Chapter

Therapeutic Options in Graves' Hyperthyroidism

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Abstract

The classical approach to treating Graves' hyperthyroidism involves rapid control of the symptoms, generally with a beta adrenergic blocker, and reduction of thyroid hormone secretion by antithyroid drugs (ATDs) and/or using one of the several modalities available, including radioactive iodine therapy (RAI), and surgery; the selection of the treatment modalities often varies according to different guidelines, patient preferences and local traditions. Thionamides are invariably used as first-line medication to control hyperthyroidism and induce remission of the disease, thereby relieving the symptoms. In case of failure of the medical therapy, which is not uncommon, definitive treatment with surgery or RAI is the standard modality of management after due consideration and discussion with the patients. However, the therapeutic options available for patients with Graves' hyperthyroidism have remained largely unchanged for the past several decades despite the current treatments having either limited efficacy or significant adverse effects. The clinical demand for new therapeutic regimens of Graves' disease has led to the emergence of several new therapeutic ideas/options like biologic, peptide immunomodulation and small molecules, currently under investigations which may lead to the restoration of a euthyroid state without the requirement for ongoing therapy, but the potential risk of immunocompromise and cost implications needs careful consideration.

Keywords: graves' disease, anti-thyroid drugs, radioactive iodine, relapse and remission, thyroidectomy

1. Introduction

Graves' disease (GD) is an autoimmune thyroid disorders characterized by multi-systemic involvement, resulting from a complex interactions between genetic and environmental factors [1, 2]. It has an annual incidence of 20 to 50 cases per 100,000 individuals and is the most common cause of hyperthyroidism, accounting for 60–80% of the cases [3]. As with the other autoimmune diseases, women are affected more than men, with a peak incidence occurring between the age of 30 and 50 years, although no age is immune to the disease. It is estimated that approximately 0.5% of men and 3% of women develop Graves' disease during their lifetime [4]. Hyperthyroidism, diffuse goiter, and/or orbitopathy are the characteristic features of

GD, although involvement of other organ systems is not rare. The age of the patient, severity and duration of the disease, determine the presentation and the course of the disease [5]. variety of characteristic symptoms and physical findings of the disease either results from hyperthyroidism (goiter in certain cases) or is a consequence of underlying autoimmunity [6]. Impaired quality of life, work disability [7, 8] and an increased risk of death [9] associated with GD render it imperative to understand the effectiveness of the different modalities of treatment available for the GD to acheive lasting euthyroidism for a favorable outcome. Clinical and biochemical features associated with elevated levels of thyroid hormone, particularly of a long duration and/or orbitopathy, elevated levels of TSH-receptor antibodies (TRAbs) along with a diffuse increase in radioactive iodine or technetium uptake scan, confirm the diagnosis of GD. The association of GD with plethora of systemic manifestations, including typical and atypical, and a relatively prolonged course on account of higher rates of recurrences and relapse responsible for significant morbidity and an increased risk of mortality warrant proper management of the disease and the associated complications [10]. The treatment for GD comprises rapid control of the symptoms, generally with a beta adrenergic blocker, and reduction of thyroid hormone levels using one of the several modalities available, including ATDs to block thyroid hormone synthesis, destruction of the thyroid gland by RAI, and or removal of thyroid gland by surgery respectively; the selection of the optimal approach often varies according to the patient preference, different guidelines, clinical factors and local traditions. The therapeutic options available for patients with Graves' hyperthyroidism have to some extent been successful in reliving the patients of signs and symptoms but lack of efficacy of ATDs in successful maintenance of remission after stopping these drugs in many patients and/or need for lifelong thyroid hormone replacement on account of the lack of functional thyroid tissue in patients treated with either radioiodine, or surgery and improvement in quality of life of in some patients has led to the need for newer therapeutic options with better disease outcome and improved degree of morbidity and mortality. The demand for new therapeutic options, combined with greater insight into basic immunobiology, has led to the emergence of novel approaches to treat Graves' disease. The novel therapeutic options under investigations like biologic, peptide immunomodulation and small molecule, may lead to the restoration of a euthyroid state without the requirement for ongoing therapy, but the potential risk of immunocompromise and cost implications needs careful consideration.

In this chapter we try to dwell upon the traditional treatment options, such as antithyroid drugs, radioiodine and or thyroidectomy, available for Graves' hyperthyroidism, besides new strategies under investigation and summarize the effective components of different modalities of management to restore euthyroidism for a favorable outcome of the disease.

2. Management options for Graves' disease

The management of GD has been largely directed towards controlling the hyperthyroidism despite the autoimmune mechanisms responsible for the syndrome. Treatment involves alleviation of symptoms and correction of the thyrotoxic state. Adrenergic hyperfunction is treated with beta-adrenergic blockade. Correcting the excessive thyroid hormone levels can be accomplished with antithyroid medications that block the synthesis of thyroid hormones or by treatment with radioactive iodine

and surgery resulting in loss of functional thyroid tissue. The therapeutic options available are: (I) antithyroid drug therapy, (II) surgery, and (III) radioiodine. These modalities are safe and cost-effective and can be the first-line treatment for hyperthyroidism not only due to GD, but also due to toxic adenoma, and toxic multinodular goiter [11]. Despite the use of these three treatments for decades, selection of the optimal therapy for GD still poses a challenge for both the physician and the patient. Each modality has its unique advantages and disadvantages with no single best therapy for all patients. A prudent approach is to make a selection after a thoughtful discussion with the patient regarding advantages, risks, and cost-effectiveness, taking into consideration the values and preferences of the patient. Autoimmune nature of the disease and lack of treatment to address the underlying autoimmune pathogenesis has turned the research focus on the potential use of immunotherapy in GD [12]. Despite the good understanding of the underlying mechanism, it is worth mentioning that the selection of the right therapy for each patient still poses a challenge to the clinician as there is no single best therapy for all patients [13].

3. Antithyroid drugs therapy for GD

ATD are used as first line therapy in the majority of patients and represent the predominant therapy in Europe, Asia, and as bridge therapy in the USA [12]. The main ATDs are thionamides, such as carbimazole (CBZ), methimazole (MMI) the active metabolite of the CBZ and propylthiouracil (PTU). CBZ, a prodrug molecule needs decarboxylation in the liver to get converted to its active substance MMI. Thionamides block the formation of thyroid hormone T3 and T4 by inhibiting enzyme thyroid peroxidase. A 12- to 18-month course of antithyroid drugs may lead to a remission in approximately 50% of patients with theoretically significant (albeit rare) adverse reactions.

Thyroid gland plays the central role in the metabolism of iodine and synthesis of thyroid hormones such as T3 and T4. Thyroid follicular cells take up the iodine from blood stream through an active transport system constituted by a transporting protein sodium iodide symporter (NIS) which is located at the basolateral membrane of these follicular cells. This iodine is used for the process of iodination whereby iodine binds to tyrosine molecule of thyroglobulin (Tg) promoted by enzyme thyroid peroxidase. The process of iodination of tyrosine molecules leads to the formation of 3-monoiodotyrosine (MIT) and 3, 5-diiodotyrosine (DIT) which is coupled afterwards leading to the formation of thyroid hormones. Triiodothyronine (T3) hormone is formed by coupling of one molecule each of MIT and DIT and thyroxine (T4) hormone is formed by coupling of two DIT molecules. These thyroid hormones are stored in the thyroid cells as colloid in a quantity enough to meet the body requirements for up to 3 months. The whole process of formation of thyroid hormones is regulated by thyroid stimulating hormone (TSH) released from anterior pituitary gland which stimulates the expression of NIS through TSH receptor (TSH-R) which then activates follicular cells. The uptake and metabolism of the radioactive iodine (I-123 and I-131) follows the same process as nutritional iodine to get incorporated into the thyroid hormones [13].

Thionamide drugs are actively transported into the thyroid where they serve as the preferential substrate for the iodinating intermediate of thyroid peroxidase and thus interfere with the iodination of tyrosine resulting in inhibition of the synthesis of T3 and T_4 hormones. This whole process results in the diversion of oxidized iodine from

the tyrosyl iodination sites in thyroglobulin. Thionamides also inhibit the coupling of iodothyronines and hence reduce the biosynthesis of thyroid hormones [14]. In addition, PTU also blocks extrathyroidal deiodination of T4 to T3 resulting in less conversion of T4 to T3, but this process of peripheral inhibition is of little clinical significance other than perhaps in the management of thyrotoxic crisis, when it is important to lower the raised serum T_3 concentration as quickly as possible.

ATDs are indicated as a first-line treatment of GD, particularly in younger subjects, and also for short-term treatment of GD before definitive therapy with RAI or thyroidectomy [6]. Available only as oral preparations, they however, have been used as retention enemas in patients in whom oral intake is not possible or is contraindicated. Alteration of intrathyroidal immunoregulatory mechanisms have been reported with ATDs which is believed to contribute to long term success of maintenance of disease remission. In addition they have been reported to have immunosuppressive effect resulting in reduction of TSHR-Ab levels, soluble IL-2 receptor (sIL-2R) and intercellular adhesion molecule-1 (ICAM-1) [15]. However, this immunomodulatory effect has proved to be short-lived as is evident from the presence of frequent relapse of Graves' hyperthyroidism in patients after drug withdrawal.

Historically, CBZ has been the drug of choice in the United Kingdom, but in all other areas of the world, MMI has been the drug of choice. The use of PTU is restricted to first trimester of pregnancy and in patients who have reacted adversely to CBZ or MMI and is also widely employed in the America.

ATDs are given consideration as first line therapy in the following category of patients with Graves' disease [16].

a. Younger patients

b. Bridge therapy as short term treatment prior to RAI or surgery.

c. Patients with mild disease (small size of goiter, negative or low TRAbs values),

d. Elderly comorbid patients at high risk of postoperative complications

e. Patients with a history of head and neck irradiation or surgery.

f. GD in pregnancy.

g. Rapid biochemical control in moderate to severe active Graves' orbitopathy (GO)

h. Lack of access to an experienced thyroid surgeon.

3.1 Carbimazole

Carbimazole, a pro-drug on oral administration is converted to methimazole in liver which is an active substance. Historically, CBZ has been the drug of choice in the United Kingdom and is also available in Europe, but is not approved for use in the United States. Conversion to active substance methimazole is rapid and almost complete either in the gastrointestinal tract or immediately on absorption, as is evident from the observation that only drug concentrations of methimazole but not carbimazole are detected in the serum and thyroid gland after ingestion. Ten milligrams of carbimazole is equivalent to 6 mg of methimazole. Carbimazole acts as the substrate

for thyroid peroxidase (TPO) and decrease the incorporation of iodide into tyrosine molecules. In addition, it also inhibits coupling of iodinated precursor molecules like mono-iodinated and di-iodinated residues to form T_4 and T_3 hormones.

Carbimazole has been preferred in some patients on account of fewer side effects such as less frequent gastrointestinal problems compared with methimazole. The starting dose of CBZ is usually between 20 to 40 mg/day depending on the severity of the hyperthyroidism. The initial high dose of the drugs can be tapered down after 4 to 8 weeks in what is referred to as the titration regimen. A maintenance dose of 5 to 20 mg of CBZ is achieved by about 4 to 6 months and this is continued for 12 to 18 months. Once a patient is on a maintenance dose of CBZ, thyroid hormone assessment is done every 2 to 4 months and the treatment continued for 12 to 18 months depending on the response to achieve the immunomodulatory role of the drug to reduce the rate of recurrence of the disease. The patients are followed on regular basis based on thyroid hormone levels and clinical status of the patient. Some studies have also advocated block and replacement regimen to avoid severe hypothyroidism during treatment where CBZ/MMI in dose of 30–50 mg daily along with thyroxin replacement is used throughout the coarse but side effects of ATD are more with this kind of regimen [17].

3.1.1 Adverse effects

Adverse effects associated with the use of antithyroid medication range from milder adverse events such subcutaneous eruptions, gastrointestinal disorders and arthralgia's to more serious complications as agranulocytosis, frank polyarthritis and hepatotoxicity (Explained in Section 2.1.2).

3.2 Methimazole

Methimazole, an antithyroid drug is an active metabolite of carbimazole- a prodrug, which belongs to the thionamide class. On entering the blood stream following oral administration, methimazole inhibits the enzyme thyroid peroxidase and thus decrease the incorporation of iodide into tyrosine residues of thyroglobulin resulting in the inhibition of the synthesis of thyroid hormones T4 and T3. Methimazole also inhibits oxidation of iodine and the coupling of iodotyrosyl residues and thus blocks the production of thyroid hormone [18].

The first line of therapeutic option for the treatment of Graves hyperthyroidism is usually Methimazole with few exceptions, due to the lower risk of hepatotoxicity compared to propylthiouracil [18]. Methimazole is usually the started from 10 to 30 mg daily in divided doses, with titration and variable maintenance doses depending on the severity of hyperthyroidism. As the disease goes in remission, dose is gradually reduced through the course of disease based on severity of the illness referred as "titration regimen". Thyroid function tests are done at 6–8 weekly intervals after initial treatment, and the dose is titrated based on T4 and T3 hormone levels. The levels of T3 & T4 are more reliable to guide the dosage of antithyroid drugs as the TSH values remain suppressed for long time. The oral route of administration and non-requirement dose adjustment except in patients with severe hepatic impairment makes the of MMI drug of choice worth consideration as ATD [18]. With the half-life exceeding 6 hours in follicular cells [19, 20], the administration of MMI in a single daily dose is considered to be effective [21, 22]. The patients with thyroid storm, require higher doses, with a starting dose of 60 to 80 mg per day with the dose divided every 4 to 8 hours, with a maximum dose of 120 mg [23].

Once a patient is on a maintenance dose of MMI, thyroid hormone assessment is done every 2 to 4 months and the treatment continued for 12 to 18 months depending on the response to achieve the immunomodulatory role of the drug to reduce the rate of recurrence of the disease.

3.2.1 Adverse effects

The adverse effects are usually not so common but serious drug reactions of methimazole seem to be dose related (40 mg/day or more). These adverse drug effects include agranulocytosis, hepatotoxicity, and teratogenicity [24].

Agranulocytosis can occur at any time during the course of MMI therapy but usually occurs in the first few months of initiation. Absolute granulocyte count of less than 500 per ml, fever and sore throat characterize the agranulocytosis. Patients are advised to stop the medication and report to the hospital for further management in case of development of such symptom. Treatment consists of stopping methimazole if the granulocyte count is less than 1000 per ml and give antibiotic treatment. Methimazole associated agranulocytosis predicts the risk of agranulocytosis due to propylthiouracil, thus necessitating the circumventing of the use of propylthiouracil in these patients.

Cholestasis characterize the MMI associated hepatotoxicity and is dose independent and shows slow recovery after discontinuation of the drug [25].

The teratogenic effects of MMI include aplasia cutis, facial dysmorphism, esophageal and choanal atresia, umbilical malformations as well as craniofacial malformations and are result of free placental crossing of the drug, especially in the first trimester. For this reason, the use of propylthiouracil in the first trimester of pregnancy is preferred [25, 26].

3.3 Propylthiouracil

Propylthiouracil is an antithyroid drug that is mostly used as a second treatment option in hyperthyroidism after MMI/CBZ owing to higher risk of hepatotoxicity. In patients with a contraindication to CBZ/MMI or radioactive iodine therapy, propylthiouracil provides an option to be used as second line treatment option. Propylthiouracil is however, preferred as the first line of treatment in patients with thyroid storm because of its greater efficacy on account of inhibition of the thyroid deiodinase resulting in the peripheral conversion of T4 to T3. Similarly in the first trimester of pregnancy, propylthiouracil is favored because of the relatively lower teratogenic profile compared to methimazole [25].

Propylthiouracil acts by inhibition of thyroid peroxidase, enzyme responsible for oxidization of iodine and its incorporation into the tyrosine molecule, resulting in inhibition of the formation of monoiodothyronine and diiodotyrosine. Unlike methimazole, propylthiouracil causes peripheral inhibition in conversion of T4 to T3 by inhibiting the enzyme deiodinase [25, 26].

The drug like CBZ is also available only as an oral preparation. The severity of the hyperthyroidism usually guides the starting dose of the propylthiouracil. The usual starting dose is 300 mg daily divided every 8 hours, with titration of the dose up to a maximum dose of 600 to 900 mg daily. However, the usual dose of propylthiouracil in patients with thyroid storm is 500 to 1000 mg daily divided every 4 hours [25, 26]. Once patient is euthyroid, the maintenance dose of propylthiouracil is around 100 to 150 mg per day.

3.3.1 Adverse effects

U.S. Food and Drug Administration's has issued a box warning highlighting higher risk of severe liver injury associated with use of propylthiouracil. As a consequence of this serious adverse effect, CBZ/MMI is preferred as first line of treatment except in patients with an adverse drug reaction to CBZ/MMI and during the first trimester of pregnancy [27, 28]. However, adverse effects of propylthiouracil has not been associated with the dose of drug unlike methimazole [24]. Hepatic injury and acute viral hepatitis like syndrome is one of the most perturbing adverse drug effects of the propylthiouracil, arising 2 to 12 weeks after starting the medication. These adverse drug reactions can occur at any time during the course of treatment but are usually observed during the first 6 months of treatment. The specific symptoms along with raised liver enzymes point to the initial diagnosis. The injury can be severe and many fatal cases have been described. The presence higher risk of hepatotoxicity in pregnancy, excludes the use of methimazole in the first trimester [25, 26].

ANCA-associated vasculitis has been associated with the use of propylthiouracil and is responsible for conditions like glomerulonephritis, alveolar hemorrhage, central nervous system compromise, and leukocytoclastic vasculitis. These conditions though less frequent, may be responsible for significant morbidity and may improve upon drug withdrawal or require additional immunosuppressive treatment [25, 26].

Agranulocytosis as an adverse reaction is seen in up to 0.5% of patients, especially in the first 3 months of treatment. The agranulocytosis may manifest with symptoms like sore throat, fever and decrease in absolute granulocyte count. Patient are educated about the possibility of this condition and instructed to stop the medication and report to the hospital for further management.

Hypersensitivity, interstitial nephritis, hypothyroidism, aplastic anemia and potential teratogenicity are the other adverse effects seen with use of propylthiouracil [25, 26].

4. Radioiodine therapy

Radioactive iodine has been used for several decades to treat thyroid disorders (both malignant and benign) and preferred first-line treatment in many cases like GD. A safe and effective management modality, RAI is used as definitive treatment for GD except for the development or worsening of thyroid eye disease in approximately 15–20% of patients [29]. RAI in GD involves systemic administration of I-131 for selective irradiation of hyper functioning thyroid gland. Radioiodine on administration is taken up by thyroid gland and is incorporated into the thyroid hormones. Ionizing damage and tissue necrosis by radioiodine is responsible for destruction of the follicle cells of the hyper functioning thyroid gland resulting in an eventual ablation of functional thyroid tissue and thus providing a definite therapy of hyperthyroidism thereby improving patient's quality of life.

Exacerbation of underlying orbitopathy apart, radioiodine therapy is well tolerated with fewer complications. The safety and efficacy of radioiodine treatment and the several beneficial effects over thyroid surgery and ATDs have been documented and are widely accepted. A beta-emitting radionuclide with a physical half-life of 8.4 days, I-131 is the radionuclide of choice to treat thyroid disorders. Beta-minus decay of I-131 results in emission of high-energy beta particles which are responsible for high

radiation, particularly to the thyroid follicular cells, gradually leading to the destruction of these cells manifesting as volume reduction and therapy outcome in GD.

Radioiodine mediated radiobiological effects are the result of the DNA damage effected through breakage of molecular bonds, and/or through the formation of free radicals leading to genetic damage, mutations, or cell death. This leads to a decrease production of thyroid hormones and/or reduction in the size of thyroid gland. However, there are no ideal methods of predicting the clinical response or of measuring the individual radio sensitivity to RAI therapy [30].

RAI has been the most preferable treatment in USA for many years, but currently there is a tendency towards ATD therapy on account of being safe and definitive therapy for GD. The goal of RAI treatment is to radiate thyroid cells to render the patient euthyroid using low doses of I-131. Hypothyroidism being an inevitable and unpredictable progressive outcome of RAI treatment, is the desired result of RAI treatment and considered as the elimination of hyperthyroidism [31]. Though the RAI therapy is safe and effective and is considered as first line therapy in many cases but is preferably indicated for individuals who are at higher risk of surgical complications, or in those with a history of prior surgery or irradiation of the head and neck, previously operated, and after failure of ATD therapy to control hyperthyroidism and/or contraindications to ATD therapy. Similarly it is preferred modality of choice in the absence of access to an experienced thyroid surgeon and in patients with right heart failure, periodic thyrotoxic hypokalemic paralysis, congestive heart failure or pulmonary hypertension [16].

Radioablation is contraindicated in pregnant and breastfeeding women, inability to follow radiation safety rules, suspicion of thyroid cancer and in moderate to severe orbitopathy [16]. Female patients of childbearing age should undergo a pregnancy test 3 days prior to radioiodine administration and provide written signed declaration confirming the non-pregnant status. Serum pregnancy test being more sensitive is preferable to urine test [32].

Patients should be advised against the conception 6 months post RAI therapy. RAI therapy should be administrated 6 weeks to 3 months after lactation is disrupted [33].

Patients must be instructed to discontinue use of all iodine containing medications and be placed on an iodine-restricted diet in order to increase radioiodine uptake (RAIU) and thus to have desired therapeutic effect. Withdrawal of ATD for 3–7 days and iodine restriction for 1 to 2 weeks before RAI administration is also recommended.

RAI administration in hyperthyroidism provides symptomatic relief within weeks. To avoid increased failure rate and reduced the rates of hypothyroidism, ATDs can be withheld for 3–7 days before and after radioiodine administration [15, 34]. Patients at a higher risk of cardiac complications especially rhythm disturbances due to severe hyperthyroidism should be put on B-adrenergic blockade.

RAI treatment may experience some side effects of radioiodine therapy despite being considered safe. Post radiation thyroiditis an adverse effect of radiation treatment manifest as transient elevation of thyroid hormones resulting in exacerbation of hyperthyroid symptoms. The risk of eventual hypothyroidism though a desired result, is high especially after treatment of GD. However, the most undesirable and potentially troublesome adverse radiation effect is potential worsening of thyroid associated ophthalmopathy. Therefore, a close monitoring of the thyroid function is warranted to detect hypothyroidism earlier on in order to be treated as soon as possible.

Post radioiodine therapy thyroid hormones return to normal levels in the majority of the patients while resolution of clinical symptoms is observed in 4–8 weeks post

therapy. Hypothyroidism sets in more than 80% of the patients 16 weeks post RAI therapy. The post radiation hypothyroidism is usually permanent however, in rare cases it may be transient and the patient may return to a euthyroid state or remain hyperthyroid. In the latter scenario there is no decrease of patients thyroid size [16]. Factors observed to affect the outcome of RAI treatment include thyroid size, iodine intake (diet or iodine containing medicine), dose regimens, compensation of hyperthyroidism, and the timing of the withdrawal of ATDs.

To assess the efficacy of the radioiodine treatment and timely detection of developing hypothyroidism or persistent hyperthyroidism close monitoring of the thyroid function is essential for favorable outcome. The review of thyroid function should be carried out within 1–2 months by assessing the values of serum TSH, FT4 and FT3 to be repeated every 4–6 weeks for the first 6 months or until the patient becomes hypothyroid and is stable on levothyroxine replacement [35].

5. Surgery

Thyroidectomy is the oldest and the preferred modality of treatment for Graves' disease and has been found to be at par with ATDs and radioiodine in reducing the serum thyroid hormone levels with normalization of hormone levels within 6 weeks of therapy [36]. The role of thyroid surgery particularly as an alternative to ATD in uncontrolled hyperthyroidism despite being on higher drug doses or in cases of recurrent hyperthyroidism is an attractive option. Surgical management again is a preferred option for patients in few conditions, such as in patients with large goiters with compressive symptoms, women desirous of conception shortly after treatment, younger patients with high risk of recurrence following medical management, nodular thyroid where malignancy may coexist. Patient's undergone surgical thyroidectomy is advised against the conception till they achieve euthyroidism either spontaneously or with levothyroxine replacement therapy. The surgical thyroidectomy does not appear to affect the course of Graves ophthalmopathy thus risk of its exacerbation and as such preferred mode of management in severe Graves' ophthalmopathy. Failure of antithyroid medications or radio-iodine therapy and patient preference to surgical approach are the other indication for thyroid surgery so are the patients who do not want the exposure to antithyroid drugs or radioiodine.

5.1 Preoperative management

The patients must reach euthyroidism to achieve hemodynamic stability, before they can undergo surgery. This will reduce the risk of complications [6, 37]. Preparation for surgery involves use of [38]:

1. Beta blockers such as propranolol (40–120 mg/day) or atenolol (25–50 mg/day) should be used until patient is clinically euthyroid that is thyroid function levels are within the normal limits

2. ATD therapy is used up until the day of surgery.

3. Use of potassium iodide (KI), saturated solution of potassium iodide (SSKI), or Lugol solution preoperatively have been shown to decrease the vascularity of the gland, thyroid blood flow and intraoperative blood loss beside acute inhibitory

effects of iodide on new thyroid hormone synthesis, referred to as the Wolff-Chaikoff effect. However, use of iodide products has not been associated with change in outcomes in few studies.

3.1 SSKI is used as 1 to 2 drops (50 mg/drop) TID and should be initiated 7 to 10 days prior to surgery and discontinued on the day of surgery.

3.2 Similarly Lugol solution (KI-iodine solution) as 5 to 7 drops (8 mg iodide/iodine per drop) daily can also be used as alternative [16].

3.3 In addition, corticosteroid like betamethasone 0.5 mg every 6 hours) or dexamethasone (2 mg orally or intravenously 4 times daily) and cholestyramine (4 grams six hourly) can be used for rapid preparation for emergent surgery to avoid the risk of thyroid storm.

Although preoperative use of these compounds has been advocated by ATA guidelines, the advantages of use of these agents preoperatively on the outcome of surgery is still debated.

4. The pre-op levels of serum calcium and vitamin D levels should be determined to establish a baseline level. Replacement therapy should be instituted if low to avoid post op hypocalcemia.

5. Postoperatively serum calcium, albumin and parathyroid hormone levels should be measured to screen for postop hypocalcemia so to have earlier detection of transient and later permanent hypoparathyroidism

6. Pre-op substitution of calcium carbonate in the dosages of 1gram for 3 weeks prior the procedure can avoid postoperative hypocalcemia.

7. Postoperatively all patients should be advised to have 1gram calcium carbonate three times a day for 2 weeks until the normalization of calcium and parathyroid hormone (PTH) levels are documented.

5.2 Total thyroidectomy versus subtotal thyroidectomy

Total thyroidectomy (removal all of the thyroid tissue) is preferred to subtotal thyroidectomy (leaving 4 to 7 grams of thyroid). The extent of thyroid resection in GD remains controversial. Total thyroidectomy versus subtotal thyroidectomy is a balance between risk of recurrence of hyperthyroidism in case of subtotal thyroidectomy and incidence of hypothyroidism seen with total thyroidectomy [38]. Total thyroidectomy is given the preference to subtotal thyroidectomy to avoid the risk of recurrence at the cost of rendering the patient on the side of hypothyroidism, in addition to avoid the second surgery to remove the residual tissue, which will be more difficult on account of scar tissue formation and distortion of tissue planes with prior surgery i.e., subtotal thyroidectomy [39]. In a systematic review and meta-analysis of total vs. subtotal thyroidectomy for GD by Feroci et al., the odds ratio (OR) of transient and permanent hypoparathyroidism favors subtotal thyroidectomy, the OR of the recurrence of hyperthyroidism favors total thyroidectomy [37]. One of the randomized trials involving 191 patients of GD by Barczynski et al., compared total thyroidectomy vs. subtotal thyroidectomy and followed these patients over a span of 5 years. Patients undergoing total thyroidectomy had a complete remission of the

disease and lower risk of hypoparathyroidism (transient and or permanent) compared to subtotal thyroidectomy cohort [39].

Total thyroidectomy offers a better chance of cure of hyperthyroidism than bilateral subtotal thyroidectomy despite the controversy regarding the extent of thyroid resection in GD and can be accomplished safely with slight increase in the risk of temporary and permanent hypoparathyroidism.

Total thyroidectomy has been endorsed as the procedure of choice for the surgical management of GD [40] despite other studies [41, 42] arguing that subtotal thyroidectomy especially when performed with a remnant thyroid tissue of less than 3 gm, may allow permanent cure of hyperthyroidism to ensure euthyroid state in a significant proportion of patients with lower risk of recurrent hyperthyroidism [43].

5.2.1 Complications

Nonfatal complications associated with surgery are hypoparathyroidism either permanent (1–3%) or transient (10%) and vocal cord paralysis and hypothyroidism.

6. Management of Graves' disease during pregnancy

Graves' disease affects approximately 0.1% of pregnancies and if inadequately treated carries a substantial risk of adverse effects in both mother and child [44]. Untreated hyperthyroidism results in increased risk of pre-eclampsia, preterm delivery, low birth weight and increased neonatal mortality and morbidity. The mother is also at increased risk of heart failure, thyroid storm and pre-eclampsia. Changes in thyroid hormone concentrations that are characteristic of hyperthyroidism must be distinguished from gestational thyrotoxicosis affecting as many as 20% of pregnancies resulting TSH receptor stimulation by elevated serum levels of human chorionic gonadotropin (hCG), especially in the first trimester to ensure the early recognition and management to have a favorable outcome. Fetal hyperthyroidism can be life-threatening, and needs to be recognized as soon as possible so that treatment of the fetus with antithyroid drugs via the mother can be initiated. Antithyroid drug treatment of hyperthyroidism in pregnant women is controversial because in utero exposure with the usual ATDs especially methimazole and/or carbimazole have been the associated with between severe birth defects and the alternative propylthiouracil with hepatotoxicity. As both propylthiouracil and methimazole are associated with birth defects, lowest effective dose of an antithyroid drug should be used to maintain thyroid function at the upper limit of the normal range in order to avoid overtreatment and subsequent fetal hypothyroidism [45]. The use of propylthiouracil in the first trimester and methimazole during the remainder of pregnancy is currently recommended on the basis of a consideration of potentially severe birth defects.

Thyroid function should be monitored monthly. In up to 50% of cases, antithyroid drugs may be discontinued after the first trimester as GD improves spontaneously during pregnancy, but postpartum relapse is common due to a rebound in autoimmunity [44]. Elevated Thyrotropin-receptor antibodies levels especially by a factor of more than 3 in the third trimester, identifies pregnancies at risk for neonatal hyperthyroidism [44]. Breast-feeding is safe with either methimazole or propylthiouracil, but methimazole is recommended for postpartum therapy and does not affect infant thyroid function in the doses commonly used [46, 47].

PTU is the preferred antithyroid agent during pregnancy, as congenital anomalies such as aplasia cutis (single or multiple lesions of 0.5 to 3 cm at the vertex or occipital area in the scalp), choanal and esophageal atresia are reported more frequently with MMI [48]. However, the incidence of these anomalies is quite rare and it is acceptable to continue MMI particularly in areas where PTU is not easily available. The PTU dosage is reduced to the lowest effective dose to maintain the fT4 towards the upper end of the reference range with monthly monitoring of thyroid functions [49]. The activity levels of Graves' disease may fluctuate during pregnancy, with exacerbation during the first trimester with improvement in later pregnancy with a higher chance of an exacerbation soon after delivery. Therefore, thyroid function should be monitored every 2 to 3 months for 1 year following delivery to detect early relapse.

7. Newer therapeutic options

Newer treatment options based on antigen-specific Immunotherapy, immunobiology such as biologics, small molecules and peptide immunomodulation under investigations are in different stages of development particularly aimed at achieving euthyroidism without the requirement for ongoing therapy.

7.1 Antigen-specific immunotherapy

The antigen-specific immunotherapies are intended to restore the immune tolerance to the immunodominant epitopes responsible for the aberrant autoimmune response. Lack of generalized immunosuppression and skewing of the immune response associated with these therapies pose no greater risk of infection or different immune-mediated conditions. A study by Pearce et al., investigated a combination of two TSHR peptides (ATX-GD-59) in 12 subjects with mild-to-moderate untreated hyperthyroidism that was administered 10 times to each participant over 18 weeks by intradermal injection, in 12 subjects with mild-to-moderate untreated hyperthyroidism. The treatment was also well tolerated, with 10/12 participants finishing the study and 7/10 subjects had improvement in their thyroid function over the 18 weeks of ATX-GD-59, with 50% normalizing their serum fT3 concentrations, reduction in serum TSHR autoantibodies suggesting that ATX-GD-59 may have a significant potential for effective disease-modifying therapeutic cure in GD [50].

7.2 Immunomodulation

Immunomodulation of B lymphocytes by directly targeting the B cells or their associated interactors and cytokines by molecules such as iscalimab (anti-CD40), belimumab (anti-BAFF), and rituximab (anti-CD20).

7.3 Blocking of signaling

Blocking of signaling of TSH receptors by small molecular TSHR antagonist and *TSHR stimulation by TSH or TRAbs* (K1–70 blocking),

7.4 Inhibition of immunoglobulin

Inhibition of immunoglobulin recycling by blocking the neonatal Fc receptor (efgartigimod and rozanolixizumab), which recycles endocytosed IgG antibody by

binding it in the acidic conditions of the lysosome and recycling it to the cell membrane for release back into the circulation [51].

These newer therapies may dawn the era of restoring a euthyroid state in the patients of GD without the need for ongoing therapy with least potential risks such as immunocompromise and render destructive radioiodine thyroid ablation and thyroidectomy obsolete.

8. Conclusions

The treatment of Graves' disease, a most common cause of hyperthyroidism should be tailored to the specific needs of each patient with the benefits and risks of each therapy explained in full. Antithyroid drugs, surgery and radioactive iodine are still therapeutic options of choice and are widely available and exercised. Antithyroid drugs continue to be the first line of treatment, except for patients with contraindications or intolerance. Surgical ablation is still an option in a smaller proportion of patients with particular conditions. Radioactive iodine therapy has gained more acceptability and in many cases it is preferred first-line treatment. RAI is a safe and effective definitive treatment for GD.

New treatment options with biological and immunomodulatory therapy are under development and in the future may be a treatment option with a lower risk of toxicity and perhaps higher rates of cure.

Conflict of interest

There is no conflict of interest.

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