Topic: NEW IMMUNO-MODULATORS FOR GRAVES’ DISEASE

Title: Rituximab in relapsing Graves' disease, a phase II study.

Authors: Heemstra KA, Toes RE, Sepers J, Pereira AM, Corssmit EP, Huizinga TW, Romijn JA, & Smit JM (Leiden, Netherlands)


SUMMARY

Objective & Design: Conventional therapies for Graves' disease (GD), consisting of medical therapy or radioiodine are unsatisfactory, because of limited efficacy & adverse events. Interventions aiming at the underlying autoimmune pathogenesis of GD may be worthwhile to explore. The authors performed a prospective, 26-week phase II study with open-ended observational extension to assess the efficacy of rituximab in patients with recurrent GD.

Methods: Thirteen patients with relapsing GD (9 females & 4 males, age 39.5 ± 9.5 years) received 2 dosages of rituximab (1,000 mg iv) with a 2-week interval. Before administration and on several periods after the administration, serum TSH, free T4, TBII and the proportion of CD19 and MS4A1 positive peripheral blood mononuclear cells were measured.

Results: The proportion of MS4A1 positive lymphocytes decreased in all 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. All remaining patients had a decrease in FT4 levels at 26 weeks (P=0.001) and an increase in TSH (P=0.011). TBII decreased in all remaining patients (P=0.003). At a follow-up time of 14-27 months, nine of these patients were still euthyroid with normal FT4 (P<0.001) and TSH levels (P=0.008).

Conclusions: Present results suggest a beneficial role of rituximab in mild relapsing GD. A subsequent randomized controlled trial with rituximab is recommended.

COMMENT

Graves’ disease (GD) is a B-cell driven organ specific autoimmune disease. The question is therefore: is it possible to deplete the B-lymphocyte population to treat GD more rationally (and perhaps also more efficiently) than with our classical therapeutic approaches, which have been used since more than half a century in such patients? Rituximab (RTX) is a chimeric mouse-human IGg1 (kappa type) monoclonal antibody specific for MS4A1, an antigen highly expressed on pre-B lymphocytes as well as on mature B lymphocytes. Thus, this antibody is directed against a surface phosphoprotein on CD20+ B lymphocytes. When RTX is fixed on CD20+ B lymphocytes, the antibody induces progressive white cell lysis and blocks B lymphocyte activation, thereby decreasing, in turn, autoantibody production (measured as TBII in this study). RTX has been used with success in various autoimmune diseases, namely lupus, thrombocytic purpura, hemolytic anemia, & rhumatoid arthritis. In thyroid diseases, RTX was first used with success in a few patients to treat Graves’ ophthalmopathy (El Fassi, Thyroid 2006; Salvi, Eur J Endocrinol 2007) In the present work, the authors report the results of a phase II pilot trial with RTX in
patients with relapsing GD. In cases with severe hyperthyroidism, RTX administration did not work. However, the majority of the mildly relapsing GD patients treated with RTX remained euthyroid 1-2 years after treatment, with a clear decrease in TBII titers, a positive and encouraging result. One of the additional difficulties was that the decrease in CD20+ B lymphocytes was not correlated with patient’s outcome, probably because peripheral lymphocytes do not provide a reliable index for what happens within the thyroid gland, thus making the selection of patients for such treatment hazardous.

In summary, as stated by the authors in their conclusions, there is a need for a controlled, larger prospective randomized trial with RTX before drawing clinically meaningful conclusions. However, the rational use of immuno-modulators in autoimmune diseases appears certainly as an interesting road to be pursued.

PS: Readers interested by this topic should read the editorial by Patrice Rodien (Eur. J. Endocrinol. 159:515,2008) and an excellent review article by C. Josseaume (Annales d’Endocrinologie 69:S29,2008). (Daniel Glinoer, M.D.; Ph.D.)

See Figures below