Non-thionamide antithyroid drug options in Graves’ hyperthyroidism

Short title: Non-thionamide therapies in Graves’ disease

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ABSTRACT

Introduction

The thionamide anti-thyroid drugs namely carbimazole, methimazole, and propylthiouracil, have been the predominant therapy modality for Graves’ hyperthyroidism for over 60 years. Although these agents have proven efficacy and favourable side-effect profiles, non-thionamide alternatives are occasionally indicated in patients who are intolerant or unresponsive to thionamides alone. This review examines the available non-thionamide drug options for the control of Graves’ hyperthyroidism and summarises their clinical utility, efficacy, and limitations.

Areas covered

We reviewed existing literature on mechanisms, therapeutic utility, and side-effect profiles of non-thionamide anti-thyroid drugs. Established non-thionamide agents act on various phases of the synthesis, release, and metabolism of thyroid hormones and comprise historical agents such as iodine compounds and potassium perchlorate as well as drug repurposing candidates like lithium, glucocorticoids, beta-blockers, and cholestyramine. Novel experimental agents in development target key players in Graves’ disease pathogenesis including B-cell depletors (Rituximab), CD40 blockers (Iscalimab), , TSH-receptor antagonists, blocking antibodies, and immune-modifying peptides.

Expert opinion

Non-thionamide anti-thyroid drugs are useful alternatives in Graves’ hyperthyroidism and more clinical trials are needed to establish their safety and long-term efficacy in hyperthyroidism control. Ultimately, the promise for a cure will lie in novel approaches that target the well-established immunopathogenesis of Graves’ disease.

KEYWORDS

Hyperthyroidism, Graves’ disease, Antithyroid drugs, Carbimazole, Methimazole, Propylthiouracil, non-thionamide agents
ARTICLE HIGHLIGHTS

- Non-thionamide anti-thyroid drugs are occasionally indicated in patients with Grave's hyperthyroidism either as adjunctive treatment in pre-surgical or severe cases, or in patients who are intolerant or unresponsive to thionamides.

- Iodine containing compounds, potassium perchlorate, lithium, glucocorticoids, beta-blockers, and cholestyramine, all act on various stages in the synthesis, release, and metabolism of thyroid hormones and have been used with varying efficacy in short term control of hyperthyroidism.

- Iodine compounds are used for rapid pre-operative control pending thyroidectomy while beta-blockers, glucocorticoids, cholestyramine, and lithium are used adjunctively for rapid control of hyperthyroidism in severe presentations.

- Glucocorticoids, cholestyramine, and potassium perchlorate have been used as adjunct therapy in amiodarone induced thyrotoxicosis while pre-therapeutic lithium has been shown to increase the effectiveness of radioactive iodine therapy.

- Novel therapeutic agents in various phases of drug design and development target key players in Graves’ disease pathogenesis including antibody producing B-cells and the TSH receptor antibody-receptor complex.

- Further clinical trials are needed to establish the safety and long-term efficacy of non-thionamide therapies in the control of hyperthyroidism. In particular, novel therapeutic approaches that address the immunopathogenesis of Grave’s disease hold promise for the future.
1. INTRODUCTION

In 1835, Robert Graves described women with enlarged thyroid glands, exophthalmos and palpitations, a condition that became widely known by the eponym, Graves’ disease [1]. Graves’ disease accounts for most cases of hyperthyroidism in iodine sufficient parts of the world and affects about 1% of the population [2, 3]. The condition is characterised by the production of TSH receptor antibodies (TRAbs) that induce hyperthyroidism through unregulated stimulation of the TSH receptor [4]. Uncontrolled hyperthyroidism is associated with significant morbidity from the multisystemic effects of thyroid hormone excess and leads to impaired quality of life [5], reduced productivity [6], and poor reproductive outcomes in women [7]. In addition, about 25-50% of patients have orbital involvement or orbitopathy which in rare instances may be complicated by sight loss [8]. Uncontrolled disease also carries an increased mortality risk from cardiovascular complications such as cardiac arrhythmias, strokes, and heart failure and prompt control of hyperthyroidism is essential for optimal long-term outcomes [9]. Furthermore, poorly controlled hyperthyroidism may culminate in the rare but potentially fatal thyroid storm, a medical emergency with mortality rates of about 5-25%, even in the best of centres [10].

Three well-established therapeutic modalities, namely antithyroid drugs, radioactive iodine, and thyroid surgery have been used successfully to treat Graves’ disease for over seven decades [11]. Despite regional variations in practice, antithyroid drugs are commonly the first line of therapy and remain the preferred choice of treatment in most parts of the world [12]. The thionamide antithyroid drugs, methimazole (MMI), its pro-drug derivative, carbimazole (CMZ), and propylthiouracil (PTU), have been successfully used to control hyperthyroidism for over 60 years [11]. The thionamides are thiourea derivatives which inhibit thyroid hormone synthesis by interfering with
thyroid peroxidase mediated iodination and coupling of tyrosine residues [13]. PTU also has additional effects of inhibiting peripheral T4 to T3 conversion [13]. Both CMZ/MMI and PTU are highly effective in controlling hyperthyroidism and oral doses are rapidly absorbed from the gastrointestinal tract with peak levels attained within two hours of dosing [13]. On initiation the clinical effects of these compounds are usually evident within 3-4 weeks and most patients report improvement in symptoms with minimal side effects [13].

One drawback to the use of thionamides however is that a small proportion of patients suffer serious side effects such as agranulocytosis [14] and liver failure [15, 16]. Such adverse effects preclude further use of thionamides and hence the need to control thyroid function with alternative pharmacological agents pending definitive treatment. Non-thionamide antithyroid therapies are also indicated in a small number of individuals who fail to respond satisfactorily to thionamides even after potential problems such as compliance, dose optimisation, and malabsorption have been excluded [17]. Lastly, adjunctive non-thionamide agents may be lifesaving in rapidly restoring thyroid function in individuals with severe thyrotoxicosis and thyroid storm [18]. This review examines the available non-thionamide therapies available for the control of hyperthyroidism and summarises their clinical utility, efficacy, and limitations.

2. METHODS

We searched Medline for articles published from 1990 to October 2022 using combinations of the following keywords: Graves’ disease, hyperthyroidism, thionamides, antithyroid drugs, carbimazole, methimazole, propylthiouracil, cholestyramine, betablocker, propranolol, iodine, iodide compound, potassium perchlorate, glucocorticoids, steroids, lithium, Rituximab and TSH-receptor antagonist. In addition, we searched treatment guidelines of the major international endocrine and
thyroid associations and obtained additional articles from the references in the initial search. Our focus was on high-quality original studies, meta-analyses, and randomised controlled trials that have contributed to knowledge and practice. Since our review was on non-thionamide drug options in Graves’ hyperthyroidism, we did not address standard aspects of care including conventional thionamide and ablative therapies or the management of Graves’ orbitopathy.

3. INDICATIONS FOR NON-THIONAMIDE THERAPIES

3.1 Adjunctive therapies

The key indications for non-thionamide therapies are listed in table 1. Non-thionamide therapies are used adjunctively to obtain rapid symptom control in newly diagnosed patients or in patients who relapse after primary therapy [19]. β-blockers are well established in this regard and are effective in controlling hyperadrenergic symptoms pending the clinical effect of antithyroid drugs which usually takes about 3-4 weeks [10, 20]. Adjunctive therapies may also be used short term in preparing patients for thyroidectomy or radioiodine therapy. A solution of Lugol’s iodine is used preoperatively to control thyroid function and to reduce thyroid gland vascularity in preparation for surgery [10].

3.2 Thyroid storm

Non-thionamide therapies are used in the management of thyroid storm where rapid control of thyrotoxicosis is essential. β-blockers and glucocorticoids are particularly useful in this regard due to their immediate action in reducing peripheral conversion of thyroxine (T4) to triiodothyronine (T3). In addition these drugs have the added advantage that they can be administered parenterally in critically ill patients [10]. Other non-thionamide therapies like cholestyramine and lithium have also been used to achieve rapid control of thyrotoxicosis in patients with thyroid storm [21].
3.3 Serious thionamide side effects

Non-thionamide therapies are indicated in patients who cannot tolerate thionamides. Minor thionamides reactions such as fever, itching or rash are reported in about 1-5% of patients, but these can be safely managed by switching from one thionamide compound to the other [22]. On the other hand, more serious side effects preclude further use of thionamides. Thionamide induced agranulocytosis has an estimated incidence of 0.1-0.4% and carries a mortality risk especially in the elderly or vulnerable [14]. PTU induced hepatotoxicity, although rarely observed, can lead to liver dysfunction, fulminant liver failure, or fatality [15]. In addition, CMZ/MMI has been associated with cholestatic liver disease and a hepatitis-like picture. CMZ/MMI has also been associated with liver failure, although this is rare and even less common than PTU induced liver failure [21]. Ultimately, patients who suffer serious side effects will need definitive therapies such as radioiodine or thyroidectomy. Pending such treatment there remains a need to control thyroid function with alternative pharmacological agents.

3.4 Thionamide refractoriness

Alternative therapies are indicated in individuals who fail to respond to thionamides [17, 23, 24] although true thionamide refractoriness is rare. In reality only a handful of cases have been reported in which all potential causes of treatment unresponsiveness including medication compliance, dose optimisation, and malabsorption have been excluded. Several mechanisms have been proposed to explain thionamide refractoriness including malabsorption, abnormal drug metabolism, decreased tissue uptake, and the presence of thionamide-binding antibodies [17, 25]. However, these mechanisms may be related to the severity of thyrotoxicosis which can usually be overcome by adequately high doses. Cases have been reported in patients that were
resistant to multiple treatments including thionamides, β-blockers, and iodine compounds, suggesting a generalised consequence of disease severity rather than specific drug defects [23, 24]. Thus, true thionamide refractoriness should only be considered in exceptional circumstances after factors such as dose, medication compliance, and malabsorption have been excluded (table 2).

4. PHARMACOLOGICAL MECHANISMS

The available thionamide and non-thionamide therapies exert their antithyroid effects through actions on multiple pathways involved in thyroid hormone production and metabolism (figure 1). In this section we briefly outline the immunopathogenesis and synthesis of thyroid hormones and present an overview of general pharmacological mechanisms in the management of hyperthyroidism.

4.1 Immunopathogenesis

In Graves’ hyperthyroidism, the key pathological event is production of the TSH receptor antibody (TRAb), a membrane glycoprotein with a binding site for the g-protein coupled TSH receptor on the surface of the thyroid epithelial cells [26]. In individuals who develop Graves’ disease, TRAbs with stimulatory and occasionally inhibitory actions are produced in response to a complex interplay of genetic predisposition and environmental triggers [4]. The immunopathogenesis involves intricate interactions between B and T lymphocytes, and with the TSH antibody-receptor complex. B-cells play multiple inter-related roles including the production of pathogenic TRAbs, antigen presentation, and the initiation and the perpetuation of the autoimmune process through T-cell interactions and production of inflammatory cytokines [27]. Ultimately, stimulatory TRAbs induce increased thyroid hormone production through unregulated stimulation of the TSH receptor and activation of cAMP-dependent signaling pathways [4].
4.2 Thyroid hormone synthesis

In the synthesis of thyroid hormone, inorganic iodide is trapped and taken up from the circulation by the sodium iodide symporter in the basolateral membrane of the thyrocyte [28]. Iodide diffuses to the apex of the cell and enters the colloid where it is oxidised to iodine and incorporated into tyrosine residues within thyroglobulin in a process catalysed by thyroid peroxidase (TPO). Iodination of thyroglobulin produces the iodotyrosines, moniodotyrosine (MIT) and diiodotyrosine (DIT), which are then coupled to form T4 and T3. When thyroid hormones are needed, thyroglobulin is transported back into the thyrocyte by endocytosis and then delivered to lysosomes where it is digested by proteases to release T3 and T4 into the circulation [28]. In addition, T4 is converted to T3 in the tissues through the action of peripheral deiodinases. The thyroid hormones are metabolised in the liver, conjugated with glucuronides and sulphates before biliary excretion [29]. The hormones are reabsorbed into the circulation through the enterohepatic pathway [30], a process that is increased in hyperthyroidism [31] (figure 1).

4.3 Overview of mechanisms

Perchlorates inhibit iodide uptake while thionamides, iodides, and lithium prevent TPO catalysed iodination of thyroglobulin and coupling of iodotyrosines [21]. Also, glucocorticoids and lithium inhibit release of thyroid hormones into the circulation [21]. Lithium may also affect thyroid function through inhibition of the hypothalamo-pituitary axis by impeding TSH action on cyclic AMP-mediated cellular pathways. Thionamides are also postulated to exert immunosuppressive effects through antibody suppression although it is unclear whether this is a consequence of their antithyroid effects rather than a direct antibody suppressive effect [13]. Some studies have also suggested that selenium has antibody suppressing effects [32]. Drugs with peripheral actions include
β-blockers, PTU, glucocorticoids, ipoiodate, and selenium which all reduce tissue conversion of T4 to T3, although with varying efficacy [21]. Cholestyramine, a bile acid sequestrant, acts by increasing intestinal T4 excretion via binding to bile acids in the gastrointestinal tract and interfering with enterohepatic reabsorption of bile [33] (figure 1).

In addition to the mechanisms affecting thyroid hormone production and metabolism described above, novel therapeutic compounds have been developed with targets on key immunological mechanisms in Graves’ disease pathogenesis. These include B-cell depletors (Rituximab), CD40 blockers (Iscalimab), TSH receptor antagonists, TSH receptor blocking antibodies, and immune modifying TSH receptor-peptides [34]. The mechanisms, clinical indications, utility, and side effects of the established non-thionamide therapies are summarised in section 5 and table 3 while the development and potential utility of novel therapeutic agents are discussed in section 6 and table 4.

5. NON-THIONAMIDE THERAPIES

5.1 Potassium perchlorate

Potassium perchlorate is a crystalline inorganic salt that exhibits a strong affinity for iodine and hence reduces thyroid hormone synthesis by competitive inhibition of iodide trapping and uptake by the sodium iodide symporter [35]. After oral administration, it is rapidly absorbed from the gastrointestinal tract attaining peak plasma concentration within 3 hours with a half-life of 6–8 hours. It is eliminated from the body via excretion in the kidney [35]. Perchlorate was widely used as an antithyroid agent in the 1950s but following reports of fatal aplastic anaemia at high doses [36] its use is now restricted as an adjunct to thionamides in individuals with type-1 amiodarone-induced thyrotoxicosis [37]. It is typically prescribed alongside thionamides at doses of 1 gram or lower, administered in 2-4 divided dose daily for 2–6 weeks [37]. Reported side
effects include abdominal discomfort, rash and agranulocytosis [37]. Rare instances of toxic bone marrow effects were reported in the 60s but these were only observed with high-dose therapy, i.e., doses exceeding 1 gram daily, and were rarely seen at doses lower than 400 mg daily [36].

5.2 Lithium

Lithium has been successfully used to treat psychiatric disorders for over a century and its pharmacokinetics and side effect profiles are well known [38]. The drug is avidly taken up by the thyroid achieving intrathyroidal concentrations that are 3-4 times higher than plasma concentrations [38]. It exerts thyroid hormone reducing effects through multiple mechanisms that affect iodide uptake, thyroglobulin iodination, coupling of tyrosine residues, and release of thyroid hormones, as well as inhibition of the hypothalamo pituitary thyroid axis [38, 39]. Lithium is used as adjuvant therapy in the management of hyperthyroidism, either in cases of thionamide intolerance, type-1 amiodarone-induced thyrotoxicosis, thyroid storm, or in preparation for surgery [21, 40]. In addition, it is used in preparation for radioiodine treatment as it improves radioiodine treatment effectiveness by increasing radioiodine retention in thyroid tissues [41].

The initial dose of lithium is 0.5–1.5 g daily, in 2-3 divided doses with dose adjustments made according to serum-lithium concentration. The drug is cleared by the kidneys in 18-36 hours, and its clearance is affected by renal impairment and age [38]. Toxic effects of lithium include thirst, polyuria, renal failure, tremors, twitching, seizures, coma and arrhythmias [42, 43]. Due to its narrow therapeutic range, serum concentrations should be monitored closely and maintained within the treatment range. Recommended maintenance levels in the UK, are 0.4-1.0 mmol/L for samples taken 12 hours after the last dose [44]. Routine monitoring should be performed
weekly after initiation of treatment or dose change. Once daily administration is preferred after stable therapeutic concentrations are achieved. The drug is available as regular and modified or slow-release Lithium carbonate tablets and also as Lithium citrate liquids [44].

5.3 Iodine compounds or iodides

Iodine containing compounds have been used to treat hyperthyroidism since the 19th century and were routinely used before the discovery of thionamides [45]. Their present-day use is confined to the treatment of thyroid storm or short term adjunctive pre-operative control of hyperthyroidism [21]. Iodine has the added benefit of reducing thyroid vascularity and minimising intraoperative blood loss in thyroid surgery [46]. The iodides reduce thyroid hormone synthesis through inhibition of thyroglobulin iodination and coupling with reduction in thyroid hormones occurring as early as 12 hours after treatment initiation [47]. This inhibitory effect, the acute Wolff-Chaikoff effect, is however transient and an “escape” from this phenomenon is seen after several weeks as the high iodide status downregulates NIS expression thereby reducing iodine transport into the thyroid [48]. Thus, it is likely that iodine treatment loses its effectiveness after 1-2 weeks and should not be continued beyond 10-14 days.

Side effects of iodine compounds are mild and uncommon and include rash, conjunctivitis, salivary gland pain, headaches, and rarely leukemoid eosinophilic granulocytosis [21, 49]. Available forms of iodine include potassium iodide (KI) which is readily available as tablets, a saturated solution of potassium iodide (SSKI), and Lugol’s solution comprising a mixture of iodine (50 mg/ml) and potassium iodide (100 mg/ml). Iodinated radiographic contrast media, namely sodium ipoiodate and iodopanoate have inhibitory effects on T4 to T3 conversion but are not widely available [10]. The American Thyroid Association (ATA) guidelines recommend the adjunctive
use of high doses of SSKI in patients with thyroid storm, administered at a dose of 5 drops (0.25 ml or 250 mg) orally every 6 hours [10]. An alternative is Lugol's solution at a dose of 0.1-0.3 mls three times a day [21].

Some studies have reported benefits of KI in patients with Graves’ disease, either as monotherapy or in combination with methimazole. In one non-randomised study in a Japanese population, drug-naive patients with mild Graves’ hyperthyroidism were treated with either KI monotherapy or MMI for 12-months. Using a propensity score analysis, the authors showed reductions in FT4, FT3, and TRAb levels in the KI group that were comparable to the MMI treatment group [50]. In a study of hyperthyroid patients with thionamide side effects potassium iodide was effective in two-thirds of cases and 40% experienced remission on potassium iodide alone [51]. In a recent study of 504 untreated patients with Graves’ disease who were treated with potassium iodide for six months, the authors observed complete (normal FT4 and non-suppressed TSH) or partial (normal FT4 and suppressed TSH) treatment response in 37% and 50% of the cohort respectively. In addition, patients who responded well initially to potassium iodide had better long-term remission rates [52].

5.4 Glucocorticoids

Glucocorticoids exhibit antithyroid effects by reducing thyroid hormone secretion and inhibiting peripheral conversion of T4 to T3 [53]. Betamethasone, dexamethasone, prednisolone, and hydrocortisone have all been used as adjunct therapy either in patients with thyroid storm, pre-operatively, pre-radioiodine therapy, or in cases of hyperthyroidism coexistent with other conditions such as pregnancy and pancytopenia [10, 21, 54]. Glucocorticoids are also effective in the treatment of type-2 amiodarone induced thyrotoxicosis and one randomised controlled study showed that prednisolone led to more rapid normalisation of thyroid function than iopanoate in patients with type-
2 amiodarone-induced thyrotoxicosis [55]. Because of their rapid effect, glucocorticoids are particularly useful in thyroid storm or in short adjunctive regimens [10]. Dexamethasone decreases serum T3 levels within 24-hours of the first dose with further reductions observed over the next 5 days [53]. International guidelines recommend that patients with thyroid storm should receive a loading dose of 300 mg of hydrocortisone intravenously, followed by 100 mg thrice daily, or alternatively 8 mg daily of dexamethasone [10, 56]. The adverse effects of high-dose glucocorticoids are well known. Glucocorticoids can cause impaired glucose control, increased blood pressure, immunosuppression, and fluid retention. Longer term use of steroids can increase the risk of peptic ulceration, reduced bone mineral density, and osteoporosis, diabetes mellitus, pituitary-adrenal suppression, as well as psychiatric reactions [57]. Thus, it is important to taper the dose of glucocorticoids once there is clinical improvement and thyrotoxicosis is controlled.

5.5 Beta-blockers

β-adrenergic blocking drugs are effective in controlling the hyper-adrenergic and hyper-metabolic symptoms of thyrotoxicosis such as anxiety, emotional lability, irritability, tremors, sweating, heat intolerance, palpitations, and tachycardia [20]. In addition, propranolol at high doses (>160 mg daily) reduces peripheral conversion of T4 to T3 [20]. The key indication for β-blockers is in patients with thyroid storm or in patients with severe symptoms at diagnosis pending the onset of action of thionamides. They should be considered in individuals with resting tachycardia, the elderly, and those with pre-existing cardiac disease [10]. Propranolol, a non-specific β-adrenergic blocking agent, is the drug of choice as it is more effective than cardio-specific β-blockers such as atenolol and metoprolol. It should be started at dose ranges of 40-160 mg daily but doses as high as 360 mg are tolerated in thyrotoxicosis.
due to increased drug clearance [10, 11]. In the management of thyroid storm guidelines recommend administering 60-80 mg of propranolol every 4 hours. An alternative agent to propranolol is esmolol infusion [10].

Several important cautions are worth noting with respect to the use of β-blockers. Although β-blockers are generally contraindicated in patients with asthma and chronic airway disease they can be used cautiously in patients with mild disease. Alternatively, calcium channel antagonists such as verapamil or diltiazem may be used to control tachycardia and tachyarrhythmias in patients intolerant to β-blockers [58]. Non-selective β-blockers should also be used carefully in patients with thyroid storm and heart failure. Cases of cardiorespiratory failure have been reported following the administration of β-blockers in individuals with thyroid storm and low output heart failure [59]. More research is needed to understand the risk factors and optimal use of β-blockers in patients with thyroid storm and heart failure.

5.6 Cholestyramine

Cholestyramine is a bile acid sequestrant that was initially used in the 1950s as an early cholesterol lowering agent prior to the advent of the statins [60]. Nowadays its main use is in the control of diarrhoea resulting from bile acid malabsorption or in treating cholestasis associated with conditions such as primary biliary cirrhosis [61]. As an anion exchange resin, cholestyramine binds bile acids in the gastrointestinal tract to form insoluble complexes that prevent their reabsorption [21]. Thyroid hormones are degraded in the liver and conjugated with glucuronides and sulphates before they are excreted in bile and subsequently reabsorbed from the intestines [29]. The liver is the main site of thyroid hormone metabolism and this enterohepatic circulation of thyroid hormones is accentuated in the thyrotoxic state [30, 31]. Thus, cholestyramine reduces thyroid hormone levels by interfering with intestinal thyroxine
reabsorption making it an effective adjunctive therapy for hyperthyroidism. Cholestyramine has been used successfully in thionamide resistant Graves’ thyrotoxicosis as well as in other thyrotoxic states such as amiodarone induced thyroiditis or thyroiditis secondary to immune modifying agents like interferon-alpha [24, 62, 63, 64].

The usual dose of cholestyramine for hypercholesterolaemia or biliary disease is 8-16 grams daily in divided oral doses. Adjunctive cholestyramine treatment at this dose was well tolerated and effective for up to 4 weeks in controlling hyperthyroidism in a series of small, controlled studies [65, 66, 67]. One study showed that low dose cholestyramine (2 grams daily) was well tolerated and equally effective as a higher dose regimen (4 grams daily) [68]. The main side effect of cholestyramine is that of gastrointestinal discomfort with symptoms such as bloating, flatulence, and constipation [69]. These features may however offer benefit in counteracting some of the gastrointestinal symptoms of thyrotoxicosis such as hyper-defecation or diarrhoea. In addition, cholestyramine can also reduce absorption of other drugs. For example, co-administration of cholestyramine with levothyroxine results in reduced treatment efficacy in individuals with hypothyroidism [70]. Thus, it is advised to avoid administering other medications one hour before or four hours after cholestyramine is ingested. A summary of the mechanisms, clinical utility, and side effects of the non-thionamide therapies discussed above are presented in table 3.

6. NOVEL THERAPEUTIC APPROACHES

Traditional antithyroid drugs affect thyroid hormone synthesis and metabolism but exert no specific effect on Graves’ disease immunopathogenesis. Thus, biochemical disease control is frequently unrelated to the immunological disease course leading to frequent episodes of relapse after antithyroid drug treatment. Newer therapeutic
approaches focus on the key immunological players in Graves’ disease pathogenesis although these therapies are still largely experimental. Emerging treatments are described below and summarised in table 4. [34]. [27].

6.1 B-cell depletors: Rituximab

Rituximab is a B-cell depleting monoclonal antibody that targets the CD20 antibody on the surface of B lymphocytes [34]. As CD20 is expressed only on haematogenic progenitor cells and not on mature antibody-secreting cells Rituximab has minimal effects on the secondary immune response [71]. In the last decade Rituximab has been used in the treatment of various autoimmune and lymphoproliferative conditions including rheumatoid arthritis, systemic lupus erythematosus (SLE), myasthenia gravis, and multiple sclerosis [72]. Although a role for Rituximab in Graves’ disease seems rational based on the critical pathogenetic role of B cells in Graves’ hyperthyroidism, trials of Rituximab in hyperthyroidism control have given mixed results [72]. Two small prospective studies showed that Rituximab was effective in controlling mild Graves’ hyperthyroidism when used as adjuvant to methimazole in newly diagnosed patients [73] or when administered alone in relapsed Graves’ hyperthyroidism [74]. In contrast a pilot study by Salvi and colleagues in patients with Graves’ disease showed no effect of Rituximab on thyroid function although Rituximab was associated with reduced proptosis [75]. A recent one-arm open label trial in 27 young people with Graves’ disease showed that adjuvant low dose Rituximab (500 mg) plus standard 12-months Carbimazole led to 40% remission rates 12 months after Carbimazole withdrawal, a response rate considered promising in young people [76]. For Graves’ orbitopathy, several studies on the effect of Rituximab on orbital disease including two randomised controlled trials have shown mixed results [77, 78].
A number of adverse effects have been reported with Rituximab including infusion reactions, articular pain, cardiopulmonary toxicity, gastrointestinal symptoms, and colitis [79]. Risk of severe infections have also been noted especially in individuals with severe immunodeficiency, pre-existing malignancy, or patients treated with multiple immunosuppressive agents [80]. A rare complication of progressive multifocal leukoencephalopathy has been reported but this condition is not unique to Rituximab and is also seen in association with other immunosuppressants [81]. A long-term safety review of Rituximab treatment in patients with rheumatoid arthritis demonstrated no overall increase in risk of adverse events when compared with placebo [82]. Several clinical trials of newer generation CD-20 depleting agents are currently underway in patients with SLE, rheumatoid arthritis, or multiple sclerosis. These next generation anti-CD20 monoclonal antibodies include ocrelizumab and ofatumumab and would hope to improve clinical utility with molecular designs to improve efficacy, tolerance, and side effect profiles [83]. Although ocrelizumab has been shown to successfully induce remission in patients with immunotherapy induced Graves’ disease [84], clinical trials are still needed to confirm the role of next generation antibodies in Graves’ disease.

6.2 CD40 blockers: Iscalimab

Iscalimab is an anti-CD40 monoclonal antibody which inhibits B-cell activation by blocking CD40-CD154 co-stimulatory pathways involved in the immune response [85]. CD40 is a tumour necrosis factor (TNF) receptor expressed on thyrocytes and antigen-presenting B cells which plays a key role in antigen presentation and antibody production [4]. Experiments in murine models show that genetic and chemical modulation of CD40 signalling affects thyroid autoantibody production and hence the severity of autoimmune thyroiditis [86]. A proof of concept study in 15 patients with
untreated Graves thyrotoxicosis showed that a 12-week course of Iscalimab led to clinical and biochemical remission in 7 patients, typically those with mild disease, with significant reduction of TRAb levels seen in 4 patients [87]. However, 4 out of the 7 responders relapsed after 24 weeks and longer trials will be needed to assess whether the effects of Iscalimab can be maintained in the long term [87].

6.3 Immunoglobulin recycling blockers: Rozanolixizumab, Efgartigimod

The neonatal immunoglobulin Fc receptor (FcRn) plays a role in the pathogenesis of immunoglobulin-G (IgG) mediated autoimmune diseases like Graves’ disease by recycling (IgG) antibodies from lysosomes and maintaining their levels in the circulation [88]. Novel FcRn blocking compounds namely Efgartigimod and Rozanolixizumab have shown promise as therapeutic agents in autoimmune disease and have been well tolerated in phase 2 studies [89]. In addition, both compounds produced sustained reduction in IgG levels both in murine models of autoimmune disease (arthritis and encephalitis) and in healthy human participants in phase 3 studies [90, 91]. Although these compounds are yet to be trialled in patients with Graves’ Hyperthyroidism, a phase-II trial of the human FcRn monoclonal antibody compound, RVT-1401, in patients with Graves’ orbitopathy has recently been completed and the results are awaited [92].

6.4 TSH receptor therapies

Therapeutic agents that act via TSH-receptor mechanisms represent a promising approach for Graves’ disease therapy as they target the pathognomonic receptor thus preventing cAMP mediated thyroid hormone production [34]. These therapies fall into three broad categories namely TSH-receptor antagonists, TSH-receptor blocking monoclonal antibodies, and immune modifying TSH-receptor peptides. Several small molecule TSH-receptor antagonists with high affinity for the receptor have been shown
to reduce thyroid hormone levels, both in mice models and in primary cultures of thyrocytes and orbital cells [93, 94]. Although these compounds are yet to be trialled in humans, they hold promise as future therapies with minimal side effects due to their targeted action. Two human TSH-receptor blocking monoclonal antibodies have been produced from B-cells of patients with Graves’ disease (5C9) and Graves’ orbitopathy (K1-70) respectively [95, 96, 97, 98]. K1-70 was shown to suppress T4 levels in animal studies [97] and was also shown to be safe, well tolerated, with thyroid hormone reducing effects in a phase-1 trial in patients with Graves’ hyperthyroidism [98]. Lastly, immune modulating TSH-receptor peptides have been designed to induce a tolerogenic immune response [99]. The TSH receptor peptide, ATX-GD-59, was shown to be safe, well tolerated, and successful in reducing thyroid hormone levels in 7 out of 10 patients in a phase-1 trial in Graves’ hyperthyroidism and further studies of this compound in Graves’ disease are awaited [100].

6.5 Selenium

Selenium is a trace element that forms an essential component of the selenoproteins with several important effects in thyroid hormone metabolism including reduction of oxidative damage in the thyroid, incorporation into key deiodinases, and modulatory effects on antibody production [32]. Selenium has been shown in several randomised controlled trials to exert beneficial immune modulatory effects in autoimmune thyroid disease [32]. In one study, selenium supplementation (100 µg twice daily) improved quality of life and slowed the progression of eye disease in 54 patients with mild Graves’ orbitopathy [101]. However, the efficacy of selenium in controlling hyperthyroidism is less certain. While some studies have shown more rapid and more significant decreases in FT4 levels in patients with Graves’ disease who received
selenium in addition to standard antithyroid drugs [102, 103] other studies showed no beneficial effect of selenium on thyroid function in Graves’ disease [104, 105].

A meta-analysis of 10 studies involving 796 patients (84% Chinese, 14% European) showed that selenium supplementation for Graves’ disease therapy reduced FT4 and TRAb levels at 6 months, but this effect was not sustained at 9 months [106]. However, the impact of background population nutrition including baseline selenium status on this meta-analysis is unclear since subgroup analyses by geographical region were not undertaken [106]. In one controlled trial, newly diagnosed Graves’ disease patients who were deficient in selenium and vitamin D were randomised to receive selenium plus vitamin D plus methimazole versus methimazole alone [107]. The authors observed significant reductions in FT4 levels, increase in TSH, and better quality of life scores in the selenium/vitamin D supplemented group compared to methimazole alone suggesting that additional nutritional factors such as vitamin D deficiency may play a role in the response to selenium supplementation [107]. Thus, further studies are needed to understand the effect of selenium supplementation on the control of hyperthyroidism. A large randomised controlled trial of selenium supplementation in patients with Graves’ disease, the GRASS trial, is currently in progress [108].

7. CONCLUSION

Conventional thionamide anti-thyroid drugs are the predominant therapy modality for Graves’ hyperthyroidism. This class of compounds have been in use for over 60 years and have proven efficacy with well-recognised side effect profiles. However, non-thionamide antithyroid drugs are occasionally indicated, whether as adjunctive treatment in pre-surgical or severe cases, or in patients who are intolerant or unresponsive to thionamides. Traditional non-thionamide agents act on various phases of the synthesis, release, and metabolism of thyroid hormones and include
agents which have been in use for many decades as well as those with established roles in other conditions. While these drugs are effective in short-term adjunctive management further studies are needed to determine whether their effects are sustained in the long-term. Novel agents in development which target the key players involved in the immune response including antibody producing B-cells, the TSH receptor antibody, and its receptor hold promise for the future.

8. EXPERT OPINION

Conventional therapies for Graves’ disease have remained unchanged for over 60 years and are safe and effective with well understood efficacy and side effect profiles [4]. Recent UK NICE guidelines recommend radioiodine as first-line therapy for Graves’ disease [109] although the impact of these recommendations on practice are still unclear [110]. A Major drawback of radioiodine or thyroidectomy is the need for lifelong thyroid hormone replacement, a situation akin to replacing one disease condition with another. Some patients will find this unsatisfactory more so as thyroid hormone replacement may be problematic in some patients who do not achieve satisfactory symptomatic or biochemical disease control [111]. In practice the thionamide antithyroid drugs remain the predominant therapeutic modality in Graves’ disease management. Thionamides are first line therapy in most parts of the world and are increasingly favoured as primary therapy even in the United States where radioiodine was traditionally preferred [12]. However, the limitations of antithyroid drugs including the risk of serious side effects such as agranulocytosis and liver failure are well-recognised [13]. Furthermore, a small proportion of patients may exhibit resistance to thionamide treatment [17] although true thionamide refractoriness is probably overestimated. Lastly, sustained remission after 1-2 years of thionamide
therapy is seen in only 40-50% of patients regardless of whether patients are treated with thionamides alone or in combination with Levothyroxine [4].

There is therefore a need for non-thionamide alternatives for the treatment of Graves’ disease. Earlier agents such as iodides were originally used to treat hyperthyroidism before the advent of the thionamides but have since been reserved for adjunctive pre-surgical treatment or for cases where thionamides are contraindicated or ineffective.

In the 2016 American Thyroid Association (ATA) hyperthyroidism guidelines the authors considered the role of iodine in primary therapy for Graves’ disease but could make no recommendations due to insufficient evidence [10]. Several drugs with established uses elsewhere, e.g., glucocorticoids, lithium, or cholestyramine, are potential candidates for repurposing in Graves’ disease therapy but have not been comprehensively investigated and are therefore not recommended as primary therapy in Graves’ disease. Further studies of non-thionamide therapies in Graves’ disease are needed. Randomised controlled trials are challenging to undertake due to the narrow indications for alternative treatments. The trials from Japan on the effectiveness of potassium iodide in Graves’ disease in the long-term are therefore encouraging in this regard [50, 51, 52]. In addition, multi-centre observational studies will provide useful insights into the effectiveness of non-thionamide agents and identify those drugs that would merit clinical trials.

Existing thionamide and non-thionamide drugs affect various stages of thyroid hormone synthesis, release, or metabolism. However, none of these therapies address the key pathogenetic drivers in Graves’ disease, i.e., the TSH receptor antibody or antibody producing B-cells. This is surprising given that Graves’ disease is the prototype of organ-specific autoimmunity with a well characterised antibody receptor interaction [26]. Thus, current research on drugs that exploit various facets of
the immune response including B-cell pathways, the TSH antibody, and TSH receptor signalling cascades, hold promise for translation into clinical practice [112]. These novel approaches are particularly exciting as they offer the possibility of rapid control of hyperthyroidism with minimal side effects and without the need for thyroid ablation due to the targeted nature of these compounds. However, while these compounds have been shown to be safe and well tolerated in phase 1 and 2 studies more work will need to be done to establish their long-term effectiveness especially in patients with severe disease.
9. REFERENCES


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** Excellent review on the use of lithium in hyperthyroidism


47. Wolff J, Chaikoff IL. The inhibitory action of iodide upon organic binding of iodine by the normal thyroid gland. The Journal of biological chemistry. 1948;172:855. Epub 1948/02/01.


** Study showing effectiveness of rituximab in mild Graves' hyperthyroidism


** Study showing effectiveness of rituximab in mild Graves' hyperthyroidism


** Trial of rituximab in young people with Graves’ hyperthyroidism


** Phase 1 study of TSH receptor peptides in Graves' disease


Table 1: Indications for non-thionamide therapies

Table 2: Approach in uncontrolled hyperthyroidism with thionamide agents

Table 3: Non-thionamide antithyroid drugs

Table 4: Novel therapeutic approaches

Figure 1: Mechanisms of action of Antithyroid Drugs

Legend

Figure 1: Schematic diagram depicting established and putative mechanisms of action of the various thionamide and non thionamide antithyroid drugs. Sites of action are described in the boxes. CMZ, carbimazole, PTU, propylthiouracil, MMI, methimazole, I-, Iodide; I+, reactive iodide; TSH, Thyroid Stimulating Hormone; TRH, Thyrotropin Releasing Hormone; T4, Thyroxine; T3, Triiodothyronine; Tg, Thyroglobulin; TPO, Thyroid Peroxidase, MIT, Monoiodotyrosine; DIT, Diiodothyrosine; D1, Deiodinase Iodothyronine Type 1; D2, Deiodinase Iodothyronine Type 2; NIS, Sodium Iodide symporter
<table>
<thead>
<tr>
<th>Table 1: Indications for non-thionamide therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid control of symptoms</td>
</tr>
<tr>
<td>Patients with thyroid storm</td>
</tr>
<tr>
<td>Preparation for definitive therapy</td>
</tr>
<tr>
<td>Severe thionamide side effects</td>
</tr>
<tr>
<td>Thionamide refractory Graves’ disease</td>
</tr>
</tbody>
</table>
Table 2: Approach in uncontrolled hyperthyroidism with thionamide agents

<table>
<thead>
<tr>
<th>Approach in uncontrolled hyperthyroidism with thionamide agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm ATD dose and administration</td>
</tr>
<tr>
<td>Ensure optimal dose and adequate duration of treatment</td>
</tr>
<tr>
<td>Assess compliance</td>
</tr>
<tr>
<td>Exclude drug malabsorption</td>
</tr>
<tr>
<td>Rule out assay interference if tests are inconsistent with clinical state</td>
</tr>
<tr>
<td>Consider switching to other thionamide</td>
</tr>
<tr>
<td>Consider non-thionamide agents pending definitive therapy</td>
</tr>
</tbody>
</table>
Table 3: Non-thionamide antithyroid drugs

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Indications</th>
<th>Mechanism</th>
<th>Examples</th>
<th>Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-blockers</td>
<td>Excess β-adrenergic activity</td>
<td>Inhibits peripheral T4 to T3 conversion</td>
<td>Propranolol, Esmolol, Metoprolol, Atenolol</td>
<td>Propranolol 40–80 mg bd to qds, oral</td>
<td>Bronchospasm in asthma or airway disease, cold peripheries.</td>
</tr>
<tr>
<td>Iodine compounds</td>
<td>Rapid control pre-surgery; adjunct therapy</td>
<td>Inhibit Tg iodination and coupling of tyrosine residues</td>
<td>Lugol’s solution (iodine 50 mg/ml + KI 100 mg/ml)</td>
<td>Lugol’s solution 0.1–0.3 mls tds</td>
<td>Rash, conjunctivitis, salivary gland pain, headache, nausea</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Rapid control; thyroid storm; adjunct therapy</td>
<td>Reduces T4 &amp; T3 secretion; inhibits peripheral T4 to T3 conversion</td>
<td>Hydrocortisone Dexamethasone Prednisolone</td>
<td>Hydrocortisone 100 mg tds IV or Dexamethasone 2 mg qds IV (for thyroid storm); Prednisolone 30-60 mg/day (adjunct treatment)</td>
<td>Impaired glucose tolerance, raised blood pressure, fluid retention, immune suppression, gastritis</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Rapid control; pre-surgery, thyroid storm; adjunct therapy, AIT-2</td>
<td>Inhibits entero-hepatic circulation</td>
<td>Cholestyramine</td>
<td>2–4 g 6-12 hourly, orally</td>
<td>Abdominal discomfort, bloating, flatulence, constipation; reduces absorption of other drugs</td>
</tr>
<tr>
<td>Potassium</td>
<td>Adjunct therapy in AIT-1</td>
<td>Inhibits iodide uptake</td>
<td>Potassium Perchlorate</td>
<td>400-1000 mg/day in 2-4 divided doses</td>
<td>Abdominal discomfort, rash, agranulocytosis, aplastic anaemia at high doses</td>
</tr>
<tr>
<td>Lithium</td>
<td>Rapid control; thyroid storm; adjunct therapy; AIT-2; pre RAI</td>
<td>Inhibits T4/T3 synthesis and secretion; inhibits Hypothalomo-Pituitary-Thyroid axis</td>
<td>Lithium carbonate</td>
<td>1–1.5 g daily in divided doses</td>
<td>Narrow therapeutic range: GI symptoms, tremors, drowsiness, incoordination, cardiac arrhythmia with severe toxicity</td>
</tr>
</tbody>
</table>

Tg, Thyroglobulin, KI, potassium iodide, tds, 3 times daily, qds, 4 times daily, RAI, radioactive iodine, AIT, amiodarone induced thyroiditis
## Table 4: Novel therapeutic approaches

<table>
<thead>
<tr>
<th>Approach</th>
<th>Compound</th>
<th>Mechanism</th>
<th>Efficacy</th>
<th>Adverse effects</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-lymphocyte depletion</td>
<td>Rituximab</td>
<td>Targets CD20 protein on B-cells</td>
<td>Uncertain efficacy in severe disease</td>
<td>Risk of infection, infusion reactions, articular pain, cardiopulmonary toxicity, gastrointestinal symptoms, colitis</td>
<td>Phase 2 RCT</td>
</tr>
<tr>
<td>CD-40 interaction blockade</td>
<td>Iscalimab</td>
<td>Blocks B-cell activation by inhibiting CD40-CD154 co-stimulatory pathway</td>
<td>Uncertain efficacy in severe disease</td>
<td>Risk of infection, possible thromboembolic risk</td>
<td>Phase 2 RCT</td>
</tr>
<tr>
<td>Immunoglobulin recycling blockade</td>
<td>Efgartigimod, Rozanolixizumab</td>
<td>Blockade of neonatal immunoglobulin Fc receptor (FcRn), reducing IgG recycling and attenuating circulating TRAb levels</td>
<td>Uncertain efficacy in severe disease</td>
<td>Risk of infection</td>
<td>Phase 2</td>
</tr>
<tr>
<td>B-cell activating factor (BAFF) blockade</td>
<td>Belimumab</td>
<td>Inhibits B-cell proliferation and antibody production through BAFF inhibition</td>
<td>Uncertain efficacy in severe disease</td>
<td>Risk of infection, risk of psychiatric events including serious depression</td>
<td>Phase 2</td>
</tr>
<tr>
<td>TSH receptor antagonist</td>
<td>ANTAG-3, VA-K-14, S37a</td>
<td>Inhibit TSH-stimulated cAMP production and TRAb-induced signalling in-vitro</td>
<td>Yet to be trialled in human studies</td>
<td>Data not yet available</td>
<td>Preclinical stage</td>
</tr>
<tr>
<td>TSH receptor blocking antibodies</td>
<td>K1-70, 5C9</td>
<td>Prevents stimulation of TSH receptor by TSH and TRAb</td>
<td>Uncertain efficacy in severe disease</td>
<td>Data not yet available</td>
<td>Phase 1</td>
</tr>
<tr>
<td>TSH receptor-specific immunotherapy</td>
<td>ATX-GD-59</td>
<td>Reduces TRAb and thyroid hormone levels by inducing a tolerogenic immune response</td>
<td>Uncertain efficacy in severe disease</td>
<td>Data not yet available</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

TRAb, TSH receptor antibody
Figure 1: Mechanisms of action of Antithyroid Drugs

Schematic diagram depicting established and putative mechanisms of action of the various thionamide and non thionamide antithyroid drugs. Sites of action are described in the boxes. CMZ, carbimazole; PTU, propylthiouracil; MMI, methimazole; I-, iodide; I+, reactive iodide; TSH, Thyroid Stimulating Hormone; TRH, Thyrotropin Releasing Hormone; T4, Thyroxine; T3, Triiodothyronine; Tg, Thyroglobulin; TPO, Thyroid Peroxidase; MIT, Monoiodotyrosine; DIT, Diiodothyrosine; D1, Deiodinase Iodothyronine Type 1; D2, Deiodinase Iodothyronine Type 2; NIS, Sodium Iodide symporter.