Chapter 6
Antithyroid Drug Therapy in Patients with Graves' Disease

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Abbreviations

ANCA	Anti-neutrophil cytoplasmic antibody
ATD	Antithyroid drug
CMZ	Carbimazole
MMI	Methimazole
PTU	Propylthiouracil
Tg	Thyroglobulin
TPO	Thyroid peroxidase
TRAb	TSH-receptor autoantibodies

Once the diagnosis of thyrotoxicosis has been made, the two most important considerations are the cause of the thyrotoxicosis and the choice of therapy. The differential diagnosis of thyrotoxicosis is discussed elsewhere [1]. If the condition is caused by Graves' disease, the three standard modalities of therapy are: antithyroid drugs (ATDs) for 12–18 months or long-term, radioiodine therapy (in some patients

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preceded and possibly also followed by ATD therapy for a period of time), and thyroid surgery (normally performed after ATD therapy has been given until the patient is euthyroid).

Patient and physician preferences among the three modalities vary, depending on the health care system, medical tradition, specialist availability, and population preference. Thus, exposure to radioactive substances is a major concern in some parts of the world, and less so in other countries. Radioiodine also may have adverse effects on thyroid eye disease. Surgery is associated with potential long-term complications and increased expense. On the other hand, only a minority of patients treated primarily with ATDs have a permanent remission, and this depends on a variety of factors including environmental iodine, genetics, underlying severity of disease, smoking, and other factors. Clearly, there is no treatment that is ideal for all patients, and individual patient preferences are of paramount importance. Primary ATD therapy given for a period of time is the first choice in many clinics around the world, especially in Europe, South America, and Asia, and this choice of therapy has also been on rise in the USA in recent years [2].

At the initial visit, ATDs, radioiodine, and surgical therapies for Graves' disease are discussed with the patient. Typically, primary Methimazole (MMI) therapy is recommended for most patients with a first episode of thyrotoxicosis and mild to moderate disease. Radioiodine therapy is typically recommended in patients with side effects to drugs or if hyperthyroidism relapses after discontinuation of ATD, and surgery is advised if there is concomitant hyperparathyroidism, if the thyroid gland contains suspicious nodules, is extremely large, or if ablative therapy is chosen and the patient suffers from moderate to severe Graves' orbitopathy. The aim of radioiodine and surgery is to ablate the thyroid, with the need for lifelong thyroid hormone replacement therapy. After 2 years of ATD therapy, the overall chance of a "remission" (normal thyroid function for >1 year off medication) will be in the order of 50 %, but is higher (70–80 %) in patients with milder biochemical disease, a small goiter, and unmeasurable serum TSH-receptor antibody (TRAb) at baseline, and much lower in patients with severe disease, large goiter, and very high TRAb levels.

Indications for ATD Therapy

The central indications for starting therapy with an ATD are that the patient is thyrotoxic (that is, the abnormal thyroid function tests are not caused by laboratory interferences or thyroid hormone resistance), that the thyrotoxicosis is caused by hyperthyroidism (that is, the patient suffers from thyroid gland hyperactivity and not from thyroiditis with passive release of hormones or excessive intake of thyroid hormone), that the patient is expected to tolerate the drug, and that the informed patient accepts the plan for therapy.

In patients with clinically and biochemically obvious hyperthyroidism caused by Graves' disease, therapy with an ATD is often initiated before results of all planned

investigations are achieved. If the patient has eye signs typical for Graves' disease, this is normally sufficient for diagnosing Graves' disease as the cause of the hyperthyroidism, and a clearly enlarged diffuse thyroid with a bruit from high blood flow also provides the correct diagnosis. Occasionally, the primary diagnosis of Graves' hyperthyroidism has to be changed to another cause of thyrotoxicosis and overall therapy plans changed, when all the results of diagnostic studies become available.

Contraindications to ATD Therapy

Previous severe side effects to the drugs, as discussed below, are absolute contraindications to their reuse. Moreover, Methimazole/Carbimazole (MMI/CMZ) should not be used in early pregnancy, as this may lead to birth defects in ~1/30 of exposed cases, and defects may be severe [3]. The use of Propylthiouracil (PTU) in early pregnancy may also be associated with an increase in risk (~1/40 may develop a birth defect), but defects tend to be less severe [4], and PTU use should be limited when possible. Suspicion of a nonhyperthyroid type of thyrotoxicosis, such as painless thyroiditis, is a relative contraindication, because the patient is exposed to the (limited) risk of side effects, and the drug will have no effect.

Mechanisms of Action

ATDs have been in use to treat hyperthyroidism for over half a century. Currently, MMI (or its derivative CMZ) is the drug of choice because of increased risks of hepatotoxicity and vasculitis from PTU. PTU is recommended in specific circumstances, described below.

The thionamide ATDs' primary mechanism of action is to inhibit the thyroid peroxidase (TPO)-mediated iodination of thyroglobulin (Tg), and thereby the synthesis of thyroid hormones, T4 and T3 (Fig. 6.1). The mechanism likely involves TPO-mediated iodination of the drugs themselves, with the drugs competing for oxidized iodine with the normal biosynthetic pathway, in which oxidized iodine is bound to tyrosine residues in Tg to form iodotyrosines. This could explain why ATDs are less effective in patients with high iodine intakes, and especially in patients having large amounts of intrathyroidal iodine (e.g., in type I amiodarone-induced thyrotoxicosis). There is also some evidence that the drugs inhibit the TPO-mediated intramolecular coupling reaction, whereby iodotyrosines are linked to form the iodothyronines T4 and T3.

In addition to this primary mechanism of action, PTU, but not MMI, decreases T4 to T3 conversion in peripheral tissues and in the thyroid gland itself, by inhibiting type I deiodinase [5, 6]. This effect may be important in the management of patients with "thyroid storm."

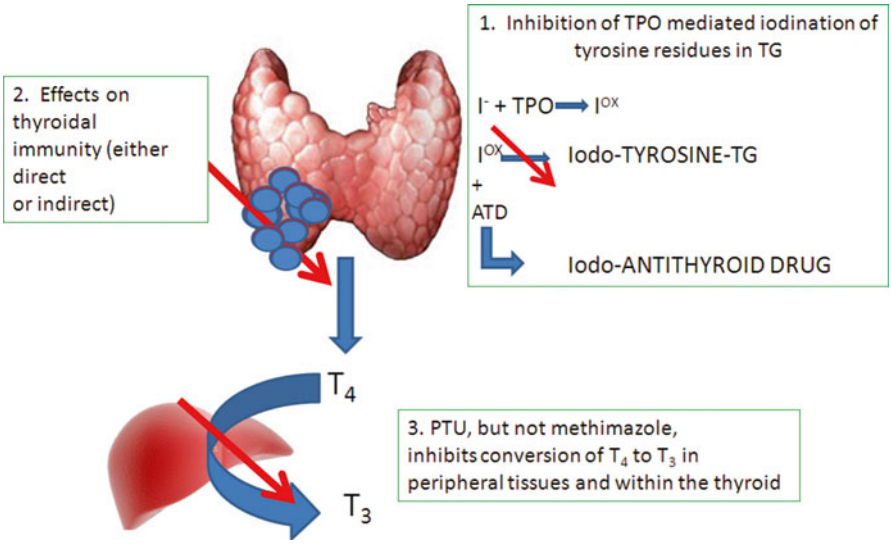

Fig. 6.1 Antithyroid drugs act in multiple ways. (1) After active transport into the thyroid, they block TPO-mediated iodination of tyrosine residues in thyroglobulin by diverting the oxidized iodine species (TPO-I ox) from the normal iodination pathway ("organification") by becoming iodinated themselves. They are not "inhibitors" of TPO in vivo. They may also inhibit the "coupling" reaction between iodotyrosines to form iodothyronines (T3 and T4) in an as yet unknown manner. (2) Antithyroid drug therapy is associated with a decline in thyroidal autoimmunity, either due to direct effects on immune cells and antigen presentation within the thyroid, or else by disrupting a dysfunctional immune system by rendering the patient euthyroid. (3) PTU, but not methimazole, inhibits T4 to T3 conversion in peripheral tissues and within the thyroid itself by inhibiting Type 1 deiodinase. It does not inhibit Type 2 deiodinase found in the brain and pituitary

Finally, ATD therapy may have immunosuppressive effects, either indirectly or directly. Some experts have proposed that the hyperthyroid state itself can perpetuate a dysregulated immune system, for example via induction of plasma cell differentiation [7] or affection of one or more among the many other mechanisms whereby thyroid hormones participate in immune system homeostasis [8]. In this construct, by making and keeping patients euthyroid, the immune system's normal tolerance to "self" is gradually restored [9]. On the other hand, there is also plentiful in vivo and in vitro evidence of multiple direct effects of ATDs on intrathyroidal immune modulatory cells [10], including effects to increase apoptosis of T lymphocytes [11] and effects on thyrocyte antigen presentation [12].

Irrespective of the mechanism, it is clear that ATD therapy is most often associated with a decline in thyroid-specific autoimmunity with a decline of circulating TRAb. Furthermore, ATD pretreatment prior to radioiodine therapy blunts the post-radioiodine rebound in circulating TRAb, thought to be responsible for worsening hyperthyroidism in the weeks and months after radioiodine treatment. This is discussed in detail later in this chapter.

Initial Doses of ATDs

The appropriate initial dose of ATD in Graves' disease depends on the biochemical and clinical severity of the disease. PTU has a less favorable pharmacokinetic profile and more side effects, and it should only be used in special situations (Table 6.1). When the difference in duration of action is taken into account, the relative activity of the two drugs is about 1:20, or in other words 5 mg MMI once daily has about the same effect as 50 mg PTU twice daily. CMZ is a pro-drug to MMI, and 10 mg of CMZ is converted in the body to yield 6 mg MMI [13]. Taking this into account, the two drugs are interchangeable.

A number of studies have addressed the effectiveness of various initial doses of MMI and PTU to normalize the thyroid function in patients with Graves' hyperthyroidism. ATDs are more effective in blocking thyroid hormone production when patients' iodine intake is low, and, conversely, the drugs' effectiveness is lower when dietary iodine is high [14]. Therefore, patients with lower iodine intakes and milder disease can quickly become hypothyroid if the dose of ATD is not tailored to the degree of biochemical disease. Based on this observation, patients with active Graves' hyperthyroidism should be advised not to take iodine containing supplements. In many populations, over the counter vitamin and mineral supplements are very popular, and GD patients should choose supplements without iodine, and they should not take supplements containing kelp.

In Europe, a multicentre study including 509 GD patients compared the effects of initial daily doses of 10 and 40 mg MMI [15]. Overall, the fraction of patients who had normalization of thyroid hormone levels at 3 weeks was 62 %, after taking 10 or 40 mg MMI per day respectively, and after 6 weeks it was 84 %. The superiority of a starting MMI dose of 40 mg per day was at the price of more patients experiencing side effects from the drug [16]. In a multivariate analysis, the time to normalization of serum T4 was shorter when patients were given 40 mg MMI, had a small or no goiter, had less elevated serum T3 at diagnosis, had no measurable TRAb, and lived in an area with a low iodine intake.

In Japan [17], a randomized prospective study comparing MMI 15 mg daily, MMI 15 mg twice a day, and PTU 100 mg three times a day concluded that MMI 15 mg daily was suitable for mild and moderate cases (Free T4 < 4.5 times above upper reference limit; 86 % had normal FT3 after 3 months), but MMI 15 mg × 2 per day was advisable for more severe cases of Graves' hyperthyroidism. PTU 100 mg three times a day was similar in effect to MMI 15 mg a day. PTU therapy resulted in more side effects than MMI, and MMI 30 mg per day was associated with more side effects than MMI 15 mg day.

Table 6.1 Indications for the use of propylthiouracil

Patient intolerant to methimazole/ carbimazole; refuses radioiodine or surgery
First trimester of pregnancy—to reduce the risk of severe birth defects
Thyrotoxic crisis to reduce T4 deiodination to T3 by deiodinase type 1

Thus, the recommended initial drug is MMI with few exceptions (Table 6.1), and the starting dose of MMI should be high enough to make patients euthyroid within a reasonable time limit (preferably 4–8 weeks); but not higher than necessary, in order to minimize the risk of iatrogenic hypothyroidism or side effects to the drug, which are dose related for MMI. The starting dose of MMI should be based on the biochemical severity; for example MMI 30 mg a day in patients with thyroid test results >2–3 times the upper reference limit, 20 mg a day if function tests are >1.5–≤2 times the upper reference limit, and 5–10 mg per day if test results are ≤1.5 times upper reference limit. No study clearly shows the superiority of splitting the initial MMI dose over the day in patients with more severe disease. On the one hand, studies on duration of TPO block suggest that a split dose may be more effective (see below); on the other hand, compliance with therapy will be better with a single daily dose regimen, and prolonged therapy with lower doses of MMI should always be given as a once daily dose.

Side Effects of Antithyroid Drugs

The vast majority of patients take ATDs without any problem. However, there are adverse reactions that can occur uncommonly, necessitating an alternate form of treatment. Most authorities divide ATD side effects into "minor" and "major" categories (Table 6.2). The minor side effects occur in 2–5 % patients, and include an itchy skin rash, GI distress, and arthralgias. Typically, these reactions occur within the first few weeks of beginning the medication. The pruritic papular skin eruption may be severe enough to require discontinuation of the drug, but in some cases it will resolve with concomitant use of antihistamines for 1–2 weeks. Switching from MMI to PTU is also a possibility, but cross-reactivity between the two drugs can occur in a minority of patients.

The "major" drug reactions are agranulocytosis, an anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis, and hepatotoxicity. It is thought that these reactions are generally mediated by immune mechanisms. Interestingly, a recent

Table 6.2 Antithyroid drug adverse reactions

	PTU	Methimazole
Minor reactions		
Fever, rash, GI distress	1–5 %	1–5 % (dose-related)
Major reactions		
Agranulocytosis	0.2–0.3 %	0.2–0.3 % (dose related)
ANCA positive vasculitis	<1 %, can occur after years of therapy. Predilection for Asians	Rare
Hepatotoxicity	1 % mild; ? 0.1–0.01 % potential life-threatening hepatocellular damage	Rare; primarily cholestatic

study suggested that patients with Graves' disease may be more susceptible to these "allergic" reactions than patients with nonimmune hyperthyroidism (e.g., toxic multinodular goiter), but this observation requires confirmation [18].

Agranulocytosis

Agranulocytosis is the most common of the major toxicities of ATDs. It is defined as an absolute granulocyte count of $<0.5 \times 10^9$/L, but most patients have extremely low counts, approaching zero. The frequency of agranulocytosis is in the range of 0.2–0.3 % and is similar for both MMI and PTU [19]. There is no dose relationship with PTU therapy, but there is a clear cut dose effect with MMI, so that this complication is extremely unusual with MMI doses in the 5–10 mg per day range [20]. Since many patients' thyrotoxicosis can be easily controlled with small doses of MMI, this should be the initial strategy for mild to moderate hyperthyroidism.

Agranulocytosis typically occurs within the first few months of initiating drug therapy, and may be more common in the elderly. It is important to recall that agranulocytosis can occur on a second exposure to the drug, typically after an interval of years, rather than weeks or months, between drug exposures [20, 21].

Some asymptomatic ATD-treated patients have been found on screening to have low white blood cell counts, suggesting that hematologic monitoring might be useful in identifying at risk patients. However, this has not been shown to be cost-effective, especially since agranulocytosis can occur quite precipitously. The typical presentation is a fulminant oropharyngeal infection with odynophagia, cervical lymphadenopathy, high fever, and malaise. Other infections, especially in the elderly, have been described including pneumonia, sepsis, and skin infections. Bone marrow examination may have predictive value, as complete absence of granulocytic precursors is associated with longer recovery times (i.e., 10–14 days).

The treatment of agranulocytosis is fairly straightforward: Immediate cessation of the ATD (and not using the other drug since cross reactivity has been described), hospitalization with broad-spectrum antibiotic coverage, and consideration of hematopoietic growth factor therapy (G-CSF or GM CSF), which has been shown to reduce the fatality rate and decrease the time of hematologic recovery [22]. Factors that predict worse outcome include older age (>65 years), lower granulocyte counts, and severe underlying comorbidities such as renal failure or cardiac or respiratory disease. Mortality rates in the 5–10 % range have been reported in recent series [23].

Vasculitis

The rheumatologic side effects of antithyroid drug therapy include both drug-induced lupus and PTU-induced vasculitis. Drug-induced lupus typically has more musculoskeletal involvement, serositis, and gastrointestinal abnormalities, whereas

vasculitis typically is associated with renal and pulmonary involvement. There is considerable overlap between these clinical syndromes, and both are associated with ANCA positivity [24]; however, pANCA (peri-nuclear ANCA) is found in both syndromes equally, while cANCA (cytoplasmic ANCA) is typically seen in patients with vasculitis. cANCA is also associated with Wegener's granulomatosis, while pANCA antibodies can be directed against a variety of proteins, typically myeloperoxidase, but also elastase, lactoferrin, and cathepsin. Cross-sectional studies have shown that 10–60 % of patients taking PTU have pANCA positivity [25, 26], but these are almost inevitably asymptomatic individuals, and the significance of this serologic finding therefore remains uncertain. Furthermore, one study showed that up to 67 % of patients with Graves' disease who had not been treated with an antithyroid drug were pANCA positive, but this antibody was directed against proteins other than myeloperoxidase [27], including cathepsin.

For unclear reasons, vasculitis is far more common with PTU therapy rather than with MMI treatment and Asian ethnicity seems to be a risk factor for its development. Interestingly, one study suggested that younger patients are more likely to develop drug-induced lupus, while older individuals may be more susceptible to drug-induced vasculitis [24]. ATD-related vasculitis typically occurs after several months of treatment, but has been reported to develop after years of treatment.

The typical presentation includes fever, polyarthritis, purpura of the acral parts of the body including the ear lobes, and, in the case of vasculitis, glomerulonephritis and/or pneumonitis (Fig. 6.2). For drug-induced lupus, recovery occurs after discontinuation of the drug, but some patients afflicted with vasculitis require glucocorticoids or other immunotherapies, including cyclophosphamide and plasmapheresis. However, in general, PTU-related vasculitis has a more benign course than idiopathic vasculitis [28].

Hepatotoxicity

It is been known for over six decades that PTU use can rarely be associated with fulminant hepatotoxicity. In contrast, MMI is rarely associated with cholestasis rather than hepatocellular dysfunction. With regard to PTU, the frequency of hepatotoxicity requiring liver transplant or resulting in death is probably in the 1/10,000 range, but milder degrees of hepatic involvement may occur as commonly as 1 % of treated patients. A recent literature review confirmed that PTU-induced hepatotoxicity occurred after a median of 120 days of drug exposure, and is not dose related [29]. Typical symptoms include malaise, nausea, jaundice, dark urine, and light-colored stools, and lethargy. Prompt recognition and discontinuation of the drug, and referral to a center capable of caring for patients with severe hepatic failure, including the availability of hepatic transplantation, is essential.

For MMI, the mean onset of hepatotoxicity in one review was 36 days [30]; once the drug is stopped, it can take many weeks for complete normalization of serum bilirubin and alkaline phosphatase levels. There have been no reported fatalities

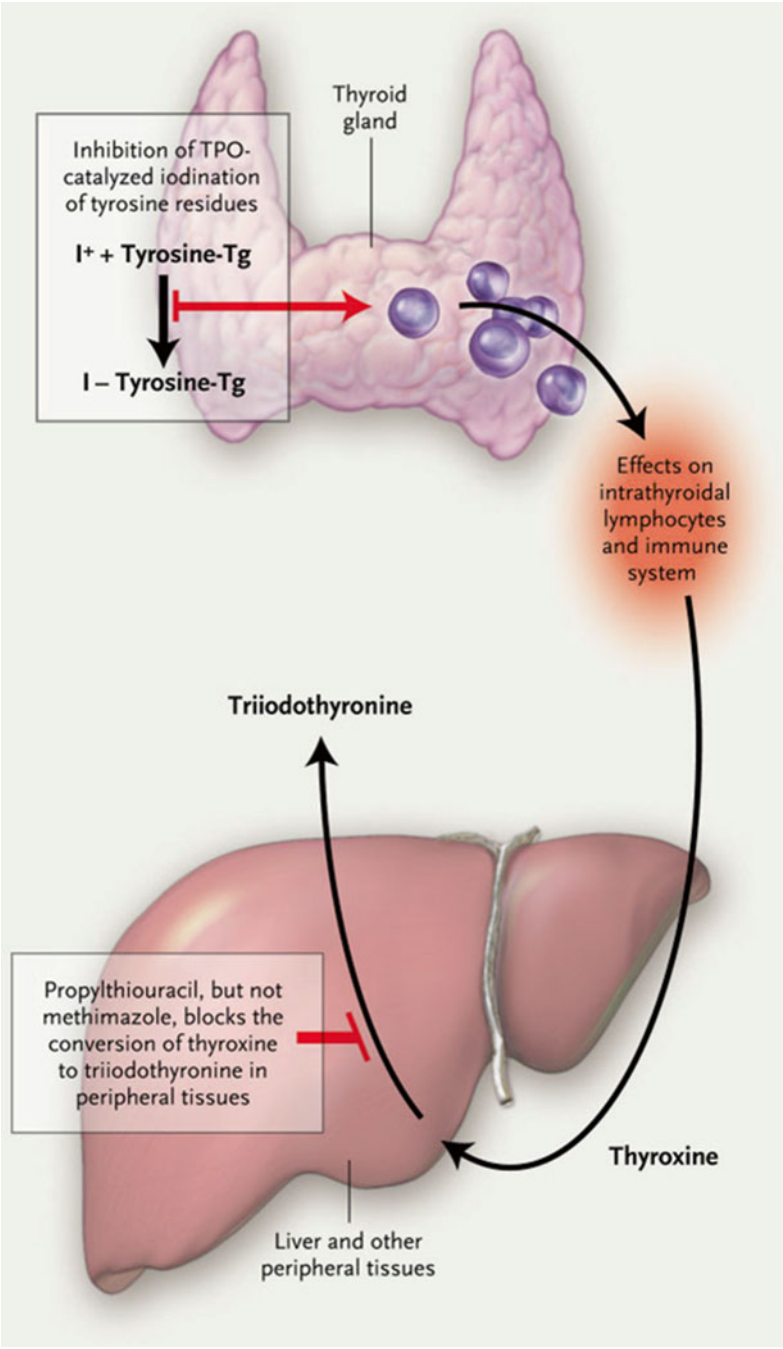

Fig. 6.2 (**a**) Multiple purpuric lesions on the face and ear. (**b**) Bilateral irregular purpuric areas on the lower legs. Lack of progression of the lesions beyond the demarcated borders illustrates their nonmigratory behavior. With permission: Chastain MA, Russo GG, Boh EE, Chastain JB, Falabella A, Millikan LE. Propylthiouracil hypersensitivity: report of two patients with vasculitis and review of the literature. J Am Acad Dermatol. 1999;41:757–64 [68]

from MMI-related cholestasis. Treatment of the underlying hyperthyroidism in patients with ATD-related hepatotoxicity might include the use of the other drug, since the two drugs have very distinct hepatotoxicities.

Adjustment of ATD Dose During Therapy

The dose of drug should be gradually reduced as thyroid function tests normalize, and a "once a day" drug regimen should be adopted as soon as possible to improve overall compliance. MMI has a considerably longer duration of action than PTU and once daily dosing is clearly effective in nearly all patients during prolonged therapy. The reason that the dose of MMI may be split over the day in patients with severe hyperthyroidism is that MMI given once a day may not lead to effective TPO blockade for a full 24 h period. In a study of the duration of MMI's inhibition of iodine organification in the thyroid, the average percent of iodine not organified (a measure of TPO blockade) after a single 5 or 20 mg dose of MMI was after 2 h: 82 and 92 %; 6 h: 69 and 84 %; 13 h: 22 and 65 %; 25 h: 3 and 27 %, with considerable differences among patients [31]; similar results were reported in another study [32].

The adjustment of the ATD dose to give rapid normalization of thyroid function without inducing hypothyroidism requires frequent assessment of thyroid function. The frequency of thyroid function testing and ATD dose adjustment differs somewhat depending on the local organization of health care and the costs of testing. For example, in the Thyroid Clinic at The Johns Hopkins Hospital in Baltimore, USA, patients are requested to have thyroid function tests (Free T4, T3, TSH) 4–6 weeks after initiation of MMI therapy, and 4–6 weeks after any adjustment to their drug dose. Testing can be done at the hospital or at various commercial laboratories. Patients are typically seen in the clinic every 12 weeks, as dose adjustments can be made via phone calls and more recently, through electronic communication. After the first follow-up visit at 12 weeks, patients are not seen again for another 3–6 months, but laboratory testing is dose every 4–6 weeks until thyroid function is stable.

In Aalborg, Denmark follow-up would mostly be organized without seeing patients. Standard thyroid function tests (TSH, T3, and T4) would be ordered in the centralized laboratory database to be performed after 2–3 weeks of ATD therapy, and then again depending on the response to therapy. Blood sampling can be performed at all hospitals in the region or at local GPs according to the preference of patients. Results of tests will be seen by the responsible endocrinologist, and forwarded by mail to the patient with information on the ATD dose and the new approximate date of testing. The first follow-up visit after initiation of therapy will be after 2–6 months, depending on the judgement of the physician at the initial visit. In both Baltimore and Aalborg, if patients experience side effects or other problems, they can contact the clinic and be seen promptly.

The standard duration of ATD therapy at the Johns Hopkins and Aalborg clinics is 18–24 months, but patients with moderate or severe Graves' orbitopathy are offered prolonged low-dose ATD therapy [33]. All patients are instructed about pos-

sible side effects of therapy and are given written information about adverse reactions, and women of childbearing age are informed about the association between use of ATD in early pregnancy and birth defects [34].

Titration Versus Block + Replacement Therapy

When patients become euthyroid during ATD therapy, the general recommendation is that the dose of the ATD should be gradually adjusted to the lowest dose that keeps the patient euthyroid (titration therapy) [35]. A different approach is to keep the initial high dose of the ATD and to add Levothyroxine (L-T4) therapy to maintain the patient in a euthyroid state (block + replacement therapy) [36]. Theoretically, this strategy could make it easier to keep the patient euthyroid during prolonged therapy, because the high dose of ATD will prevent excess thyroid hormone secretion in the event of worsening of disease activity. Also, the risk of overtreatment leading to hypothyroidism will be lower, because of the replacement therapy that is being given. However, this regimen is not recommended [35], because the higher ATD dose increases the risk of side effects.

Even if the dose of ATD should be kept low when possible, a more cautious "partial block + replacement" is used by some physicians in an attempt to stabilize thyroid function and prevent episodes of hyper- and hypothyroidism, especially in patients with moderate to severe Graves' disease, and in those patients whose thyroid function is difficult to control on MMI alone, with episodes of both hyperthyroidism and hypothyroidism. This type of therapy implies drug titration with reduction of the MMI dose to ~5–10 mg daily, and then a gradual addition of L-T4 to keep the serum TSH around 1 mU/L [33].

ATD Withdrawal and Remission of Graves' Disease During ATD Therapy

Over a 12–24 month period of ATD therapy, the majority of patients experience some degree of resolution of the autoimmune abnormality. As noted above, it is uncertain whether this phenomenon is caused by a restoration of the euthyroid state, because hyperthyroidism itself is causing or perpetuating the disordered immune function, or if it is a direct effect of the drugs to impair organ-specific autoimmunity.

In many patients thyroid function can be kept stable using a small dose of MMI (2.5–10 mg given once daily). At that point, assuming that the TRAb has become normal, the ATD is withdrawn with the hope for a prolonged remission with no need of medication. Several studies have investigated the association between the duration of therapy and the risk of relapse after ATD withdrawal [36]. These studies have shown that a shortening of therapy duration below 1 year increases the risk of relapse, but there is no evidence that prolonging therapy to longer than 18 months will reduce the risk. Notably, a major advantage of more prolonged therapy is that the majority

of patients stay euthyroid on such therapy, even if the dose of ATD is low [33]. Accordingly, several investigators have suggested the possibility of prolonged, possibly life-long ATD therapy to patients with a high risk of relapse, and who reject ablative therapy followed by lifelong hormone replacement therapy [37, 38].

Withdrawal of ATD therapy is most commonly done by simply stopping the medication, but some clinicians gradually withdraw the medication, guided by thyroid function testing [39]. The decision to withdraw or taper medication is based on the preference of the patient after being informed about the risk of relapse, that, among other factors will depend on the length of time that the patient has been on therapy (typically 12–24 months), and also on the TRAb level (see below). In patients who are offered more prolonged ATD therapy, the dose should be kept low, to minimize the risk of ATD side effects. Moreover, because of the risk of ANCA positive vasculitis during prolonged administration, and also the small risk of severe liver failure, PTU is not suitable for prolonged ATD therapy.

Relapse of Hyperthyroidism After ATD Withdrawal

The risk of relapse differs substantially among patients depending on a number of factors (Table 6.3). Relapse risk may be as low as 10 % in patients who initially had no goiter [40], no eye signs [41], mild hyperthyroidism [42], and who had very low or unmeasurable TRAb values at the time of diagnosis [43]. On the other hand, the risk of relapse may be ~90 % if the drug is withdrawn after 1 year of therapy in patients with active moderate to severe Graves' eye disease [44], and it is also high in patients who remain TRAb positive and who had a large goiter at diagnosis [45], in patients who smoke cigarettes [46], and in children [47].

The predictive value of the patient becoming TRAb negative during therapy has been much discussed, but most recent studies have shown a clear predictive value. A typical result was obtained in a prospective Swedish study where ATD was given for 18 months, and follow-up was 3.5 years [48]. Among patients who had become TRAB negative, 29 % had relapse of hyperthyroidism, whereas the risk of relapse was 89 % in patients who were still TRAb positive at the time of ATD withdrawal

Table 6.3 Factors that increase the risk of relapse after withdrawal of ATD therapy

Childhood
Large goiter
Severe thyroid dysfunction at diagnosis
Short duration of ATD therapy
Active orbitopathy at time of ATD withdrawal
Presence of TSH-receptor antibodies at time of withdrawal
Active smoker
High iodine intake
Postpartum period

[49]. Typically, relapses tend to occur within the first 6 months after drug discontinuation, but patients can relapse at any time. The postpartum period is a time when relapse is especially common [50].

After a relapse, ATD therapy may be initiated again following the principles discussed above, or the patient may desire radioiodine therapy or surgery. As noted above, patients may develop antithyroid drug side effects, including agranulocytosis, after resuming a drug that previously had been taken without incident months or even years earlier [21]. Thus, patients should be reeducated about drug adverse reactions whenever the ATD is restarted.

A Syndrome of Persistent Thyroid Drive

A small fraction of patients treated with ATD do relatively poorly, with difficulty controlling thyroid function even if high doses of ATD are given. The clinical picture of this "syndrome of persistent thyroid drive" [51] was described in the early 1980s [52–54] and it consists typically of an increase in goiter size (with a bruit), high levels of TRAb, a relatively high serum T3 compared to the serum Free T4 level, and a clinically unstable condition.

In a prospective Swedish study, four out of 71 patients initially randomized to be treated with ATD developed this syndrome and finally underwent surgery [49]. If only serum FT4 and TSH but neither serum T3 nor TRAb are measured during ATD therapy it may be difficult to recognize such patients, and noncompliance with therapy may be erroneously suspected. The recommended therapy in such patients is surgical thyroidectomy [55] preceded by high-dose ATD plus potassium iodide therapy, or radioiodine if the patient rejects surgery. Radioiodine may be less effective in patients with severe disease [56].

Antithyroid Drug Therapy Prior to Radioiodine Treatment

Theoretically, it would be reasonable to obtain a euthyroid state prior to the administration of radioactive iodine, especially in elderly patients or in those with underlying cardiovascular disease. This is because radioiodine treatment has been associated with an exacerbation of thyrotoxicosis in the days, weeks, and months following its administration [57, 58], likely related to acute inflammation early on, and to an increase in TRAb levels weeks to months later [59].

In one meta-analysis, there was a suggestion that pretreatment with ATDs led to better outcomes, including fewer instances of atrial fibrillation and fewer fatalities, but the number of events was very small [60]. In a randomized controlled trial, in which patients received either MMI therapy to normalize thyroid function prior to radioiodine treatment or were simply given radioiodine without ATD pretreatment, patients in the pretreatment group had more stable and normal thyroid function, with

less of a tendency to have marked increases in thyroid hormone levels following radioiodine therapy [61]. In another similarly designed study, thyroid hormone levels rose after MMI was stopped, but they were always lower than the thyroid hormone levels in the non-pretreated group, and pretreated patients had better symptom scores than the non-pretreated group for the month following radioiodine treatment [62]. The lower thyroid hormone levels following radioiodine treatment in the MMI pretreated patients may be related to the observation that ATD pretreatment prevents or attenuates the rise of TRAb levels following radioiodine treatment [63].

There is some evidence to support restarting ATDs 7 days after radioiodine administration in patients considered to be at risk for cardiovascular complications, owing to the fact that thyroid hormone levels may be more stable with ATD treatment both before and after radioiodine administration [64]. Since ATDs interfere with iodine utilization by the thyroid gland, the drug must be stopped for about 3 days prior to radioiodine administration; stopping it for longer than 3 days is not necessary [65].

Based on this evidence, the American Thyroid Association recommended that ATD pretreatment should be considered for patients undergoing radioiodine therapy who are extremely symptomatic, had free T4 levels >2–3 times the upper limit of reference range, or were elderly, had underlying cardiovascular disease or other comorbidities (e.g., atrial fibrillation, heart failure, pulmonary hypertension, and those with renal failure, infection, trauma, poorly controlled diabetes mellitus, and cerebrovascular or pulmonary disease) [35]. While some studies have suggested that ATDs can interfere with the efficacy of radioiodine treatment, this may be less of a problem with MMI than with PTU [66, 67], and increasing the radioiodine administered activity by 10–15 % likely would negate this effect [60].

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