MINI REVIEW

Remission of Graves' disease during anti-thyroid drug therapy. Time to reconsider the mechanism?

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Abstract

Therapy of Graves' hyperthyroidism with thionamide anti-thyroid drugs is accompanied by a gradual remission of the autoimmune aberration in the majority of patients. The most likely mechanism behind this remission has been considered to be a direct immunosuppressive effect of thionamide drugs. However, a number of findings in clinical studies of patients with Graves' disease indicate that remission is probably not caused by a special effect of thionamide drugs. Many studies have shown that remission is linked to restoration of the euthyroid state, and that it is independent of drug dose and type. Moreover, similar remission is observed when patients become euthyroid after thyroid surgery. In an explanatory model described, it is assumed that the autoimmune aberration of Graves' disease is often basically quit mild and self-limiting. Patients may become ill by the running of a vicious cycle of hyperthyroidism worsening the autoimmunity, and autoimmunity worsening the hyperthyroidism. Once patients are made euthyroid by one or the other drug or by thyroid surgery, the majority of patients will gradually enter remission of the disease. The conclusion that remission is associated with restoration of the euthyroid state, and that it is not a special drug effect, highlights the importance of making and keeping patients with Graves' disease euthyroid.

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Graves' disease is a common disorder having autoimmunity against the thyroid-stimulating hormone (TSH) receptor as the central pathogenetic element. The disease may have a number of clinical manifestations, the most common being thyrotoxicosis caused by generation of TSH receptor activating autoantibodies (Graves' hyperthyroidism).

Graves' hyperthyroidism may be treated by anti-thyroid drugs, either alone or in combination with other treatment modalities. The two drugs in common use (methimazole (MMI) or its pro-drug carbimazole, and propylthiouracil (PTU)) are both thionamides and they exert their anti-thyroid effect by inhibition of thyroid peroxidase catalysed synthesis of thyroid hormones. Thereby, thyroid hormone secretion gradually diminishes, and the patient becomes euthyroid.

Similar to other autoimmune diseases, Graves' disease may fluctuate in activity, and patients may occasionally enter remission without any specific therapy being given (1). Such spontaneous remission may be one reason that a fraction of patients treated with MMI or PTU for a period of time, remain euthyroid after stop of medication. However, already more than 20 years ago, evidence accumulated that treatment with anti-thyroid drugs was accompanied by remission of Graves' disease beyond the natural history of the autoimmune aberration (2–7).

The mechanism behind the remission was suggested to be a direct immunosuppressive action of the thionamide drugs (5), and this is still considered to be the most likely mechanism (8). This hypothesis is supported by many *in vitro* experiments showing direct effects of thionamide drugs on the immune system (8). The hypothesis explains why Graves' disease tends to enter remission during anti-thyroid drug therapy, and also why a considerable proportion of patients experience relapse of the disease after stopping medication.

However, over the years, experience has accumulated from clinical studies of patients with Graves' hyperthyroidism that does not fit the immunosuppressive hypothesis (Table 1).

The first study to question seriously the correctness of the immunosuppressive hypothesis was published by Wenzel and Lente (9). In a longitudinal study of patients with Graves' hyperthyroidism, they found similar remission of Graves' disease during therapy with thionamides and with perchlorate. Remission as evaluated by the average fall in thyroid stimulating immunoglobulins in serum is shown in Figure 1, panel A. The authors concluded that similar immunosuppressive actions by the two classes of drugs (thionamides and perchlorate) could not be ruled out, but that this was unlikely. More likely, the remission was linked to restoration of immunological regulation as the patients

Table 1 Findings in clinical studies on the remission of Graves' disease during anti-thyroid drug therapy.

1. Remission is independent of the type of drug (methimazole, propylthiouracil, and perchlorate)
2. The fall in TSH receptor antibodies in blood is similar whether the patient is made euthyroid by drugs or by surgical therapy
3. Remission follows euthyroidism independent of drug dose
4. Remission is independent of the additional use of levothyroxine

TSH, thyroid-stimulating hormone.

became euthyroid again. Such a mechanism had previously been argued for by Volpe (10). Perchlorate has some effects on the immune system (8), but is not likely that such effects would lead to exactly the same fall in TSH receptor antibodies as observed during MMI therapy (Fig. 1, panel A).

Another important study suggesting that remission is not a specific drug effect was published by Torring *et al.* (11). In a prospective randomized study of patients with Graves' hyperthyroidism, they observed similar rates of remission of Graves' disease in patients made euthyroid by anti-thyroid drugs and by subtotal thyroidectomy followed by levothyroxine replacement (Fig. 1, panel B). This finding supports that remission of Graves' disease is linked to euthyroidism, and not to the administration of

anti-thyroid drugs. Thyroid surgery removes both thyroid antigens and thyroidal lymphocytes, and it leads to an acute release of antigens into the circulation. It is likely that such changes would alter the autoimmune aberration of Graves' disease. It is, however, not to be expected that the fall in TSH receptor antibodies caused by such mechanisms would be nearly identical to the fall observed during therapy with anti-thyroid drugs (Fig. 1, panel B).

If remission of Graves' disease during anti-thyroid drug therapy was caused by an immunosuppressive effect of the drugs, it would be expected that the use of higher doses of drugs would lead to a more rapid and probably more sustained remission of the disease. Such an effect was proposed by Romaldini *et al.* (12) based on preliminary studies. Subsequently, a number of prospective randomized studies have been performed to elucidate the putative dose response effect of thionamides on remission of Graves' disease. Some of the studies have been designed to evaluate another hypothesis as well. That is the hypothesis set forward by Hashizume *et al.* (13) who published that the administration of levothyroxine may prevent relapse of Graves' hyperthyroidism after stop of treatment with anti-thyroid drugs. In a recent comprehensive review, including

Figure 1 Results of studies indicating that remission of Graves' disease is not a special effect of thionamide drugs. (A) The fall in thyroid-stimulating hormone (TSH) receptor antibodies in serum is similar during therapy of Graves' hyperthyroidism with methimazole ($n=13$) and perchlorate ($n=18$). Curves are mean curves calculated from data published by Lente and Wenzel (9). TSH receptor antibodies were determined by a bioassay using human thyroid cells. The response to thyroid-stimulating immunoglobulins (TSI) in test sera was compared with the response to pooled normal human serum. (B) The fall in TSH receptor antibodies (TR-Ab) in serum is similar during therapy with a thionamide drug ($n=59$) and after subtotal thyroidectomy followed by L-thyroxine replacement ($n=65$). TR-Ab was measured by a competitive inhibition assay. Curves are tendency lines of mean values published by Torring *et al.* (11) as previously described (21). Dotted horizontal lines indicate upper reference range for the assay.

meta-analyses of randomized controlled trials, Abraham *et al.* (14) concluded that neither the dose of thionamide drug nor the use of additional levothyroxine had any importance for the remission of Graves' disease during drug therapy or for the risk of relapse after stop of drugs.

It might be speculated, that thionamide drugs exert their maximal *in vivo* immunosuppressive effects already at very low doses, and that this is the cause for the lack of dose-response in clinical studies. Still, this lack of dose effect is another argument that remission of Graves' disease during anti-thyroid drug therapy is not caused by an immunosuppressive effect of the drugs, but that remission is linked to restoration of euthyroidism.

Hyperthyroidism has a series of effects on the immune system and on the interaction between thyroid antigens and the immune system. As discussed by Volpe (15), such effects may worsen the autoimmune aberration of Graves' disease. A simplified model of remission of Graves' disease is shown in Figure 2. In this explanatory model, it is assumed that the autoimmune aberration of Graves' disease is often basically quite mild and self-limiting, with a high tendency to enter remission. The reason that many patients become rather severely ill and that they do not enter remission is that a self-enhancing cycle starts running. In this vicious cycle, hyperthyroidism leads to worsening of the autoimmune aberration, and autoimmunity leads to generation of more TSH receptor antibodies and worsening of the hyperthyroidism. Once that cycle is broken by making the patient euthyroid by

one or the other drug or by surgery, most patients will gradually experience remission of the disease. Euthyroidism caused by radioiodine destruction of the thyroid gland is different, because radioiodine therapy has a particular direct effect on thyroid autoimmunity (16).

Autoimmunity is complex and the model described may well turn out to be too simple. On the other hand, it is important for optimal therapy of hyperthyroidism to consider whether remission during anti-thyroid drug therapy is caused by a direct immunosuppressive effect of the drugs or reestablishment of the euthyroid state of the patient. The former hypothesis suggests that the use of higher doses of drugs may be of benefit. As discussed, this idea has turned out to be a dead end. It only leads to more side effects of the drugs (8, 14).

Acceptance of the latter mechanism highlights the importance of making and keeping the patient with Graves' disease euthyroid. This may occasionally include more prolonged use of MMI. To minimize the risk of side effects, the lowest possible dose of the drug should be used. Several investigators have reported that such therapy may prevent relapse of overt Graves' disease (17–20). One mechanism behind such a protective effect of low dose MMI therapy may be a decrease in the risk of reactivation of the vicious cycle illustrated in Figure 2. An additional possibility would be that the risk of relapse is diminished by keeping thyroid iodine content low, as discussed in a previous article (21).

Figure 2 Illustration of the hypothesis that remission of Graves' disease during therapy is linked to restoration of immunological regulation as the patient becomes euthyroid again (15). It is assumed that Graves' disease has a high tendency to spontaneous remission in most patients. However, remission is hindered by the running of a vicious cycle: the hyperthyroid state worsens the autoimmune aberration that leads to generation of more TSH receptor-stimulating antibodies (TSH-R-Ab), etc. The cycle is broken when the patient is made euthyroid by drugs or surgery, and this is followed by a gradual remission in the majority of patients. The figure is modified from Laurberg *et al.* (21).

References

- Codaccioni JL, Orgiazzi J, Blanc P, Pugeat M, Roulier R & Carayon P. Lasting remissions in patients treated for Graves' hyperthyroidism with propranolol alone: a pattern of spontaneous evolution of the disease. *Journal of Clinical Endocrinology and Metabolism* 1988 **67** 656–662.
- Pinchera A, Liberti P, Martino E, Fenzi GF, Grasso L, Rovis L, Baschieri L & Doria G. Effects of antithyroid therapy on the long-acting thyroid stimulator and the antithyroglobulin antibodies. *Journal of Clinical Endocrinology and Metabolism* 1969 **29** 231–238.
- Schleusener H, Finke R, Kotulla P, Wenzel KW, Meinhold H & Roedler HD. Determination of thyroid stimulating immunoglobulins (TSI) during the course of Graves' disease. A reliable indicator for remission and persistence of this disease? *Journal of Endocrinological Investigation* 1978 **1** 155–161.
- Fenzi GF, Hashizume K, Roudeboush CP & DeGroot LJ. Changes in thyroid-stimulating immunoglobulins during antithyroid therapy. *Journal of Clinical Endocrinology and Metabolism* 1979 **48** 706.
- McGregor AM, Petersen MM, McLachlan SM, Rooke P, Smith BR & Hall R. Carbimazole and the autoimmune response in Graves' disease. *New England Journal of Medicine* 1980 **7** 302–307.
- Docter R, Bos G, Visser TJ & Hennemann G. Thyrotrophin binding inhibiting immunoglobulins in Graves' disease before, during and after antithyroid therapy, and its relation to long-acting thyroid stimulator. *Clinical Endocrinology* 1980 **12** 143–153.
- Bech K & Madsen SN. Influence of treatment with radioiodine and propylthiouracil on thyroid stimulating immunoglobulins in Graves' disease. *Clinical Endocrinology* 1980 **13** 417.
- Cooper DS. Antithyroid drugs. *New England Journal of Medicine* 2005 **3** 905–917.
- Wenzel KW & Lente JR. Similar effects of thionamide drugs and perchlorate on thyroid-stimulating immunoglobulins in Graves' disease: evidence against an immunosuppressive action of thionamide drugs. *Journal of Clinical Endocrinology and Metabolism* 1984 **58** 62–69.
- Volpé R. The pathogenesis of Graves' disease: an overview. *Clinics in Endocrinology and Metabolism* 1978 **7** 3–29.
- Torring O, Tallstedt L, Wallin G, Lundell G, Ljunggren JG, Taube A, Saaf M & Hamberger B. Graves' hyperthyroidism: treatment with antithyroid drugs, surgery, or radio iodine – a prospective, randomized study. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 2986–2993.
- Romaldini JH, Bromberg N, Werner RS, Tanaka LM, Rodrigues HF, Werner MC, Farah CS & Reis LC. Comparison of effects of high and low dosage regimens of antithyroid drugs in the management of Graves' hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism* 1983 **57** 563–570.
- Hashizume K, Ichikawa K, Sakurai A, Suzuki S, Takeda T, Kobayashi M, Miyamoto T, Arai M & Nagasawa T. Administration of thyroxine in treated Graves' disease. Effects on the level of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. *New England Journal of Medicine* 1991 **4** 947–953.
- Abraham P, Avenell A, Park CM, Watson WA & Bevan JS. A systematic review of drug therapy for Graves' hyperthyroidism. *European Journal of Endocrinology* 2005 **153** 489–498.
- Volpe R. The immunomodulatory effects of anti-thyroid drugs are mediated via actions on thyroid cells, affecting thyrocyte-immunocyte signalling. *Current Pharmaceutical Design* 2001 **7** 451–460.
- Bonnema SJ, Bartalena L, Toft AD & Hegedus L. Controversies in radioiodine therapy: relation to ophthalmopathy, the possible radioprotective effect of antithyroid drugs, and use in large goitres. *European Journal of Endocrinology* 2002 **147** 1–11.
- Shizume K. Long term antithyroid drug therapy for intractable cases of Graves' disease. *Endocrinologia Japonica* 1978 **25** 377–379.
- Slingerland DW & Burrows BA. Long-term antithyroid treatment in hyperthyroidism. *Journal of the American Medical Association* 1979 **30** 2408–2410.
- Lippe BM, Landaw EM & Kaplan SA. Hyperthyroidism in children treated with long-term medical therapy: twenty-five percent remission every two years. *Journal of Clinical Endocrinology and Metabolism* 1987 **64** 1241–1245.
- Azizi F, Ataie L, Hedayati M, Mehrabi Y & Sheikholeslami F. Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine. *European Journal of Endocrinology* 2005 **152** 695–701.
- Laurberg P, Andersen S & Karmisholt J. Antithyroid drug therapy of Graves' hyperthyroidism: realistic goals and focus on evidence. *Expert Review of Endocrinology and Metabolism* 2006 **1** 91–102.

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