SUMMARY

Aim and methods: The authors performed a retrospective analysis of serum thyrotropin receptor antibody (TRAb) concentrations in 58 patients with Graves’ disease (GD) at the onset of the disease, at the end of 18 month with methimazole (MMI) treatment, and after MMI withdrawal in order to evaluate the correlation between the presence of these antibodies and the relapse of hyperthyroidism. Sixty healthy subjects were enrolled as a control group.

Results: Before MMI treatment, the best cut-off TRAb value for identifying patients with GD was 1.45 UI/L (specificity 100%; sensitivity 98.3%). At the end of MMI treatment, serum TRAb concentrations were significantly lower than those measured at baseline, but they were still significantly higher than those found in the control subjects. At the end of MMI treatment, 44 patients (75.9%) had positive TRAb values (>1.45 UI/L). After MMI withdrawal (median of 15 months), 34 patients (58.6%) became hyperthyroid, 4 patients (6.9%) became hypothyroid, and 20 patients (34.5%) remained euthyroid. There was a significant correlation between serum TRAb concentrations at the end of treatment and the percentage of patients who became hyperthyroid and the time of appearance of hyperthyroidism. All 4 patients with TRAb values below 0.9 UI/L at the end of MMI treatment remained euthyroid throughout the follow-up period. Among the 27 patients who had serum TRAb values higher than 4.4 UI/L, 23 developed hyperthyroidism and 4 hypothyroidism. The TRAb values between 0.9 and 4.4 UI/L did not discriminate between the 27 patients (46.6%) who remained euthyroid from those who had relapse of hyperthyroidism. Thus a different TRAb cut-off at the end of treatment was calculated to identify patients who became again hyperthyroid. This TRAb cut-off value was 3.85 UI/L (sensitivity 85.3%; specificity 96.5%). All but 1 patient who had serum TRAb values above 3.85 UI/L became hyperthyroid after MMI was withdrawn (positive predictive value 96.7%). In these patients, relapse of hyperthyroidism was independent of the changes in serum TRAb concentrations and occurred after a median period of 8 weeks (range 4-48 weeks). Hyperthyroidism also developed in 5 of 24 patients who had serum TRAb concentrations lower than 3.85 UI/L at the end of MMI treatment. In these 5 patients the relapse of hyperthyroidism occurred after a median period of 56 weeks (range 24-120 weeks) and was always accompanied by an increase in serum TRAb concentrations.

Conclusions: TRAb persist in the blood of most patients with GD after 18 months of MMI treatment. Both the frequency and the time of appearance of hyperthyroidism are closely correlated with serum TRAb concentrations at the end of MMI treatment. Our data would suggest that TRAb maintain stimulating activity after a full course of MMI treatment in the large majority of patients with GD. However, it is likely that the potency of these antibodies and/or the thyroid response to them change during treatment, as suggested by the different values measured in euthyroid control subjects and in euthyroid patients after MMI treatment.
COMMENT

Present investigation is a retrospective study of 58 patients with newly diagnosed Graves’ disease (GD) treated with a full course of antithyroid drugs (ATD). The study shows that TRAb persists in most patients and that the time of recurrence of hyperthyroidism is closely correlated with serum TRAb values at the end of MMI treatment. At the end of MMI treatment, mean serum TRAb was 4.4 UI/L (i.e. 3-fold lower than values at diagnosis), still significantly higher than in control subjects. Furthermore, 76% of patients still had a positive TRAb value (> 1.45 UI/L). There was a significant correlation between TRAb value at the end of MMI and recurrence of hyperthyroidism (in 59%) and development of hypothyroidism (in 7%).

See Figures below

In this study, the TRAb radioreceptor assay that was used did not permit discrimination between stimulating, blocking or neutral antibodies. However, the data suggest that the antibodies maintain stimulating activity after a full course of MMI treatment in a majority of patients. Because most remitting patients and approximately 1/3 of those with a relapse had TRAb values overlapping the ‘normal range’ at the end of MMI treatment, the authors conclude that measurement of these antibodies is not useful in predicting the clinical course after MMI withdrawal. However, they also indicate that persistence of TRAb in the blood of patients with GD, after ATD therapy has been discontinued, may play a role in the relapse of hyperthyroidism, especially in patients who maintain a TRAb value above 4.4 UI/L.

(Daniel Glinoer MD, PhD)