Rituximab appears to have a significant effect on thyroid eye disease that requires further randomized controlled studies

Silkiss RZ, Reier A, Coleman M, Lauer SA. Rituximab for Thyroid Eye Disease. Ophthal Plast Reconstr Surg 2010. DOI: 10.1097/IOP.0b013e3181c4dfde

SUMMARY

BACKGROUND

The medical treatment of thyroid eye disease (TED) continues to be problematic. Glucocorticoid therapy provides acute control of periocular inflammation and long-term or high-dose glucocorticoid therapy is effective but associated with systemic side effects. Regional external beam radiotherapy may improve extraocular motility impairment, but efficacy in the improvement of diplopia, proptosis, eyelid fissure height, and eyelid swelling has not been established as the best therapy for this disorder. If at all possible, medical therapy should prevent progression of the disease or control acute and long term inflammation, with a favorable safety profile. Immunobiologic therapy that targets specific components of the immune system with genetically engineered monoclonal antibodies may provide acute and long-term efficacy and a safe form of therapy. Rituximab is an intravenously administered chimeric mouse-human monoclonal antibody that targets the CD20 antigen on pre-B and mature B lymphocytes. Hematopoietic stem cells, pro-B cells and normal plasma cells do not express the CD20 antigen, thus rituximab does not induce significant immunosuppression. The Food and Drug Administration approved rituximab in 1997 for the treatment of B-cell non-Hodgkin lymphoma, and in 2006 it was approved for the treatment of rheumatoid arthritis and is now being studied as a possible treatment for a number of other autoimmune diseases. Limited information has suggested that rituximab results in B cell depletion in the thyroid gland of patients with Graves' disease, and a study of the decline in production of specific thyroid stimulating autoantibodies has been reported.

This is a prospective, open-label, interventional clinical trial study that reports the results of a phase I/II safety and efficacy trial of 12 patients treated with rituximab for TED and their 1-year posttreatment clinical course.

PATIENTS AND METHODS

This is a 2-center study registered as Clinicaltrials.Gov number NCT00424151, which recruited patients 18 years of age or older with relevant orbitopathy and Clinical Activity Scores (CAS) of 4 or greater. The demographic data that were collected comprised patient sex, age laterality of the orbitopathy (1 or 2 eyes), ethnicity, and smoking status at the time of presentation, with serum autoantibody levels including thyroid stimulating immunoglobulin (TSI) >125, thyrotropin (TSH) receptor antibody, or antithyroid peroxidase antibodies. Patients were required to have active ophthalmopathy not reversible with short-term glucocorticoid therapy and were offered rituximab as an alternative to long-term glucocorticoid therapy, radiation therapy, or surgery, and were required to have negative serology for hepatitis B, and C, and HIV. The exclusion criteria were hematologic abnormalities, a history of malignancy, psychiatric disorders, cardiac or pulmonary disease, pregnancy, or active lactation. Patients had pretreatment ophthalmic and systemic evaluation exophthalmometer examination. The severity of disease activity or thyroid –associated ophthalmopathy was evaluated by CAS and the Thyroid Associated Ophthalmopathy Scale (TAOS). The CAS scale used a scale of 0 to 8, based on 5 items: orbital pain, chemosis, edema, conjunctival and eyelid injection. The TAOS scoring was also used to quantify the effect of treatment. This scoring system assesses orbital pain, chemosis, eyelid edema, conjunctival injection, and eyelid injection on a scale of 0 to 2, and total scores from these 5 items range from 10 to 10). Hematologic and serologic data were collected at week 0 (pretreatment baseline, 4, 8, 16, 24, 36, and 52 weeks after the second infusion of rituximab.

RESULTS

The mean age of the 12 patients that entered into the study was 52.1 years (range 34 to 80), 5 (41.7%) were men and 7 (58.3%) were women, 7 (58.3%) were white, 5 (41.7%) were Hispanic, 4 (33%) were smokers, 1 (8%) had unilateral and 11 (91.7%) had bilateral orbitopathy. Hyperthyroidism was present for 1 year or less in 7 patients, 2 to3 years in 2 patients, and 4 years in 1 patient, and 1 was euthyroid. Seven were treated with oral thyroid suppression (propylthiouracil, methimazole, or Cytomel, and 2 patients did not require treatment for hyperthyroidism, and none had pretibial myxedema.

Twelve patients with active TED were treated with 2 courses of rituximab over a 2-week period, and there were no adverse effects of the rituximab infusions and no reported side effects during the 1-year post infusion observation period.

The mean exophthalmometer reading was 20.16 mm (range 15 to 31), palpable fissure was 11 mm (range 8 to 16), and the degree of diplopia was none in 7 patients (58.3%), minimal in 1 (8.3%), moderate in none, and severe in 4 patients (33%). Symptomatic keratopathy was present in 5 patients (41.7%) and absent in 7 (58.3) patients. Visual acuity based on a Snellen chart was 20/20 in 14 patients (58.3%), 20/25 to 20/30 in 7 (29%), 20/40 to 20/60 in 2 (8.3%) and one patients had CF (count fingers). The mean Hertel reading was 20.16 mm, (range 8 to 16).

The mean CAS score was 5.5, with a median baseline score of 5.3, and there were statistically significant decreases from baseline for weeks 4,8,16, 24, 36, and 52 ($P<0.01$). The mean decreases ranged from –2.3 to –4.7, and the median decreases ranged from –2.5 to –4.5, *(Figure 1)*.

The mean baseline TAOS score was 10.4, (median baseline score 9.0), and there were statistically significant decreases from baseline for weeks 4,8,16, 24, 36, and 52 ($P<0.05$). The mean decreases ranged from –3.3 to –8.0, with a median range of –3.0 to –6.5 *(Figure 2)*.

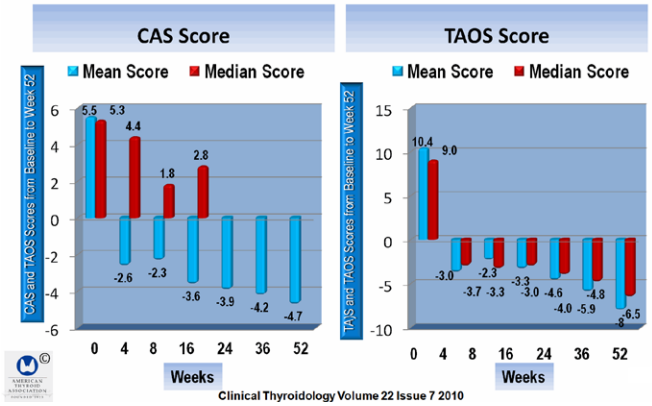

Figure 1.

The mean baseline TSI score was 251.3%, with a median score of 214.0% but there were no statistically significant changes from baseline at any of the follow-up visits

The mean baseline TSH score was 3.45 IUm/L with a median baseline score of 1.11 IUm/L. There were no statistically significant changes from baseline at any of the follow-up visits (P>0.05) CD 19 levels started to increase 36 weeks post infusion. CD19 levels started to increase 36 weeks post infusion, but the changes were minimal.

CONCLUSION

Twelve patients with active TED were treated with 2 courses of rituximab over a 2-week period. There were no adverse effects of the rituximab infusions and no reported side effects during 1year after the infusion of the drug. There was a significant improvement in CAS scores that was observed 1 month after infusion of rituximab that was sustained throughout the 12-month observation period.

COMMENTARY

This is a relatively small study that suggests rituximab, an anti-CD20 monoclonal antibody, given over a 2-week period has no obvious adverse effects during 1-year post-perfusion period, and CAS scores that were observed within a month of rituximab infusions that appears to persist for 1-year.

Several studies support research on rituximab for Graves' disease. A prospective controlled, nonrandomized study by El Fassi et.al (1) that was published in 2007 studied 20 patients with newly diagnosed Graves' disease, 10 of which received 375 mg of rituximab, and 10 did not receive the drug. Four patients in the rituximab group remained in remission with a median follow-up of 705 d (range, 435-904 d), whereas all the patients not in the rituximab group had relapsed by d 393 (P < 0.05). All of the patients in remission had initial TRAb levels below 5 IU/liter (normal, <0.7 IU/liter); whereas none of the five patients not treated with rituximab had correspondingly low TRAb levels were in remission (P< 0.01). The group that was treated with rituximab did not have an affect on autoantibody levels to a greater extent than did MMI monotherapy. The conclusion of the study was that rituximab therapy may induce sustained remission in patients with Graves' disease with low TRAb levels. However, the fact that the rituximab did not affect autoantibody levels seemed to suggest the drug is ineffective in patients with high TRAb levels. The concluded that at present, high cost, low efficacy, and potential side effects do not support use of rituximab in uncomplicated Graves' disease

Hasselbalch et.al (2) suggested that B-cell depletion with rituximab may be a targeted therapy for Graves' disease and autoimmune thyroiditis. Salvi (3) studied a patient with Graves' disease with hyperthyroidism and ophthalmopathy that was unresponsive to steroid and was thus treated with rituximab. The ophthalmopathy responded to rituximab therapy by ameliorating the eye signs with a decrease in the CAS score from 5 to 2 in 3 months, while the patient had peripheral B-cell depletion. However hyperthyroidism did not improve during the 6 months of B-cell depletion and serum TSH-receptor antibodies (TRAb) levels did not significantly change after rituximab therapy. They concluded that the persistence of Graves' hyperthyroidism suggests that a single cycle of rituximab does no result in complete lymphocyte depletion in thyroid tissue and this no decline in serum TRAB was observed.

A prospective, 26-week phase II study by Heemstra et.al(4) of 13 patients with relapsing Graves' disease (9 females and 4 males, age 39.5 ± 9.5 years, received 2 dosages of rituximab, 1000 mg intravenously with a 2-week interval. Before administration and on several periods after the administration of TSH, free thyroxine (FT4), thyrotropin binding inhibitory immunoglobulins (TBII) and the proportion of CD19 and MS4A1-positive peripheral blood mononuclear cells were measured. The proportion of MS4A1-positive lymphocytes decreased in all the patients from 5.8% at baseline to 1.4% at 26 weeks (P=0.007). Four patients with high initial FT4 levels did not respond to treatment. The remaining patients all had a decrease in FT4 levels at 26 weeks (P=0.001) and an increase in TSH levels (P=0.011). Thyroid binding immunoglobulin (TBII) decreased in all the remaining patients (P=0.003). At a 14 to 27 month follow-up, nine of the patients were still euthyroid with normal FT4 (P<0.001) and TSH levels (P=0.008). The authors concluded that the study results suggest a beneficial role of rituximab in mild relapsing Graves' disease. A subsequent randomized controlled trial with rituximab was recommended.

In conclusion, rituximab appears to be a drug with promise, but requires larger prospective randomized studies to settle the differences reported in the literature.

— Ernest L. Mazzaferri, MD, MACP

References

1. El Fassi D, Nielsen CH, Bonnema SJ et al. B lymphocyte depletion with the monoclonal antibody rituximab in Graves' disease: a controlled pilot study. J Clin Endocrinol Metab 2007;92:1769-72.

2. Hasselbalch HC. B-cell depletion with rituximab-a targeted therapy for Graves' disease and autoimmune thyroiditis. Immunol Lett 2003;88:85-6.

3. Salvi M, Vannucchi G, Campi I et al. Efficacy of rituximab treatment for thyroid-associated ophthalmopathy as a result of intraorbital B-cell depletion in one patient unresponsive to steroid immunosuppression. Eur J Endocrinol 2006;154:511-7.

4. Heemstra KA, Toes RE, Sepers J et al. Rituximab in relapsing Graves' disease, a phase II study. Eur J Endocrinol 2008;159:609-15.