REVIEW

Rituximab in the Treatment of Thyroid Eye Disease: A Review

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ABSTRACT

Graves disease is an autoimmune thyroid disease classically characterised by a clinical triad consisting of hyperthyroidism, diffuse goitre, and thyroid eye disease. Thyroid eye disease is an immunologically mediated condition in which humoral immunity is thought to play a central role. Thyroid eye disease is traditionally treated with high-dose glucocorticosteroids and surgical orbital decompression. However, responses are inadequate and alternative treatment options are needed. Rituximab, an anti-CD20 monoclonal antibody, shows promise as a novel therapeutic option for thyroid eye disease. There are 43 cases of thyroid eye disease treated with rituximab in the medical literature, and larger studies are warranted to determine the long-term effectiveness of rituximab. Rituximab may represent an attractive new treatment option for thyroid eye disease, especially in the case of disease that is refractory to current treatment strategies.

Keywords: Biologic therapy, Graves disease, Graves orbitopathy, ophthalmopathy rituximab, thyroid-associated orbitopathy, thyroid eye disease

INTRODUCTION

Graves disease (GD) is an autoimmune thyroid disease (AITD) defined by a clinical triad consisting of hyperthyroidism, diffuse goitre, and thyroid eye disease (TED), also referred to as Graves ophthalmopathy or thyroid-associated ophthalmopathy.¹ These disorders are immunologically mediated conditions that classically involve the humoral immune system. Treatment of TED has traditionally been limited to high-dose glucocorticosteroids and surgical orbital decompression, but responses to glucocorticosteroids are inadequate^{2,3} and additional treatment options are needed. Rituximab, an anti-CD20 monoclonal antibody that leads to B-lymphocyte depletion, shows promise as an effective therapeutic agent for TED. In this article, the immunological process of GD and TED are discussed, followed by a review of currently available data for patients with TED who have been treated with rituximab.

Ninety to 98% of GD patients will experience eyelid findings.⁴ Eyelid retraction is the most common eyelid finding in this patient population and worsens with attentive gaze; this is referred to as Kocher sign.⁵ Patients with eyelid retraction frequently demonstrate lateral lid flare, a finding that is rarely found in other disease processes. Patients with this finding present with eyelid retraction that is more prominent laterally than medially, resulting in a temporally flared eyelid contour. Eyelid retraction and its pathogenesis will be discussed further in the section “Immunological Pathogenesis of Orbital Manifestations of Graves Disease”.

Other eyelid findings include lagophthalmos and “lid lag”, a term used to describe the delay in the upper eyelid’s downward excursion with relation to eye movement in down gaze. Fifty percent of GD patients experience conjunctival injection and irritation, and 20% manifest orbital pain, proptosis, eyelid oedema, or diplopia. Most importantly, 3–5% develop

Received 6 February 2015; revised 27 March 2015; accepted 6 April 2015; published online 15 June 2015

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vision-threatening pathology, namely, corneal exposure, with resultant ulceration or compressive optic neuropathy.⁶

THE IMMUNOLOGICAL BACKGROUND OF GRAVES DISEASE

The fundamental process by which GD produces a hyperthyroid state is via antibody-mediated stimulation of the thyrotropin receptor. This receptor is a G-protein-coupled receptor for thyroid-stimulating hormone (TSH), which is secreted by the pituitary gland.⁷ Patients with GD produce a polyclonal mixture of antibodies against the thyroid-stimulating hormone receptor, which can result in various downstream effects. Some of these antibodies activate the receptor, whereas others block or neutralise the receptor.⁸ It is the activating, or stimulating, autoantibodies that lead to the typical biochemical features of GD, including elevated thyroid hormones and low or undetectable levels of thyroid-stimulating hormone.⁵ Although GD is considered a classic autoantibody-mediated disease, additional factors may play a role in the ultimate expression of the disease phenotype. For example, T-cell help is thought to be important for differentiation of autoantibody-producing B cells into plasma cells,⁹ and the role of T regulatory cells and interleukin-23/interleukin-17 in the pathogenesis of GD are now being explored more actively.^{7,10}

The initial inciting factor in autoimmune thyroid disease (AITD) is still unknown and may vary among individuals.¹¹ Based on family and twin studies, it is thought that both genetic and environmental factors play a role, with an estimated 80% of AITD susceptibility being attributable to genetics, and the remaining 20% to other environmental factors.¹² The first major susceptibility gene associated with GD was HLA-DR3, a class II human leucocyte antigen (HLA) molecule.¹³ Specifically, an amino acid substitution in the peptide binding pocket of this molecule results in a structural change that confers risk for GD, likely by allowing pathogenic peptides to bind the pocket and be recognised by auto-reactive T cells.¹³ Immune regulatory genes are also thought to be important, and whole-genome linkage scanning has shown a strong linkage of CD40 to GD. Ultimately, it has been found that increased translation of CD40 in GD patients leading to increased expression of CD40 on B cells results in a higher likelihood that they become activated and produce antibodies.¹³ Interestingly, when looking at the thyroid-stimulating hormone receptor gene itself, several single-nucleotide polymorphisms have been investigated for association with GD, but results have been conflicting and inconclusive thus far.¹³

In addition to genetic susceptibility, there are environmental insults that have also been implicated

in the development of AITD. Although the mechanism of action is unclear, it is thought that iodine contributes to development of AITD, and epidemiological studies have shown that AITDs are more common in areas of iodine sufficiency as opposed to iodine deficiency.¹¹ Similarly, smoking is known to increase the risk of developing GD, possibly by altering the thyroid-stimulating hormone receptor structure to make it more immunogenic.¹¹ Infections, both bacterial and viral, may also play a role in development of AITD through various mechanisms that could include molecular mimicry, release of sequestered antigens via cell destruction, or through bystander activation of T cells.¹³ The most common medications thought to play a role in the pathogenesis of AITD include interferon alpha, interleukin-2, lithium, amiodarone, and highly active antiretroviral therapy.¹³ Lastly, many environmental pollutants have been shown to be toxic to thyroid cells and capable of promoting AITD. These include polyaromatic hydrocarbons, perfluorinated chemicals, phthalates, and bisphenol A, which is commonly used in plastics manufacturing.¹³

Although it is well established that both genetic and environmental factors are important in the development of AITD, the way in which they interact is still unclear. There has been recent emphasis on the role of epigenetics as a possible mechanism by which genetics and environmental factors interact to confer an increased susceptibility to disease. Epigenetics has already been shown to be important in other autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis.¹³ Further investigation is needed to examine the potential role of epigenetics in AITD.

IMMUNOLOGICAL PATHOGENESIS OF ORBITAL MANIFESTATIONS OF GRAVES DISEASE

TED has many clinical manifestations that can be explained by the immunological pathogenesis of the disease. It has been hypothesised that the thyroid and orbital tissues share a common antigen. The ocular manifestations of GD result from enlarged extraocular muscles and orbital fat secondary to the interaction of orbital autoantibodies, fibroblasts, and cytokines.¹⁴ Hydrophilic glycosaminoglycans are produced and promote further tissue oedema when inflammation develops in orbital muscles and fat.¹⁵

Lehman *et al.* have suggested a likely pathway for the orbital manifestations of TED. They describe a pathway in which TED is triggered by binding and activation of orbital fibroblasts by autoantibodies.¹⁶ Chemokines are released by activated orbital fibroblasts, which then recruit T lymphocytes into the orbit. These T lymphocytes interact with fibroblasts

and promote further cytokine production and secretion of T-cell-activating factors. As a result of these interactions, fibroblasts proliferate and extracellular matrix molecules, and fat are deposited in the orbital tissues.¹⁶

The orbit is an enclosed space; the anterior orbital septum restricts movement of orbital contents anteriorly, and the bony orbit restricts movement in the other directions. When inflammation of the orbital contents occurs, many patients develop proptosis. However, this anterior movement of the globe is limited, and apical crowding exacerbated by enlarged extraocular muscles may develop, causing compression of the optic nerve, which results in loss of colour vision, visual acuity, visual field, and an abnormal pupillary response.

The hydrophilic glycosaminoglycans deposited in the disease also result in eyelid erythema, upper and lower eyelid oedema, and festoons. Eyelid retraction results from increased sympathetic stimulus to Muller muscle, contraction of the levator muscle, tight restriction of the inferior rectus muscle, and scarring between the lacrimal gland fascia and the levator muscle, causing the pathognomonic lateral flare.¹⁷ In contrast, lower eyelid retraction occurs as a result of exophthalmos, and not the lower eyelid retractors. Inflammation of the extraocular muscles and deposition of fibroblasts leads to fibrosis and continued contracture of these muscles; failure of the muscles to relax limits eye movement and when asymmetric, causes diplopia.¹⁵ Finally, corneal findings in TED are a result of exposure and rapid tear evaporation secondary to poor blink and increased vertical fissure height.⁶

RITUXIMAB TREATMENT IN THYROID EYE DISEASE

Despite the role of autoimmunity in the pathogenesis of GD, the medical treatment approach has centred around symptom control and reduction of thyroid hormone synthesis, not immunosuppression. Recently, however, biologic immunosuppressive therapy for GD treatment has become a potential option with the use of rituximab. Rituximab is a high-affinity monoclonal antibody composed of an antigen binding region of murine origin and a constant region of human immunoglobulin (Ig) G1.¹⁸ Its target is CD20 (cluster of differentiation), a B-cell surface marker that is found on pre-B and B cells, but typically not stem cells or plasma cells.² Rituximab works by depleting CD20+ cells by both antibody- and complement-mediated pathways along with induction of apoptosis.¹⁹ B-cell depletion is noted within days of administration and lasts approximately 4–6 months until the B-cell population is replenished by new CD20+ B cells from differentiation of

progenitor cells.^{18,19} The B-cell population typically reaches normal levels 9–12 months after infusion of rituximab.¹⁸ Despite its depletion of B cells, rituximab typically does not result in low immunoglobulin levels, although IgM can be decreased after multiple retreatments.¹⁹

Available dosing regimens for rituximab include four consecutive weekly intravenous infusions of 375 mg/m² of body surface area (typically used for haematologic disorders) or two intravenous infusions of 1000 mg given 2 weeks apart (typically used in autoimmune disease).¹ Rituximab is considered to be relatively safe, with mild infusion-related reactions being the most commonly reported adverse event.¹⁸ Infusion times range from 3 to 4 hours. Because immunoglobulin levels are usually maintained, there are relatively few infection-related adverse events, although rarely a fatal reactivation of JC virus causing progressive multifocal leukoencephalopathy has been reported.^{18,19} Through B-lymphocyte depletion and subsequent decreased production of pathogenic antibodies, rituximab shows promise as an effective treatment for TED and has been increasingly described in recent case reports and case series.²⁰

Intra-thyroidal B-lymphocyte depletion in GD has been reported after the use of rituximab²¹ as early as 7 days after treatment. However, reports differ with regard to the effects of rituximab on anti-thyroid antibody levels. A case series of nine patients by Mitchell *et al.* reported a significant reduction in thyrotropin receptor binding inhibitory immunoglobulin levels and clinical improvement in all patients.²⁰ Additionally, a study by El Fassi *et al.* of 10 patients with GD who were treated with rituximab, compared with 10 patients who were not, demonstrated a reduction in the production of anti-thyroid peroxidase antibodies and thyroid-stimulating antibodies.²² Interestingly, overall anti-thyrotropin receptor antibody serum levels were not decreased, but observations suggest that B-cell depletion causes an alteration of the balance between anti-thyrotropin receptor antibody fractions, favouring non-stimulating anti-thyrotropin receptor antibodies over the stimulating anti-thyrotropin receptor antibodies.^{22,23} In their study of 10 patients with TED treated with rituximab, Vanucchi *et al.* did not demonstrate any reduced anti-thyroid antibody levels, but instead suggest that rituximab may exert its effects in GD by inhibiting multiple B-cell functions, including antigen presentation.²³

To date, the results of 43 cases of rituximab use for TED are available (Table 1).^{20,24–30} Various doses of rituximab were used in these patients: 375 mg/m² weekly for a total of 4 weeks in eight patients, 1000 mg every 14 days for two doses in 26 patients, 500 mg every 14 days for two doses in six patients, 1000 mg weekly for a total of two doses in one patient, and a single dose of 100 mg in two patients.

TABLE 1 Published reports of rituximab use in thyroid eye disease^a.

Author	Patients	TED present	Treatment	Optic neuropathy present	CAS ^b pre-treatment / post-treatment	Change in NOSPECS Class after treatment ^c	Patients with improvement in TED
El Fassi <i>et al.</i> ²⁴	2	Yes	RTX ^d 375 mg/m ² body surface area every 7 days for 4 weeks, no glucocorticosteroid pretreatment	NR ^e	5.5 (5–6) / 1.5 (1–2)	Motility improved by 1 class; proptosis improved by 2 mm (0–3 mm)	2
Mitchell <i>et al.</i> ²⁰	9	Yes	RTX every 14 days with concomitant methylprednisolone. Three patients received cumulative dose of 2 g, six received 1 g (500 mg each dose) RTX 1 g every 14 days for 2 doses	4 patients. One required emergency orbital decompression despite treatment	6 (1–8) / 2 (0–7)	Improved in 6 patients, improved by 2 classes in 4 patients with optic neuropathy 2 patients unchanged 1 patient worsened	6
Khanna <i>et al.</i> ²⁵	6	Yes	RTX 1 g every 14 days for 2 doses	4 patients	5.5 (5–7) / 1.3 (0–2)	Visual acuity improved in 4 patients with optic neuropathy Proptosis unchanged Motility unchanged Compressive optic neuropathy developed Motility improved	6
Krassas <i>et al.</i> ²⁶	1	Yes	RTX 1g every 14 days for 2 doses	0 pretreatment	4.5 (2–7) / 4.5 (2–7)	Motility improved by 1 class	0
Madaschi <i>et al.</i> ²⁷	1	Yes	RTX 1g every 14 days for 2 doses	NR	5 / 0	Motility improved	1
Salvi <i>et al.</i> ²⁸	9	Yes in 7, 2 with lid signs	RTX 1 g every 14 days for 2 doses	NR	4.7 / 1.8 in 7 patients with TED	Motility improved by 1 class Proptosis improved by 1.5 mm	7 with Graves ophthalmopathy, 2 with lid sign
Salvi <i>et al.</i> ²⁹	3	Yes	RTX 100 mg single dose in 2 patients RTX 1 g every 7 days for 2 weeks in 3rd patient	NR	5.5 (5–6) / 2.5 (2–3) in patients treated with 100 mg rituximab 6 / 3 in 1 patient treated with 1g rituximab for 2 doses	Proptosis improved by 2.1 mm (1.5–3 mm) in patients treated with 100 mg rituximab	3
Silkiss <i>et al.</i> ³⁰	12	Yes	RTX 1 g every 14 days for 2 doses	NR	5.5 / 0.8	NOSPECS not reported. TAO ^f score improved 4 points	12
Total	43						

^aThe table does not include studies in which results clinical responses for thyroid eye disease were not reported.^bClinical Activity Score. Average scores for multiple patients in the corresponding report followed by range, when available.^cNOSPECS class changes in proptosis indicate mean changes for individual eyes as measured by Hertel exophthalmometry, followed by the range of changes reported.^dRTX = rituximab.^eNR = not reported.^fTAO = The TAO scoring was also used to quantify the effect of treatment. This scoring system assesses orbital pain, chemosis, eyelid oedema, conjunctival injection, and eyelid injection on a scale of 0–2, and total scores from these five items range from 0 to 10).³⁰

TABLE 2 Items of the clinical activity score (CAS). 1 point is given for each item present.

Sign of inflammation	Point for each item	Symptom
Pain	1	Painful, oppressive feeling on or behind the globe, during the last 4 weeks
	1	Pain on attempted up, side, or down gaze, during the last 4 weeks
Redness	1	Redness of the eyelid(s)
	1	Diffuse redness of the conjunctiva, covering at least one quadrant
Swelling	1	Swelling of the eyelid(s)
	1	Chemosis
	1	Swollen caruncle
Impaired function	1	Increase of proptosis of ≥ 2 mm during a period of 1–3 months
	1	Decrease of eye movements in any direction $\geq 5^\circ$ during a period of 1–3 months
	1	Decrease of visual acuity of ≥ 1 line(s) on the Snellen chart (using a pinhole) during a period of 1–3 months

TABLE 3 NOSPECS classification for ocular changes in thyroid eye disease.

Class	Grade	Signs
0		No signs or symptoms
1		Only signs
2		Soft tissue involvement, with symptoms and signs
	o	Absent
	a	Minimal
	b	Moderate
	c	Marked
3		Proptosis
	o	<23 mm
	a	23–24 mm
	b	25–27 mm
	c	≥ 28 mm
4		Extraocular muscle involvement
	o	Absent
	a	Limitation of motion in extremes of gaze
	b	Evident restriction of motion
	c	Fixation of a globe or globes
5		Corneal involvement
	o	Absent
	a	Stippling of cornea
	b	Ulceration
	c	Clouding, necrosis, perforation
6		Sight loss (visual acuity [†])
	o	>0.67
	a	0.67–0.33
	b	0.33–0.10
	c	<0.10

Note. Adapted from Mourits *et al.*,³¹ modified slightly from classification of Werner.³²

†Expressed as a decimal, i.e. 20/20 = 1.0, 20/30 = 0.67, 20/60 = 0.33, 20/200 = 0.10.

In general, patients improved clinically and exhibited improvements in the Clinical Activity Score (CAS) of the disease^{2,31} and NOSPECS score of disease severity.^{32,33} The CAS and NOSPECS activity measures are summarised in Table 2 and Table 3, respectively.

CAS was designed as a disease activity measurement to distinguish between patients with active ophthalmopathy who may respond to immunosuppressive treatment and patients with fibrotic end stage disease who do not.³¹ Mourits *et al.* used four of the five well-known classical signs of inflammation (pain, redness, swelling, and impaired function) to develop the CAS, which is composed of 10 items. This scoring system was tested in a prospective, double-blind trial of 43 patients with moderate to severe Graves ophthalmopathy treated with prednisone or retrobulbar irradiation. NOSPECS classification was used as a comparison. Using a CAS cut-off point of ≥ 4 , the CAS carried 86% specificity and 55% sensitivity in predicting whether patients had a favourable response to immunosuppressive therapy. Positive predictive value was 80%, and negative predictive value was 64%. NOSPECS is a disease activity measure as an acronym named after its components: N=No signs or symptoms, O=Only signs, S=Soft tissue involvement, P=Proptosis, E=Extraocular muscle involvement, C=Corneal involvement, S=Sight loss.³³ This disease activity scoring system was first published in 1969 and then modified in 1977.³² NOSPECS has been used to assess TED, although it has not been validated in large populations.

Of seven patients with TED in a study reported by Salvi *et al.*, all had significant improvement in proptosis and CAS, with follow-up ranging from 5 to 18 months. Proptosis, degree of inflammation, and motility impairment all improved after the use of rituximab, and none of the patients experienced relapse during follow-up. Rituximab did not appear to have an effect on hypothyroidism. Although available data vary with regard to the effects of rituximab on hyperthyroidism,^{24,28,34} beneficial effects may be limited to patients with relapsing GD and mild hyperthyroidism.³⁵

Three studies investigating the effects of rituximab on GD have been completed, of which two were

targeted specifically for patients with TED.^{30,36,37} One of these studies has published outcomes and was conducted by Silkiss *et al.* as a prospective, open-label, interventional clinical trial evaluating 12 patients with GD reported TED.³⁰ The authors reported no change in thyroid-stimulating immunoglobulin or thyroid-stimulating hormone levels. However, a statistically significant improvement in CAS scores was observed at each of the monthly visits over a 1-year follow-up.³⁰ Controlled trials involving the use of rituximab use in TED are currently ongoing, with mixed preliminary results. Publication of detailed results from these investigations is still pending.

Although most of the cases identified in the literature show favourable effects of rituximab on TED, one case report describes worsening of TED in a patient who received rituximab after having failed corticosteroid treatment. Despite achieving B-cell depletion, the patient's condition worsened, resulting in compressive optic neuropathy. He had corneal ulceration, an afferent pupillary defect, colour desaturation, papilloedema, and visual acuity 2/10 in the left eye. An urgent three-wall orbital decompression improved the ophthalmopathy significantly.²⁶

Rituximab has been generally well tolerated by patients with GD. However, based on limited evidence, rituximab may cause or aggravate inflammatory bowel disease such as ulcerative colitis.³⁸ Additionally, arthralgias thought to be due to circulating immune complexes have been reported.³⁹ However, the more common side effects observed in these patients are usually infusion related and may include hypotension.³⁹ Although most monoclonal antibodies can potentially cause a cytokine-mediated infusion reaction, a high-sensitivity reaction has occurred in up to 77% of patients receiving a first infusion of rituximab for non-Hodgkin lymphoma.⁴⁰ The incidence of high-sensitivity reactions decreased with subsequent infusions, and premedication is recommended to minimise this occurrence. Most adverse events are mild to moderate and self-limiting. The most common related events observed during the treatment period (including 30 days of follow-up) include transient fever (30% of patients), chills (23%), asthenia (23%), and pruritis (20%). Infusion-related events (on the infusion day) include fever, chills, pain, and throat irritation that usually resolve in less than 1 week without treatment or without interrupting the infusion.⁴¹ Infections are generally mild to moderate and do not commonly require hospitalisation.⁴¹

CONCLUSION

Both GD and TED itself are consequences of an autoimmune process, with antibodies playing a central role in pathogenesis. As a result, rituximab is an attractive alternative to the currently limited

treatment options for TED. Results are variable with regard to the value of rituximab as treatment for thyroid disease.^{20,22,23} However, as reviewed here, preliminary outcomes of rituximab use in TED are favourable and warrant larger studies to determine its long-term effectiveness in TED. Additionally, investigations are needed to lend insight into the optimal dosing and use of rituximab in disease that is refractory to current standard therapies.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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