symptoms and disease manifestations. All this is simultaneously driven by an improved understanding of the role of T and B cells, orbital fibroblasts and the complex interplay between these cells. Future studies should be multi-centered with larger cohorts and a standardized treatment regimen. We look forward to the fulfilment of the promise shown in these early studies as the role of T-cell immunomodulatory treatment evolves.

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