1. Abstract

Graves' disease (GD) is the most common cause for hyperthyroidism in iodine-replete areas. The disease is caused by the appearance of stimulating TSH receptor autoantibodies (TRAb) leading to hyperthyroidism. Blocking and neutral TRAb have, however, also been described. TRAb can be measured either by competition assays, assays using a bridge technology or bioassays (for discriminating stimulating vs. blocking antibodies). Therapy of GD with antithyroid drugs belonging to the group of thionamides is the first-line treatment to be continued for 12 up to 18 months. In case of relapse, thyroid ablative therapy including radioiodine therapy or thyroidectomy, respectively, should be performed. Risk factors for relapse are a large thyroid volume, persistence of high TRAb serum titer, smoking, and others. Within this review, we will give insights into the pathogenesis of GD including the pathogenesis of Graves' ophthalmopathy. We also describe recent developments of TRAb measurement, which is used for the diagnosis of GD as well as for outcome prediction. Finally, we discuss therapy aspects as well as the important issue of GD and pregnancy.

2. Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in iodine-replete areas. It is characterized by the presence of antibodies directed against the TSH receptor (TRAb) (1). GD has an incidence of about 40/100,000 per year (2). GD is more common in women than in men and most frequently seen in patients between 30 to 50 years of age. In addition to hyperthyroidism, extrathyroidal manifestations may be present including Graves' ophthalmopathy (GO), thyroid dermopathy, and acropachy (3). Genetic and environmental factors contribute to the occurrence of this autoimmune disorder. Medical treatment of GD relies on the use of antithyroid drugs (ATDs) (4, 5), but, owing to the large recurrence rate of hyperthyroidism, thyroid ablation by either radioiodine (RAI) treatment or thyroidectomy is required in about half of the cases. The aim of the present review article is to give an overview on the recent understanding of the pathogenesis of GD as well as clinical aspects for diagnosing, predicting prognosis, and treating GD patients.
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3. ETIOLOGY AND PATHOGENESIS OF GRAVES’ DISEASE

3.1. Role of genetic factors

It is generally accepted that GD has a strong hereditary component implementing a significant role of genetic factors. Many studies have confirmed human leukocyte antigen (HLA), CD40, CTLA-4, PTPN22, Tg, and TSHR being the main genes contributing to GD.

The HLA complex is located on chromosome 6 and contains sequences encoding genes involved in the regulation of the immune response (6). Three major classes of HLA genes exist: i) Class I, including histocompatibility genes expressed on the surface of most cells (HLA-A, -B, and -C); ii) Class II, including histocompatibility genes expressed exclusively on leukocytes and immune competent cells (HLA-DR); and iii) Class III, including a heterogeneous group of genes encoding molecules that are involved in the immune response and other non-immune proteins like histones and olfactory receptors (7, 8). The association between HLA and GD was first shown for the HLA class I allele HLA-B8 (7, 9, 10). Later, HLA class II alleles were described to have a stronger impact on GD risk: DRB1, DQA1*0501, DOB*03, and DQB1*02 (11-13). Further analyses identified DRB1*03 encoding an arginine at S74 as the critical amino acid conferring a genetic susceptibility to GD (14). Interestingly, protective HLA phenotypes, e.g. DRB1*07, have also been described (12, 15).

The surface molecule CD40 is a member of the tumor necrosis factor receptor (TNFR) superfamily. It is involved in diverse functions of the immune system, e.g. activation of B-cells and other antigen presenting cells, antibody secretion, affinity maturation, and generation of memory cells (16). The CD40 relationship with GD is postulated due to its coexpression with HLA-DR in GD thyroid epithelial cells (17) and due to a disease associated C/T single-nucleotide polymorphism (SNP) at the 5’-untranslated region (18). Nevertheless, the impact of SNP remains controversial (reviewed in (19)).

The cytotoxic T-lymphocyte-associated Protein 4 (CTLA-4, CD152) is a surface molecule responsible for the down-regulation of the immune response (20). It is expressed on cytotoxic T cells as well as regulatory T cells (21). The two SNPs A49G and C60T are well accepted as risk factors for GD (22-25). The functional relevance of the latter mentioned SNP is believed to be due to a reduced expression of the mRNA encoding the soluble form of the molecule (26).

A further gene being associated with GD is protein tyrosine phosphatase, non-receptor type 22 (PTPN22). PTPN22 is a strong inhibitor of T cell activation (27). A missense SNP in exon 14 (Arg620Trp) was associated with GD (28) and other autoimmune diseases (29).

TSHR is the primary autoantigen in GD. It has been for long a candidate susceptibility gene and the object of many genetic studies (19) representing intron 1 SNPs playing a role in GD development. Within a 40-kb region at least 5 major GD-associated SNPs have been identified (rs179247, rs2284720, rs12101255, rs12101261, and rs2268458) (reviewed in (19)). But how do these SNPs that are located in a noncoding region of TSHR could refer risk to GD? The following two mechanisms modifying the peripheral tolerance and the central tolerance have been proposed: (i) alternative splicing and generation of soluble TSHR and (ii) modulation of TSHR expression in the thymus: The human TSHR is a member of a family of cell surface hormone receptors which are characterized by an extra-membranous portion, seven transmembrane loops, and an intracellular domain (30, 31). After post-translational cleavage the TSHR comprise an extracellular A-subunit (394 amino acids; encoded by exon 1-9) and a B-subunit (transmembrane and intracellular; 349 amino acids; encoded by exon 10) coupled by disulphide bridges. The A-subunit is supposed to be recognized by the immune system (32, 33). Of note, TSHR may undergo post-translational intra-molecular cleavage into distinct A and B-subunits at or nearby the cell surface. Reduced disulphide bridges result in the B-subunit being embedded in the plasma membrane (33, 34). Additionally, truncated TSHR transcripts have been described (35-37). If translated, two of them (ST4 and ST5), would encode most of the entire extracellular region, but not the transmembrane domain of the TSHR, potentially representing soluble receptors. Interestingly, it has been proposed that these soluble receptors may favour the generation of an autoimmune response (38). Furthermore, an association between the two TSHR SNPs rs179247 and rs12101255 and the expression of ST4 and ST5 and resulting the production of the soluble A-subunit have already been described (39).

A further point in GD's etiology and pathology is the role of the central tolerance, which is influenced by the expression of self-antigens (e.g. TSHR) within the thymus for negative selection of autoreactive T cell clones. The question is, whether polymorphisms of particular tissue-restricted genes encoding autoantigens would influence their level of expression in the thymus, becoming thereby a risk source of autoimmunity. This phenomenon was already described for some SNPs, e.g. rs179247, rs2268458, and rs12101261 (38, 40). Here, individuals carrying the protective genotype, showed a higher intra-thymic TSHR mRNA level, compared to those carrying the predisposing genotype (38, 40).
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3.2. Role of environmental factors

Besides the hereditary component, the impact of various non-genetic factors on the etiology of GD is also generally accepted (reviewed in (8)). Although the underlying mechanisms are not clarified, an association between various factors and the development of GD were described. GD is much more frequent in women than in men, with a female-to-male ratio ranging from 5 to 10. A major factor in determining the frequency of GD is dietary iodine supply, whereas it is still unclear if a genetic susceptibility is additional mandatory. After treatment with immune-modulating drugs the development of higher serum autoantibody levels can be observed. Epidemiologic studies with seasonal and geographic variation indicate a possible role of infections (e.g. superantigens from Yersinia enterocolitica) in the pathogenesis of GD. Thus a definitive identification of the etiologic organism and a reasonable explanation of its role in the pathogenesis are lacking (reviewed in (8)).

4. DIAGNOSIS OF GRAVES' DISEASE

4.1. Clinical aspects and thyroid hormones

A low basal serum TSH level has the highest sensitivity and specificity for diagnosing hyperthyroidism and should, therefore, be used as an initial screening parameter for diagnosing hyperthyroidism (41). If GD is, however, strongly suspected, diagnostic accuracy improves when serum TSH, free T4, and free T3 are also assessed. Due to hormone-binding proteins, measurement of free hormones is recommended rather than the measurement of total hormone level.

Clinicians distinguish the following two stages of hyperthyroidism: (i) overt hyperthyroidism: serum free T4, T3, or both are elevated, serum TSH is subnormal (usually <0.01 mU/L in a third-generation assay); and (ii) subclinical hyperthyroidism: serum T4 and serum T3 or free T3 are normal, serum TSH concentration is subnormal. The appearance of TSHR autoantibodies (TRAbs) is presumed to be highly specific for the diagnosis of GD. Therefore, the diagnosis GD is usually confirmed by demonstrating elevated TRAbs. For quantification of TRAbs three different types of assay technology exist: competition assays, bioassays, and assays applying bridge technology. Competition assays, also named TSH Binding Inhibition Immunoglobulin (TBI) assays and TRAb assays are the most widely used assays. The first generation of these assays was based on the ability of TRAbs in test sera to inhibit binding of radiolabelled TSH to detergent solubilised TSHR preparations with the radiolabelled TSH-TSHR complexes precipitated with ethylene glycol (45, 46). These assays reached a sensitivity of 2 IU/l (47). The disadvantages of the first generation TRAb assays were the requirement of multiple centrifugation steps and the use of radioactive material leading to the development of the 2nd generation assays. These assays used TSHRs attached to plastic surfaces for binding of labelled TSH (labelled with ¹²⁵I, a chemiluminescence reagent, or biotin), high affinity monoclonal antibodies, and patients TRAB (45). TRAbs presented in the patients' serum bind to the immobilised TSHR. Following, the tubes or plate wells, respectively, are washed prior to adding labelled TSH (45). Using this assay method, the sensitivity of TRAb testing improved to about 1 IU/l (47). Of note, this assay system has also been used for outcome prediction (remission vs. relapse) of GD. The 3rd generation assays use the monoclonal TRAb M22 instead of TSH (45). Again, the sensitivity was improved reaching down to 0.4 IU/l (47). This improvement was based on using the monoclonal antibody M22, the binding of which to TSHR does not dissociate in contrast to labelled TSH (45). This assay also exists in an automated system (48). Sensitivity and specificity of 98 and 99% have been described (49). However, these assays are unable to distinguish the TRAb types (stimulating or blocking).

In contrast to the competition assays, bioassays are able to distinguish the TRAb types by measuring increased production of cyclic AMP in cellular systems (50-53). These bioassays also exhibit high specificity but are delicate and laborious. A recently commercialized bioassay (Thyretain) detects the stimulatory activity of TRAb by a chimeric TSHR and a cyclic AMP response element (CRE)-reporter gene and luciferase signalling (53). It has been FDA-approved for diagnostic use in the clinical laboratory setting. The standardization of the Thyretain bioassay (51) as well as a standardized rapid bioassay with detection of thyroid stimulation using cyclic AMP-gated calcium channel and aequorin (50) have been published.

Most recently, a new assay system has been established, which directly detects the concentration of stimulating TRAb in sera of patients by applying a bridging technology (54). Within this assay autoantibodies are detected by binding with one arm to a capture receptor on the solid phase and bridging with the other arm.

4.2. Detection of TSH receptor antibodies (TRAb)

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5. THERAPY

5.1. Antithyroid drug therapy

ATD exert their effects by inhibition of thyroid peroxidase, the enzyme involved in thyroid hormone synthesis. In addition, ATD may also have some immuno-modulating effects. Long-term restoration of euthyroidism, which is observed in about 50% of patients after ATDs withdrawal, is thought to be due to spontaneous remission of the autoimmune process rather than by a specific or direct effect of ATDs. It is conceivable; however, that pharmacological control of hyperthyroidism may indirectly contribute to remission by reducing autoantigen exposure by the resting thyroid gland. The commonly observed decrease in serum TRAb concentration during ATD treatment might reflect either mechanism (58).

The aim of the therapy is to achieve euthyroidism (5). The following ATDs are used: methimazole (MMI; alternative name: thiamazol), carbimazole, and propylthiouracil (PTU). Of note, carbimazole is rapidly converted to MMI in the serum (59). The initial dose of ATD is dependent on the severity of hyperthyroidism, the thyroid volume, and iodine exposure. While carbimazole and MMI are effective as a single daily dose, PTU has to be administered two or three times daily (due to a shorter duration of action). In order to achieve the normalization of thyroid function while preventing hypothyroidism and minimizing adverse drug effects, the dose of ATD should be titrated (mainly dependency to fT4 and the TSH levels) to a maintenance level. For this reason, periodic evaluation of thyroid status in patients taking ATD is necessary. The frequency of fT3 und fT4 has to be determined individually. At the start of ATD therapy, one or two determinations per month are usual.

The most frequent, if even rare, severe adverse effects of ATD are hepatotoxicity and agranulocytosis, usually occurring within the first 2 months after therapy initiation (60, 61). Therefore, it is recommended that patients taking ATD should be subjected to a detailed white blood cell count as well as a stringent monitoring of liver function and hepatocellular integrity. Within the first 6 weeks of therapy a two-week interval for testing blood values is recommended (depending on the grade of hyperthyroidism). Subsequently, the interval may be prolonged to monthly testing (62). Further adverse effects are allergic skin reactions, pruritus, and vasculitis.

If the patient is euthyroid (normal TSH level) the therapy should be stopped. Repeated thyroid hormone analyses are, however, still necessary during follow-up. According to the American Thyroid Association Guidelines, patients are considered to be in remission if they have had a normal serum TSH, fT4, and total T3 for at least one year after discontinuation of ATD therapy (59). Other authors consider a state of remission if euthyroidism is documented for several months. Of note, the major drawback of ATD therapy is the high relapse rate, which varies across studies from 30 to 70% (63).

The complications of overt hyperthyroidism, tachycardia in particular, can be relieved by beta-blockers. Here, nonselective b-adrenergic receptor blockers (e.g. propanolol) are preferred. These blockers inhibit additionally the conversion of T4 to the biological active T3. Of note, a recent study showed a higher mortality in patients suffering from thyrotoxicosis treated with nonselective beta-blockers in comparison to patients treated with beta-1-selective ones (64). Due to these observations, the currently common procedure should be reconsidered.

5.2. Ablative therapy

Ablative therapy (surgery, RAI) should be applied to GD patients who (i) do not develop remission 12 – 18 months after ATD therapy or (ii) become hyperthyroid after completing a course of ATD therapy.

It depends on the patients’ symptoms and clinical characteristics which of the ablative therapies should be chosen: in case of moderate enlargement of the thyroid gland (<40 ml) and absent endocrine orbitopathy, RAI therapy is preferred; in case of a thyroid volume of ≥40 ml, distinctive endocrine orbitopathy or the rare case of suspected malignancy, thyroidectomy is frequently chosen (62). The latter has a high cure rate reaching a nearly 0% risk of recurrence of hyperthyroidism once the whole thyroid gland is removed.

Of note, female patient breast-feeding or planning a pregnancy within the next 6 months should not undergo RAI therapy. Additional relative contraindications are given in the case of high-volume goitre, distinct trachea compression, or tracheomalacia.
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5.3. Follow-up

Relapse can occur even years after finishing therapy (65). Risk factors for relapse after a course of ATD therapy are amongst others a higher thyroidal volume as demonstrated in a study by Mohlin et al. (66). Following 219 GD patients, treated at least for 6 months with ATD, for relapse goiter patients showed a significantly lower remission rate (~ 50%) in contrast to non-goiter patients (~60%) (66). Persistently elevated TRAb levels (≥ 10 IU/l 6 months after initial diagnosis) seem also to represent a further risk factor for relapse prediction as mentioned above (67). Further studies confirm the impact of persistently elevated TRAbs. Investigating 266 GD patients who completed a course of ATD therapy a high TRAb at diagnosis and/or positive TRAb at cessation of therapy were described to suggest a high likelihood of relapse, mostly within the first two years (68). Interestingly, Vos et al. also confirmed these risk factors by his prediction model (69). He aimed to calculate recurrence risk before a course of ATD, based on clinical and genetic parameters. Here, again a larger goiter size at diagnosis and higher serum TRAb levels but also PTPN22 C/T polymorphism and some HLA subtypes were described as independent predictors for recurrence (69). Additionally, a severe orbitopathy at initial diagnosis seems to be associated with a higher risk for relapse or could rather be an indication of increased TRAb levels. On the other hand, development of a mild hypothyroidism during the course of ATD therapy potentially indicates a better prognosis (63).

6. GRAVES’ OPHTHALMOPATHY

Graves’ ophthalmopathy (GO; also known as Graves’ orbitopathy), is an inflammatory autoimmune disorder as part of GD (70). While the majority of patients with this condition experience only mild eye irritation and redness, some 3–5% suffer from severe disease. Disease manifestations variably include redness and swelling of the conjunctivae and lids, forward protrusion of the globes (proptosis), ocular pain, debilitating double vision, and even sight loss due to compressive optic neuropathy or breakdown of the cornea (71). From a mechanistic standpoint, these features derive largely from progressive enlargement of the orbital adipose tissues and extra-ocular muscles within the confines of the bony orbit (72).

There are several risk factors for developing GO in GD. Patients with GO are more likely to be women by a 2:1 ratio while men with GD appear to be at higher risk for the development of severe GO (73). There are also racial differences in the prevalence of GO with Asians having a lower likelihood of developing the disease than Caucasians (74). In addition genetic factors apply as outlined above. Another important risk factor is smoking (75). It was the primary risk factor identified for GO outcome with an odds ratio among smokers vs. nonsmokers of 5.2 in a recent trial of patients with newly diagnosed Graves’ hyperthyroidism treated with either radioactive iodine or ATDs (76). Potential antigens within the context of GO is the TSH receptor and IGF 1 receptor. It is suggested that IGF 1 receptors in retro-bulbar tissue are targeted by stimulatory autoantibodies thereby causing the tissue to grow. Therefore, inhibition of the IGF 1 receptors represents a new therapeutic strategy showing a clear clinical benefit in GO patients (77). This indicates a strong pathological role of the IGF 1 receptor in GO. Within this review we will, however, only focus on the TSH receptor as potential antigen in GO.

6.1. The Role of TSH receptor in Graves’ ophthalmopathy

There is a close relationship between the onset of Graves’ hyperthyroidism and the onset of clinically apparent GO; regardless of which occurs first, the other develops in 80% of patients within 18 months (78). GO can be diagnosed in 25–50% of patients with Graves’ hyperthyroidism. However, when sensitive imaging techniques are used, evidence of ocular involvement is detectable in the majority of patients (75). These clinical observations suggest that Graves’ hyperthyroidism and GO share etiologic factors. That said, it is notable that GO is seen on occasion in patients with no thyroid dysfunction. However, using adequately sensitive assays, autoantibodies directed against the thyrotropin receptor (TRAb) can be detected in essentially every patient with GO (79). Further, levels of TRAb correlate with the severity and clinical activity of the disease (53, 80) and high TRAb levels in early GO predict a poor prognosis (81). As autoantibodies directed against TSHR on thyroid follicular cells stimulate the production of thyroid hormone in Graves’ hyperthyroidism, it was postulated early on that immunoreactivity against TSHR in the orbit may play a role in GO pathogenesis.

Insight into the link between the thyroid and the orbit was gained by the demonstration that orbital fibroblasts express TSHR (82, 83). Studies from several laboratories are in general agreement that TSHR mRNA and protein are present in both GO and normal orbital tissues and fibroblast cultures, and that significantly higher levels of the receptor are detectable in GO cells (84–86). Further, a positive correlation has been demonstrated between TSHR mRNA levels in individual GO orbital adipose tissue specimens and the activity of the patient’s disease, suggesting a role for TSHR in the development of the clinical disease (87). TSHR signaling pathways in orbital fibroblasts are similar to those found in thyrocytes (88), including
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activation of both adenylyl cyclase/cAMP and phosphatidylinositol 3-kinase (PI3K)/pAkt cascades (89). In order to investigate whether TSHR activation plays a role in adipogenesis in GO orbital fibroblasts, Zhang and colleagues introduced an activating mutant TSHR into these cells and demonstrated an increase in adipocyte differentiation, as shown by 2 to 8-fold elevations in levels of early to intermediate adipocyte markers (90). In addition, Bahn and coworkers found increased expression of late adipocyte genes (adiponectin and leptin) and accumulation of lipid in GO orbital fibroblasts cultured in the presence of a stimulatory monoclonal TRAb (termed M22) or bovine TSH. This was inhibited by co-treatment with the PI3-kinase inhibitor LY294002, suggesting that PI3K/pAkt signaling in part mediates TRAb and TSH-induced adipogenesis in these cells (91).

Perhaps the strongest evidence to date that TSHR is the primary autoantigen in GO lies in a recently developed animal model. The protocol, developed by Moshkelgosha and colleagues, involves genetic immunization of inbred mice with human TSHR ectoderm plasmid using close field electroporation (92). The animals develop TSHR stimulating or blocking antibodies and either hyperthyroidism or hypothyroidism. In addition, following prolonged immunization, inflammatory cell infiltrates consisting of CD3+CD4+ T cells, macrophages and mast cells can be demonstrated in the extraocular muscles in the majority of animals. Outward signs of orbital involvement include inflammation of the eyelids and conjunctivae. Expansion of the orbital adipose tissues is evident in about 10% of animals and magnetic resonance imaging (MRI) reveals hypertrophy of extraocular muscles and proptosis in most. While useful animal models of Graves’ hyperthyroidism have long been available (93), this is the first demonstrating convincing eye changes similar to those seen in human GO. It is likely that the chronic stimulation of TSHR accomplished in this model, as well as the unique electroporation protocol, allowed for induction of GO in these animals.

7. GRAVES’ DISEASE AND PREGNANCY

GD is the most common cause of hyperthyroidism in women of childbearing age occurring in approximately 0.2% during pregnancy. It has to be distinguished from a gestational transient thyrotoxicosis which is also characterized by elevated fT4 and suppressed serum TSH (1-3% of pregnancies). For this, additionally to the determination of TRAb, the medical story, physical examination and maternal Total T3 may be useful (94).

Preconception counseling for women with GD should point out the urgent recommendation to postpone pregnancy until a stable, euthyroid state is reached. Previous studies described obstetric and medical complications (e.g. pregnancy loss, prematurity, intrauterine growth restriction, stillbirth, thyroid storm) related to maternal hyperthyroidism (94-99). Therefore, effective management of maternal hyperthyroidism during the pregnancy is mandatory. The women should also be informed about the potential teratogenic effects and increased risk of birth defects associated with both PTU and MMI use during the early pregnancy (94).

A particular challenge in the treatment of pregnant women with GD is that TRAb, ATD , and most maternal thyroid hormones can cross the placenta barrier. Subsequently maternal hyperthyroxinemia leads to fetal exposition. In addition, the fetal thyroid reacts to maternal stimulating TRAb with hyperthyreoidism mostly at or after gestation week 20. Of particular importance in the therapy of pregnant patients is the fact that all ATD tend to be more potent in the fetus than in the mother. From this follows the aim to use the lowest effective dose of ATD resulting in maternal serum free T4 / total T4 at the upper limit or moderately above the reference range (94).

In newly pregnant women suffering from GD, who are euthyroid under a low dose of MMI (5–10 mg/d) or PTU (100– 200 mg/d), discontinuation of ATD medication during pregnancy should be considered. In case of cessation of medication, clinical examination and measurement of TSH, free T4 / total T4 should be performed every 1-2 weeks. Of course, clinical factors e.g. TRAb level, goiter size, results of recent thyroid function tests should be taken into account. If pregnant women remain clinically and biochemically euthyroid under these conditions test intervals may be extended to 2–4 weeks during the second and third trimester (94). If therapy is required, ATD are generally used. Birth defects associated with ATD have similar incidence but the risk of severe birth defects is lower for PTU than MMI. Therefore PTU is preferred during the first trimester of pregnancy. Of note, due to PTU’s hepatotoxicity, its use should be limited to the first trimester of pregnancy (100). The given dose should be adapted to severity of symptoms and the degree of hyperthyroxinemia. In general, the American Thyroid Association recommends the following initial dose: MMI, 5–30 mg/d (typical dose in average patient 10–20 mg); carbimazole, 10–40 mg/d; and PTU, 100–600 mg/d (typical PTU dose in average patient 200–400 mg/d) (59). The equivalent potency of MMI to PTU is approximately 1:20 (e.g. 5 mg MMI = 100 mg of PTU) (100-103).

Additionally, beta-adrenergic blocking agents, such as propranolol 10–40 mg every 6–8 hours or cardiac-specific beta-blocker nebivolol may be used for controlling hypermetabolic symptoms until patients have become euthyroid on ATD therapy (94).
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