Medical Treatment of Hyperthyroidism: State of the Art

Author A. Fumarola, A. Di Fiore, M. Dainelli, G. Grani, A. Calvanese

Affiliation Dipartimento di Medicina Sperimentale, UOC Endocrinologia A, "Sapienza" Universitá di Roma, Rome, Italy

Key words
- Hyperthyroidism
- Graves' disease
- Thionamides

Abstract

Methimazole (MMI) and propylthiouracil (PTU) are the main antithyroid drugs used for hyperthyroidism. They inhibit the synthesis of thyroid hormone at various levels and are used as the primary treatment for hyperthyroidism or as a preparation before radioiodine therapy or thyroidectomy. MMI is the drug of choice because of its widespread availability, longer half-life and small number of severe side effects. Drugs of second choice are potassium perchlorate, beta blockers, iodine, lithium carbonate and glucocorticoids. Rituximab, a monoclonal antibody directed against human CD20, was recently proposed as a biological therapy for cases of Graves' disease unresponsive to traditional drugs.

Introduction

Hyperthyroidism is a commonly found endocrine pathology, with a prevalence of 2% in women and 0.2% in men, and an incidence of 20/1 000 000/year in general population, with a male/female ratio of 1/5–7 (Abraham et al., 2005; Dasgupta and Savage, 2005).

Causes of hyperthyroidism are Graves' disease, toxic multinodular goitre, solitary hyperfunctioning nodules, autoimmune postpartum, subacute thyroiditis, tumours that secrete thyrotropin, drug-induced thyroid dysfunction. However, the most prominent cause of hyperthyroidism in iodine-sufficient areas is Graves' disease (80% of all hyperthyroidism cases) (Abraham et al., 2005; Dasgupta and Savage, 2005; Streetman and Khanderia, 2003), while autonomous hyperfunctioning adenomas are more common in regions of iodine deficiency (Bauch, 1998; Iagaru and McDougall, 2007).

Graves' disease is characterised by an evident familial predisposition, with a peak of incidence between 20–40 yr, and by association with autoimmune pathologies such as thyroiditis, pernicious anemia and diabetes mellitus type 1 (Streetman and Khanderia, 2003). This illness has unknown autoimmune aetiology and is characterised by the presence of circulating antibodies that bind to the TSH receptor and activate it, stimulating the growth and the activity of thyroid cells. The positivity of such antibodies correlates with the disease state, both active and recurring (Streetman and Khanderia, 2003; Pearce and Braderman, 2004).

The aim of therapy is to monitor the condition of hyperthyroidism using medical, radioiodine or surgical treatment.

First Choice Antithyroid Drugs

Thionamides

Chemical and pharmacokinetic characteristics

The first-choice drugs used in the treatment of Graves' disease are thionamides. They include propylthiouracil (PTU), methimazole (MMI) and carbimazole (CBZ). The latter is rapidly metabolised into methimazole and has the same chemical and pharmacological properties (Streetman and Khanderia, 2003; Pearce and Braderman, 2004).

PTU and MMI are almost completely absorbed after oral administration, reaching their peak serum-concentration, dose-correlated, within 1–2 h after ingestion. Although both drugs are effective in controlling hyperthyroidism, MMI normalises thyroid activity more rapidly compared to PTU (Okamura et al., 1987; Homsanit et al., 2001). The half-life of MMI is 6–8 h and its action lasts 40 h. The half-life of PTU is 1–2 h and

received 30.11.2009
first decision 21.01.2010
accepted 15.02.2010

Bibliography
DOI http://dx.doi.org/10.1055/s-0030-1253420
Published online: 2010
Exp Clin Endocrinol Diabetes

ISSN 0947-7349

Correspondence
Prof. A. Fumarola
Dept. of Experimental Medicine
Sapienza Universitá di Roma
V. le Regina Elena, 324
00161 Rome
Italy
Tel.: + 39/06/4997 2094
Tel.: + 39/06/4997 2586
angela.fumarola@uniroma1.it

its action lasts 24 h (Streetman and Khanderia, 2003; Pearce and Braderman, 2004; Cooper, 2005). These drugs bind serum proteins differently: the MMI is more liposoluble and is free in the serum, while the 80–90 % of PTU is bound to albumin. Both drugs cross the placenta and are found in maternal milk at different concentrations (MMI/PTU = 4–7) (Streetman and Khanderia, 2003).

Pharmacodynamic characteristics

MMI and PTU are actively concentrated by the thyroid against a concentration gradient. Their primary effect is to inhibit the intra- and extra-thyroid hormonal synthesis.

Intra-thyroid effects

- Inhibition of iodide organification
- Inhibition of iodide incorporation in the thyrosine residues of thyroglobulin
- Inhibition of pairing of iodothyrosines

These effects are determined by inhibition of thyroid peroxidase action. This enzyme is a glycoprotein with a heme group fixed to the cellular membrane of the thyroid follicle on the luminal side. After the catching of iodide through NIS (NA + /I- symporter), that is organificated into iodine through an intermediated compound (TPO-Iox). Subsequently, this compound reacts with thyrosine residues of thyroglobulin to form monoiodothyrosine (MIT) and diiodothyrosine (DIT). From the pairing of one MIT and one DIT molecule derives triiodothyronine (T3), while from two DIT derive tetraiodthyronine or thyroxine (T4). Thionamides, with chemical structure similar to thyrosine residues, compete with them to bound to TPO-Iox, blocking the action of TPO and so the subsequent steps of hormone synthesis.

- Immunosoppressive effects. Several studies showed that antithyroid drugs can directly promote the apoptosis of intrathyroidal lymphocites (Mitsiades et al., 2000), and reduce the expression of HLA class-II molecules (Zantut-Wittmann et al., 2001), the number of activate T-cells and natural-killer cells (Wang et al., 1988). Moreover, it can be hypothesized that the thyroid-function normalization itself could be sufficient to reduce the immunological response (Volpé, 2001).

Extra-thyroid effects

- Inhibition of the conversion of T4 to T3, due to the blocking of deiodinase-type-1 action (Koenig, 2005). It has been reported that PTU, but not MMI, reacts with the selenenyl iodide intermediate of deiodinase-type-1 to form a selenenyl sulfide and thereupon blocking the conversion of T4 to T3 during the monodeiodination reaction (Roy and Mugesh, 2006).
- Inhibition of thyroid-hormone transcriptional effects, due to the impaired bound to T3 nuclear receptors and to the recruitment of co-suppressor, and/or to the dissociation of co-activators (Takagi et al., 1990).

Clinical use of thionamides

Antithyroid drugs can be used both in the primary treatment of hyperthyroidism (long-term therapy: 1–2 yr) and as a preparation for radiometabolic or surgical treatment (short-term therapy: weeks or months). The elective indication for pharmacological therapy are: mild or moderate hyperthyroidism, slight increase of gland volume, pediatric or adolescent age, pregnancy or breast-feeding, and ophtalmopathy that could be worsened by radiometabolic therapy (**Table 1**). On the contrary, the thyonamides are not generally considered drugs of first choice in hyperthyroid subjects with elevated probability of recurrence, such as patients with multinodular toxic goitre, autonomous nodule, voluminous goitre, persistently elevated levels of anti TSH-receptor antibodies (**Table 2**) (Cooper, 2005).

Table 1 Thionamide first-choice indications.

– mild/moderate hyperthyroidism
– mild thyroid volume increase
– orbitopathy
– pregnancy and breast-feeding
– young age

Table 2 Conditions increasing relapse rates.

– goiter
– multinodular toxic goiter
– autonomous single nodule
– persistence of high rates of TRAb

Table 3 Differences between MMI and PTU.

	MMI	PTU
inhibition of thyroid peroxidase	yes	yes
inhibition of T4 to T3 conversion	no	yes
albumine binding	low	high
half-life (hours)	6–8	1–2
duration of clinical action (hours)	40	12–24
intrathyroid storing	major	minor
time to reach normal serum hormone levels (weeks)	2–4	10–15
patients' compliance	better	worse

Methimazole vs. Propylthiouracil

Initial doses: effectiveness and remission

In the therapy of Graves' disease, the choice of MMI or PTU is controversial (**Table 3**). The initial dose is still a matter of debate: generally the initial dose of MMI is 10–30 mg per day in one oral administration, while that of PTU is 100–300 mg per day every 6 h. Different studies have compared the therapy at low doses to that at higher doses. The "European Multicentre Trial" compared the treatment with 10 mg of MMI to that with 40 mg, for a period of 12 months, followed by another period of 12 months of follow-up. This study demonstrated that 85 % of patients treated with 10 mg vs. 92 % of those treated with 40 mg reached euthyroidism after 6 weeks of treatment, concluding that the two dosages had similar efficacy (Reinwein et al., 1993; Homsanit et al., 2001).

A prospective randomised study, carried out in a period of 2003 and 2004 in Japan, compared 3 groups of patients treated with 15 mg of MMI, 30 mg of MMI and 300 mg of PTU, over a 1 year period. The results showed that in the case of mild or moderate hyperthyroidism (FT4 < 7 ng/dl), the efficacy in lowering the serum levels of thyroid hormones was the same for all 3 groups. On the contrary, in the case of severe hyperthyroidism (FT4 ≥ 7 ng/dl), the group treated with a high dose of MMI reached a more rapid normalisation of FT4 levels both with respect to the group treated with a lower dose of MMI and to the group treated with PTU (Nakamura et al, 2007).

However, different randomised prospective studies have shown that the dosage does not significantly influence the percentage of remissions (Reinwein et al., 1993).

Therefore, in case of mild or moderate hyperthyroidism it is sufficient to use methimazole in low doses, while in the case of severe hyperthyroidism, in order to reach euthyroidism in a

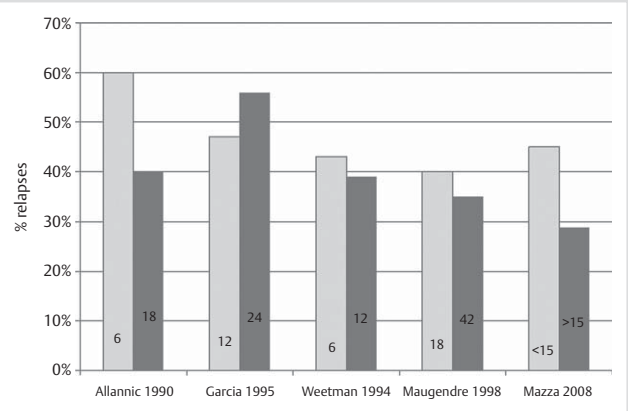

Fig. 1 Different treatment length effect on relapse rate (numbers on the bars: months of treatment). Updated from Cooper, 2003.

shorter time, a higher dose of MMI is recommended. Currently, PTU is not recognised as a drug of first choice in the treatment of hyperthyroidism, because of its lower adherence rates (due to the necessity of taking the drug several times a day) and major toxicity, leading in particular to severe liver failure (Cooper and Rivkees, 2009).

Maintenance doses during treatment

Maintenance doses correspond to 5–10 mg every day for MMI and 50–100 mg for PTU. The duration of the therapy should be between 12 and 18 months. A comparison between 4 randomised prospective studies has showed that periods of treatment inferior to 12 months lead to a higher possibility of recurrence, while periods superior to 18 months do not lead to higher percentages of remissions (**Fig. 1**) (Cooper, 2003). In the management of thionamide therapy it is important to know that these drugs do not block the release of pre-formed thyroid hormones and that, therefore, the state of euthyroidism is usually reached within 4–12 weeks. Furthermore, it has to be considered that different factors influence the rapid control of hyperthyroidism, such as the initial levels of thyroid hormones, iodine pool, and intrathyroid hormonal deposits, the size of the gland, and the stage of the disease. A recent meta-analysis has included 12 trials comparing the administration of levothyroxine in addition to a thionamide therapy (the so-called block-and-replace regimen) with the thionamide therapy alone (titration regimen) and has demonstrated that their effectiveness is comparable. However, the block-and-replace regimen requires higher doses of thyonamides and is associated with significantly higher rates of reported side effects: it is therefore not advised (Abraham et al., 2005).

Side effects

Thionamides can be associated with a variety of side effects with different severity levels, grouped as minor and major (Streetman and Khanderia, 2003; Pearce and Braderman, 2004). Minor side effects are found in 1–5% of patients (Cooper, 2005) treated with MMI or PTU; it is shown that for MMI such side effects are dose-correlated, while for PTU the correlation is less clear (Nakamura et al., 2007; Cooper, 2005) (**Table 4**).

Minor side effects include pruritis, cutaneous rash, urticaria, fever, arthralgia, nausea, sickness and olfaction disorders (more frequent during therapy with MMI). Often these effects can resolve spontaneously; in case of persistence, the administered thionamide can be replaced by another available drug (Pearce,

Table 4 Thionamides side effects.

Side effects	PTU	MMI
minor	1–5%	1–5% (dose-correlates)
major agranulocytosis	0.2–0.5% (unclear correlation between severity and drug dose)	0.2–0.5% (dose-correlates)
liver toxicity	acute hepatitis (1%?) severe liver failure	cholestatic jaundice

2006). Major side effects include agranulocytosis, hepatotoxicity, aplastic anemia and vasculitis, and occur in approximately 0.2–0.5% of the cases (Cooper, 2003; Cooper et al., 1983). Agranulocytosis is defined as a decrease of the number of granulocytes to < 500 per mm^3 and is reported in approximately 0.35% of patients treated with PTU or MMI (Tajiri and Noguchi, 2004). This can be caused by two mechanisms: one immune-mediated by antigranulocyte antibodies (Berkman et al., 1983; Fibbe et al., 1986; Toth et al., 1988), the other correlated with direct toxic damage (the thionamides reach high concentrations in granulocytes). (Bandyopadhyay et al., 2002). Most cases of agranulocytosis occur within the first 3 months of therapy, but can also arise after a year or more. The most common symptoms of such conditions are fever and pharyngodynia; sepsis can often follow due to the presence of Pseudomonas Aeruginosa. In such cases, it is necessary to immediately interrupt the thionamide therapy and administer broad-spectrum antibiotics and growth factors (G-CSF) to avoid the fatal evolution of agranulocytosis.

Furthermore, occasionally a condition of granulocytopenia, defined by levels of granulocytes < 1500 per mm^3, can be found in patients with Graves' disease. For this reason, it would be opportune to perform a complete blood-cell count before the start and during pharmacological treatment. If during the treatment the number of granulocytes decreases to <1 000 per mm^3, it will be appropriate to interrupt the treatment, while for values between 1 000 and 1 500 per mm^3, it will be recommended to strictly monitor the dose. (Streetman and Khanderia, 2003; Cooper, 2005; Andersohn et al., 2007).

Another major side effect is hepatotoxicity (0.1–0.2%), which generally arises in the first 3 months of treatment. Cases of cholestatic jaundice have been reported in association with MMI therapy, and acute hepatitis, sometimes associated with serious liver injury and necrosis, has been reported in association with the administration of PTU. Over the past 20 years, 22 severe liver-injury adverse events (9 deaths and 5 liver transplants) have been reported to the FDA Adverse Event Reporting System (AERS) Program (Bahn et al., 2009; Cooper and Rivkees, 2009). The Food and Drug Administration (FDA) recommends to consider PTU as a second-line drug, to be used solely for patients who are intolerant of methimazole, or for women in their first trimester of pregnancy (Cooper and Rivkees, 2009; Kuehn, 2009).

It should be taken into account that, apart from thionamide therapy, hyperthyroidism itself can cause alterations in liver-function test. Therefore, in order to distinguish an alteration due to hyperthyroidism from one caused by thionamides it is useful to perform a dosage of AST, ALT, gamma-glutamyltransferase, alkaline phosphatase and bilirubin before starting treatment. The liver function test therefore must be requested at diagnosis and monitored over time; usually it can return within the normal range when the euthyroid status is reached and just a small

	Any side effect	Liver function impairment	Cutaneus rash	Decrease of WBC count (<1000 per mm^3)
PTU 300 mg	52%	27%	22%	5%
MMI 15 mg	14%	9%	7%	0.7%
MMI 30 mg	30%	7%	22%	0%

Table 5 Thionamide dose-side effect correlation (from Nakamura, 2007).

increase of transaminases is not an absolute contraindication against the use of thionamides (Cooper, 2005).

Although it is a rare condition, vasculitis has been found more frequently in association with PTU therapy than with MMI therapy (Cooper, 1999; Cooper, 2005). The sierological pattern of such patients mimics systemic lupus erythematosus (SLE), as it is characterised by the presence of ANCA (antineutrophil cytoplasmic antibodies, Gunton et al., 2000; Noh et al., 2001). The clinical manifestations consist of acute renal insufficiency, arthritis, ulcerations, rash, and respiratory symptoms such as sinusitis and haemoptysis. Although such symptomatology resolves with the suspension of thionamides, in the most severe cases it is necessary to start a therapy with glucocorticoids and cyclophosphamide (Streetman and Khanderia, 2003; Cooper, 2005).

A recent study (Nakamura et al., 2007) showed that side effects occur in 52% of patients treated with 300 mg of PTU, in 30% of patients treated with 30 mg of MMI, and in 14% of patients treated with 15 mg of MMI. Therefore, it can be assumed that lower doses of MMI are accompanied by a lower frequency of adverse effects (**Table 5**).

In conclusion, the use of MMI as a first-choice antithyroid is preferable for the following reasons:

- a more rapid normalisation of serum thyroid hormone levels (Homsanit et al., 2001)
- less frequent occurrence of major, life-threatening side effects (Cooper and Rivkees, 2009)
- wider availability (PTU is not available in many countries; Cooper, 2005)

Monitoring of therapy

During thionamide therapy, it would be necessary to monitor both the effectiveness of treatment and the possible occurrence of side effects. Patients are checked every 4–6 weeks during the initial stages of treatment and every 2–3 months thereafter with evaluation of FT3, FT4, TSH, complete blood-cell count, and liver-function test. It should be taken into account that TSH can remain suppressed even if thyroid-hormon levels are normal. It is important to assess the thyroid volume and vascularization through ecocolordoppler ultrasonography and to verify the presence of TSH-receptor antibodies (TRAb) at the time of diagnosis and every 6 months (Cooper, 2003; Iagaru and McDougall, 2007; Homsanit et al., 2001).

Thionamides and radiometabolic therapy

Radiometabolic therapy can be associated with both long- and short-term side effects. Among the first is radio-induced thyrotoxicosis, a condition of acute release of thyroid hormones in circulation with a potential exacerbation of hyperthyroidism (Walter et al., 2007; Koornstra et al., 1999; Bonnema et al, 2003; Chiovato et al., 1998). This can occur both in a subclinical form (10%; Walter MA et al., 2007), with a small increase in the concentration of thyroid hormones, and in a more severe form with thyrotoxicosis and thyroid storm (0.3%; McDermott et al., 1983). The mortality associated with the latter condition is 25%, principally due to cardio- and cerebrovascular events (Nayak and Burman, 2006). The use of thionamides before radiometabolic therapy could reduce the degree of biochemical and clinical condition, even if such use still remains debated (Walter et al., 2007).

Some studies show that although an increase of FT3 and FT4 can occur in patients pretreated with antithyroid drugs, the levels reached are lower than those found in non-pretreated patients. Such a difference could be linked to the fact that patients pretreated with thionamides start the radiometabolic therapy with lower baseline serum-levels of hormones than non-pretreated patients (Burch et al., 2001). Two mechanisms seem to be involved in this thionamide action: the depletion of thyroid hormonal deposits before radiometabolic therapy, and the slowdown in the production of TSH-receptor antibody after therapy. In addition, the use of MMI would bring a more rapid control of thyrotoxicosis than the use of PTU (Cooper, 2003). Alongside these studies, others, among which a recent systematic review with a meta-analysis of 14 randomised control trials (Walter et al., 2007), have shown that the effect of thionamides on the attenuation of biochemical and clinical thyrotoxicosis in the weeks following radiometabolic therapy has not been systematically monitored. For this reason, it remains uncertain whether thionamides should be used in such conditions.

Another controversial question is the role of thionamides in the efficacy of radiometabolic therapy and the difference in the percentages of radio-iodine therapy failures between PTU and MMI. Pretreatment with thionamides reduces the uptake of radioiodine and in addition inhibits thyroperoxidase. A recent meta-analysis (Walter et al., 2007) has demonstrated that both drugs increase the rate of radiotherapy failure, without a significant difference between PTU and MMI. Nonetheless, non-randomised studies included in the meta-analysis suggested more definite and prolonged negative effects with PTU. The study suggests that the efficacy reduction can be compensated for by higher doses of radioiodine, while the use of MMI would be preferable to that of PTU and must be interrupted three days before the beginning of radioiodine therapy. The indications for treatment with thionamides before radiotherapy particularly concern older patients and patients with serious cardiovascular diseases.

The main long-term side effect of radiometabolic therapy is hypothyroidism (80–90%), which can occur even some years after treatment. Such a condition is due to necrosis, reduced replication of the residual follicular cells, atrophy, fibrosis and chronic inflammatory conditions that can lead to permanent thyroid damage (Bonnema et al., 2003). In the previously cited meta-analysis it was shown that the administration of thionamides during or after radioiodine treatment reduces the risk of hypothyroidism, although this fact remains still uncertain (Cooper, 2003; Walter et al., 2007; Chiovato et al., 1998).

Antithyroid Drugs of Second Choice

Potassium perchlorate

Potassium perchlorate can be used in the treatment of thyrotoxicosis due to excess of exogenous iodine, particularly in type-1 amiodarone-induced thyrotoxicosis. The drug competitively inhibits the uptake of iodide by thyroid cells and accelerates its release. The initial dose is 250 mg every 6 h by oral administration. It must be underlined that this substance can produce various side effects, among which the most serious is bone-marrow depression, which can lead to medullary aplasia.

Beta blockers

Beta-adrenergic blockers play an important role in the management of patients with Graves' disease, particularly as an adjuvant therapy associated with antithyroid drugs, if there are no contraindications. Many typical symptoms of hyperthyroidism, such as palpitations, anxiety, tremors and heat intolerance mimic the effects of an excessive beta-adrenergic activity which explains the efficacy of beta-blockers. Propranolol is one of the most used, because, in addition to reducing the sympathetico-mimetic effects, it also inhibits the peripheral conversion of T4 into T3. The initial dose of propranolol is 12–20 mg 3 times per day for oral administration and is gradually reduced as thyrotoxicosis improves. Atenolol (25–50 mg per day) can be used in alternative to propranolol, particularly in patients with bronchopathy, as it is the most cardioselective beta-blocker (Streetman and Khanderia, 2003; Pearce and Braderman, 2004).

Inorganic iodide and Iodinated contrast media

Iodine is a necessary element for the correct function of the thyroid gland. A sudden increase of circulating iodine causes an antithyroidal effect, the Wolff-Chaikoff effect. An excess of iodide blocks the action of thyroperoxidase with a reduction of oxidation and organification of iodide and consequently causes a rapid block of thyroid hormone release. Even if patients affected by Graves' disease are subject to this inhibitory action more than healthy subjects, this effect has a very short action. Actually, potassium iodide, administered orally as Lugol solution (61 mg of iodide per drop) or as a saturated solution (SSKI 40 mg of iodide per drop) is not considered the therapy of first choice in the treatment of hyperthyroidism, since the inhibitory effect is transitory and the elimination period is approximately 10–14 days. Nowadays, Lugol solution can be used as a pretreatment to a total thyroidectomy intervention since it reduces the glandular vascularisation; in the management of severe forms of thyrotoxicosis as it establishes a rapid block of thyroid hormone release; and as an adjuvant therapy in radiometabolic treatment. In the latter case, potassium iodide should be administered one week after the dose of radioiodine, to avoid interfering effects.

Iodinated contrast media, such as sodium ipoiodate and iopanoic acid, reduce the peripheral conversion of T4 into T3 by approximately 70 %, and can be used in the thyrotoxicosis crisis, in pre-operatory preparation and as an alternative therapy for patients allergic to antithyroid drugs. The side effects are minimal and include cutaneous rash, nausea, vomiting, diarrhea, dysuria and, only in rare cases, acute renal failure and thrombocytopenia (Pearce and Braderman, 2004).

Lithium Carbonate

The antithyroidal effect of lithium has been noted since 1960, even though its exact mechanism of action is still unclear. However, it seems that lithium, similarly to iodide, blocks the release of thyroid hormones for a transitory period. For this reason and for possible side effects linked to its administration, the use of lithium carbonate in the treatment of hyperthyroidism in Graves' disease is limited. Sometimes it can be used as an adjuvant to radiometabolic therapy to prevent an increase of serum thyroid-hormone concentration (Streetman and Khanderia, 2003; Pearce and Braderman, 2004).

Glucocorticoids

Glucocorticoids are used in thyrotoxicosis in which iodine produces a destroying effect on the thyroid tissue, such as in the initial phases of subacute thyroiditis or in type-2 amiodarone-induced thyrotoxicosis. The effect of the glucocorticoids is two-fold, anti-inflammatory action and a reduction in the peripheral conversion of T4 into T3. One can use methylprednisolone at a dose of 20–40 mg/die or dexamethasone at a dose of 3–6 mg/die, achieving euthyroidism generally within 1–3 weeks. Steroids are gradually reduced and suspended only 2–3 months after the start of the treatment in order to avoid possible relapses.

Biologic drugs

Rituximab (RTX) is a B-cell depleting chimeric monoclonal antibody directed against human CD20, a cell surface antigen present on pre-B and mature B cells (El Fassi et al., 2006). It was the first monoclonal antibody approved by the FDA in December 1997 for the treatment of relapsed or refractory indolent non-Hodgkin lymphoma (Boye et al., 2003). It has subsequently been applied in various hematologic (Boye et al., 2003) and autoimmune diseases, including multiple myeloma (Treon et al., 2002), Waldenström's macroglobulinemia (Byrd et al., 1999), idiopathic thrombocytic purpura (Arnold et al., 2007), bullous pemphigoid, pemphigus vulgaris (Carr and Heffernan, 2007), systemic lupus erythematosus (Thatayatikom and White, 2006), haemolytic anaemia (Franchini, 2007), and rheumatoid arthritis (Smolen et al., 2007).

RTX was recently proposed as a therapy for cases of Graves' disease unresponsive to traditional antithyroid drugs (Heemstra KA et al., 2008), and particularly for Graves' ophthalmopathy (Salvi et al., 2007).

RTX targets the immunopathological mechanisms causing the disease, and induces a transient B-cell depletion (lasting 4–6 months), probably reducing the extention of B-cells germinal centres into thyroid tissue and retrorbital soft tissue, even without reducing the overall concentration of serum TRAbs. It has been proposed that the effects of RTX may be mediated by decreasing B-cell antigen presentation and production of pathogenic autoantibodies from the stromal mileau of inflamed thyroid tissues (El Fassi et al., 2007).

Only two controlled studies were performed: one was mainly addressed to assess the RTX efficacy in Graves' hyperthyroidism (El Fassi et al., 2009), and the other in Graves' ophtalmopathy (Salvi et al., 2007). El Fassi et al. showed that infusion of RTX with concomitant administration of MMI was more effective than MMI alone in inducing subsequent sustained remission of patients with Graves' disease, even without significant decrease in the total IgG and TRAbs levels during the observation period. However, the biologic activity of TRAbs – evaluated through measuring the cAMP production in Chinese-hamster cells transfected with human TSH receptor and incubated with patients' sera – was considerably reduced (El Fassi et al., 2009).

Salvi et al. showed that RTX, if compared to standard i.v. glucocorticoid therapy, caused an earlier and more pronounced decrease of clinical activity score of Graves' ophtalmopathy, with lower relapse rates. All nine patients showed a clinical improvement in ophtalmopathic subjects after RTX infusion, but thyroid function was not affected, with persistence of hyperthyroidism and elevated serum TRAb values (Salvi et al., 2007).

A randomized controlled therapeutic trial is required to confirm these preliminary data.

It can be questionable if an expensive biologic drug should be used for a benign disease like Graves' hyperthyroidism (other options, like radioiodine, are available); its usefulness is more acknowledged for Graves' ophtalmopathy, where it could be used as an alternative to glucocorticoids and to prevent a disease progression leading to surgical decompression (Rodien, 2008).

Several – even if rare – adverse effects were reported in patients treated with RTX, such as infusion reactions (McLaughlin et al., 1998), serum sickness (D'Arcy and Mannik, 2001), ulcerative colitis and arthritis (El Fassi et al., 2008; Goetz et al., 2007; Papadakis KA et al., 2003), acute thrombocytopenia (Ram et al., 2009), psoriasis (Dass et al., 2007). Moreover, the FDA has recently warned against an increased risk of progressive multifocal leucoencephalopathy, a serious and usually fatal demyelinating disorder caused by JC polyoma virus (Carson et al., 2009).

In conclusion, RTX administration for Graves' disease is off-label and experimental: because of the limited experience, the high cost, the peculiar side-effect profile, and the availability of alternative well-studied therapies, RTX currently should not be considered as an option in uncomplicated Graves' disease.

Summary

MMI and PTU inhibit the synthesis of thyroid hormone at various levels and are used as the primary treatment for hyperthyroidism or as a preparation before radioiodine therapy or thyroidectomy. MMI is the drug of choice because of its widespread availability, longer half-life and less frequent serious side effects. PTU should be reserved to patients who are intolerant of MMI, or to women in their first trimester of pregnancy.

The initial dose of MMI is usually 10–30 mg per day in one oral administration, while that of PTU is 100–300 mg per day every 6 h. Maintenance dose is 5–10 mg per day for MMI and 50–100 mg for PTU. The titration regimen and the block-and-replace regimen have a comparable effectiveness: however, the latter is not advised because of higher doses requested and higher rates of reported side effects.

During thionamide administration, it would be necessary to monitor both the effectiveness of treatment and the possible occurrence of severe side effects (mainly agranulocytosis and liver toxicity). Patients should undergo evaluation of FT3, FT4, TSH, complete blood-cell count, and liver-function test every 4–6 weeks during the initial stages of treatment and every 2–3 months thereafter.

Drugs of second choice are potassium perchlorate, beta blockers, iodine, lithium carbonate and glucocorticoids.

Rituximab, a B-cell depleting monoclonal antibody, was recently proposed as a biological therapy for cases of Graves' disease unresponsive to traditional drugs. However, RTX currently should not be considered as an option in uncomplicated Graves' disease, due to the limited experience, the high cost, and the peculiar side-effect profile.

Conflict of Interest: None.

References

1 *Abraham P*, *Avenell A*, *Park CM et al.* A systematic review of drug therapy for Graves' hyperthyroidism. Eur J Endocrinol 2005; 153: 489–498
2 *Allannic H*, *Fauchet R*, *Orgiazzi J et al.* Antithyroid drugs and Graves' disease: a prospective randomized evaluation of the efficacy of treatment duration. J Clin Endocrinol Metab 1990; 70: 675–679
3 *Andersohn F*, *Konzen C*, *Garbe E.* Systematic Review: Agranulocytosis Induced by Nonchemotherapy Drugs. Ann Intern Med 2007; 146: 657–665
4 *Arnold DM*, *Dentali F*, *Crowther MA et al.* Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med 2007; 146: 25–33
5 *Bahn RS*, *Burch HS*, *Cooper DS et al.* The Role of Propylthiouracil in the Management of Graves' Disease in Adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. Thyroid 2009; 19 (7): 673–674
6 *Bandyopadhyay U*, *Biswas K*, *Banerjee RK.* Extrathyroidal actions of antithyroid thionamides. Toxicol Lett 2002; 128: 117–127
7 *Bauch K.* Epidemiology of functional autonomy. Exp Clin Endocrinol Diabetes 1998; 106: S16–S22
8 *Berkman EM*, *Orlin JB*, *Wolfsdorf J.* An anti-neutrophil antibody associated with a propylthiouracil-induced lupus-like syndrome. Transfusion 1983; 23: 135–138
9 *Bonnema SJ*, *Bennedbaek FN*, *Gram J et al.* Resumption of methimazole after 131I therapy of hyperthyroid diseases: effect on thyroid function and volume evaluated by a randomised clinical trial. Eur J Endocrinol 2003; 149: 485–492
10 *Boye J*, *Elter T*, *Engert A.* An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab. Ann Oncol 2003; 14: 520–535
11 *Burch HB*, *Solomon BL*, *Cooper DS et al.* The effect of antithyroid drug pre-treatment on acute changes in thyroid hormone levels after 131I ablation for Graves' disease. J Clin Endocrinol Metab 2001; 86: 3016–3021
12 *Byrd JC*, *White CA*, *Link B et al.* Rituximab therapy in Waldenstrom's macroglobulinemia: preliminary evidence of clinical activity. Ann Oncol 1999; 10: 1525–1527
13 *Carr DR*, *Heffernan MP.* Off-label uses of rituximab in dermatology. Dermatol Ther 2007; 20: 277–287
14 *Carson KR*, *Focosi D*, *Major EO et al.* Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. Lancet Oncol 2009; 10: 816–824
15 *Chiovato L*, *Fiore E*, *Vitti P et al.* Outcome of thyroid function in Graves' patients treated with radioiodine: role of thyroid-stimulating and thyrotropin-blocking antibodies and of radioiodine-induced thyroid damage. J Clin Endocrinol Metab 1998; 83: 40–46
16 *Cooper DS*, *Goldminz D*, *Levin AA et al.* Agranulocytosis associated with antithyroid drugs. Effects of patient age and drug dose. Ann Intern Med 1983; 98: 26–29
17 *Cooper DS*, *Rivkees SA.* Putting propylthiouracil in perspective. J Clin Endocrinol Metab 2009; 94 (6): 1881–1882
18 *Cooper DS.* Antithyroid Drugs in the Management of Patients with Graves' Disease: An Evidence-Based Approach to Therapeutic Controversies. J Clin Endocrinol Metab 2003; 88: 3474–3481
19 *Cooper DS.* Antithyroid drugs. N Engl J Med 2005; 352: 905–917
20 *Cooper DS.* The side-effects of antithyroid drugs. Endocrinologist 1999; 9: 457–467
21 *D'Arcy CA*, *Mannik M.* Serum sickness secondary to treatment with the murine-human chimeric antibody IDEC-C2B8 (rituximab). Arthritis Rheum 2001; 44: 1717–1718
22 *Dasgupta S*, *Savage MW.* Evaluation of management of Graves' disease in District General Hospital: achievement of consensus guidelines. Int J Clin Pract 2005; 59: 1097–1100
23 *Dass S*, *Vital EM*, *Emery P.* Development of psoriasis after B cell depletion with rituximab. Arthritis Rheum 2007; 56: 2715–2718
24 *El Fassi D*, *Banga JP*, *Gilbert JA et al.* Treatment of Graves' disease with rituximab specifically reduces the production of thyroid stimulating autoantibodies. Clin Immunol 2009; 130: 252–258
25 *El Fassi D*, *Clemmensen O*, *Nielsen CH et al.* Evidence of intrathyroidal B-lymphocyte depletion after rituximab therapy in a patient with Graves' disease. J Clin Endocrinol Metab 2007; 92: 3762–3763

26 *El Fassi D*, *Nielsen CH*, *Hasselbalch HC et al*. The rationale for B lymphocyte depletion in Graves' disease. Monoclonal anti-CD20 antibody therapy as a novel treatment option. Eur J Endocrinol 2006; 154: 623–632
27 *El Fassi D*, *Nielsen CH*, *Kjeldsen J et al*. Ulcerative colitis following B lymphocyte depletion with rituximab in a patient with Graves' disease. Gut 2008; 57: 714–715
28 *Fibbe WE*, *Claas FHJ*, *Van der Star-Dijkstra W et al*. Agranulocytosis induced by propylthiouracil: evidence of a drug dependent antibody reacting with granulocytes, monocytes and haematopoietic progenitor cells. Br J Haematol 1986; 64: 363–373
29 *Franchini M*. Rituximab in the treatment of adult acquired hemophilia A: a systematic review. Crit Rev Oncol Hematol 2007; 63: 47–52
30 *Garcia-Mayor RVG*, *Paramo C*, *Luna-Cano R et al*. Antithyroid drug and Graves' hyperthyroidism. Significance of treatment duration and TRAb determination on lasting remission. J Endocrinol Invest 1992; 15: 815–820
31 *Goetz M*, *Atreya R*, *Ghalibafian M et al*. Exacerbation of ulcerative colitis after rituximab salvage therapy. Inflamm Bowel Dis 2007; 13: 1365–1368
32 *Gunton JE*, *Stiel J*, *Clifton-Bligh P et al*. Prevalence of positive anti-neutrophil cytoplasmic antibody (ANCA) in patients receiving anti-thyroid medication. Eur J Endocrinol. 2000; 142 (6): 587
33 *Heemstra KA*, *Toes RE*, *Sepers J et al*. Rituximab in relapsing Graves' disease, a phase II study. Eur J Endocrinol 2008; 159: 609–615
34 *Homsanit M*, *Sriussadaporn S*, *Vannasaeng S et al*. Efficacy of single the daily dosage of Methimazole vs. Propylthiuracil in the induction of euthyroidism. Clin Endocrinol (Oxf) 2001; 54: 385–390
35 *Iagaru A*, *McDougall R*. Treatment of Thyrotoxicosis. J Nucl Med 2007; 48: 379–389
36 *Koenig RJ*. Regulation of type 1 iodothyronine deiodinase in health and disease. Thyroid 2005; 15: 835–840
37 *Koornstra JJ*, *Kerstens MN*, *Hoving J et al*. Clinical and biochemical changes following 131I teraphy for hyperthyroidism in patients not pretreatred with antithyroid drugs. Neth J Med 1999; 55: 215–221
38 *Kuehn BM*. FDA focuses on drugs and liver damage: labeling and other changes for acetaminophen. JAMA 2009; 302 (4): 369–371
39 *Maugendre D*, *Gatel A*, *Campion L et al*. Antithyroid drugs and Graves' disease–prospective randomized assessment of long-term treatment. Clin Endocrinol (Oxf) 1999; 50: 127–132
40 *Mazza E*, *Carlini M*, *Flecchia D et al*. Long-term follow-up of patients with hyperthyroidism due to Graves' disease treated with methimazole. Comparison of usual treatment schedule with drug discontinuation vs. continuous treatment with low methimazole doses: a retrospective study. J Endocrinol Invest 2008; 31: 866–872
41 *McDermott MT*, *Kidd GS*, *Dodson LE Jr et al*. Radioiodine-induced thyroid storm. Case report and literature review. Am J Med 1983; 75: 353–359
42 *McLaughlin P*, *Grillo-López AJ*, *Link BK et al*. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998; 16: 2825–2833
43 *Mitsiades N*, *Poulaki V*, *Tseleni-Balafouta S et al*. Fas ligand expression in thyroid follicular cells from patients with thionamide-treated Graves' disease. Thyroid 2000; 10: 527–532
44 *Moriyama K*, *Tagami T*, *Usui T et al*. Antithyroid Drugs Inhibit Thyroid Hormone Receptor-Mediated Transcription. J Clin Endocrinol Metab 2007; 92: 1066–1072
45 *Nakamura H*, *Noh JY*, *Itoh K et al*. Comparison of Methimazole and Propylthiouracil in Patient with Hyperthyroidism Caused by Graves' Disease. J Clin Endocrinol Metab 2007; 92: 2157–2162
46 *Nayak B*, *Burman K*. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am 2006; 35: 663–686
47 *Noh JY*, *Asari T*, *Hamada N et al*. Frequency of appearance of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) in Graves' disease patients treated with propylthiouracil and the relationship between MPO-ANCA and clinical manifestations. Clin Endocrinol (Oxf) 2001 May; 54 (5): 651–654
48 *Okamura K*, *Ikenoue H*, *Shiroozu A et al*. Reevaluation of the effects of methylmercaptoimidazole and propylthiouracil in patients with Graves' hyperthyroidism. J Clin Endocrinol Metab 1987; 65: 719–723
49 *Papadakis KA*, *Rosenbloom B*, *Targan SR*. Anti-CD20 chimeric monoclonal antibody (rituximab) treatment of immune-mediated thrombocytopenia associated with Crohn's disease. Gastroenterology 2003; 124: 583
50 *Pearce EN*, *Braderman LE*. Hyperthyroidism: advantages and disadvantages of medical therapy. Surg Clin North Am 2004; 84: 833–847
51 *Pearce EN*. Diagnosis and management of thyrotoxicosis. BMJ 2006; 332: 1369–1373
52 *Ram R*, *Bonstein L*, *Gafter-Gvili A et al*. Rituximab-associated acute thrombocytopenia: an under-diagnosed phenomenon. Am J Hematol 2009; 84: 247–250
53 *Reinwein D*, *Benker G*, *Lazarus GH*. A prospective randomised trial of antithyroid drugs dose in Graves' disease therapy. J Clin Endocrinol Metab 1993; 76: 1516–1521
54 *Rodien P*. Rituximab in Graves' disease. Eur J Endocrinol 2008; 159: 515–516
55 *Roy G*, *Mugesh G*. Bioinorganic chemistry in thyroid gland: effect of antithyroid drugs on peroxidase-catalyzed oxidation and iodination reactions. Bioinorg Chem Appl 2006; 23214
56 *Salvi M*, *Vannucchi G*, *Campi I et al*. Treatment of Graves' disease and associated ophthalmopathy with the anti-CD20 monoclonal antibody rituximab: an open study. Eur J Endocrinol 2007; 156: 33–40
57 *Smolen JS*, *Keystone EC*, *Emery P et al*. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2007; 66: 143–150
58 *Streetman DD*, *Khanderia U*. Diagnosis and Treatment of Graves' disease. Ann Pharmacother 2003; 37: 1100–1109
59 *Tajiri J*, *Noguchi S*. Antithyroid drug-induced agranulocytosis: special reference to normal white blood cell count agranulocytosis. Thyroid 2004; 14: 459–462
60 *Takagi S*, *Hummel BC*, *Walfish PG*. Thionamides and arsenite inhibit specific T3 binding to the hepatic nuclear receptor. Biochem Cell Biol. 1990; 68: 616–621
61 *Thatayatikom A*, *White AJ*. Rituximab: a promising therapy in systemic lupus erythematosus. Autoimmun Rev 2006; 5: 18–24
62 *Toth EL*, *Mant MJ*, *Shivji S et al*. Propylthiouracil-induced agranulocytosis: an unusual presentation and a possible mechanism. Am J Med 1988; 85: 725–727
63 *Treon SP*, *Pilarski LM*, *Belch AR et al*. CD20-directed serotherapy in patients with multiple myeloma: biologic considerations and therapeutic applications. J Immunother 2002; 25: 72–81
64 *Volpe R*. The immunomodulatory effects of anti-thyroid drugs are mediated via actions on thyroid cells, affecting thyrocyte-immunocyte signalling: a review. Curr Pharm Des 2001; 7: 451–460
65 *Walter MA*, *Briel M*, *Christ-Crain M et al*. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. BMJ 2007; 334: 514–520
66 *Wang PW*, *Luo SF*, *Huang BY et al*. Depressed natural killer activity in Graves' disease and during antithyroid medication. Clin Endocrinol (Oxf) 1988; 28: 205–214
67 *Weetman AP*, *Pickerill AP*, *Watson P et al*. Treatment of Graves' disease with the block-replace regimen of antithyroid drugs: the effect of treatment duration and immunogenetic susceptibility on relapse. Q J Med 1994; 87: 337–341
68 *Zantut-Wittmann DE*, *Tambascia MA*, *da Silva Trevisan MA et al*. Antithyroid drugs inhibit in vivo HLA-DR expression in thyroid follicular cells in Graves' disease. Thyroid 2001; 11: 575–580