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Advances and Prospects in Pharmacotherapy for Graves' Disease

Shujie Yu*, Hongyan Wu#

The First Affiliated Hospital of Yangtze University, Jingzhou, China
Email: #413629509@qq.com

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Abstract

Objective: To systematically review recent advances in the pharmacotherapy of Graves' disease (GD) and provide evidence-based recommendations for individualized clinical management. **Methods:** We conducted a comprehensive literature search of PubMed, Cochrane Library, and CNKI databases for studies published within the past ten years focusing on antithyroid drugs (ATDs), biologics, and small-molecule targeted therapies. **Results:** Traditional ATDs remain first-line therapy for GD; however, relapse rates following discontinuation approach 50%. Novel targeted therapies—including anti-CD20 monoclonal antibodies (rituximab), anti-CD40 monoclonal antibodies (iscalimab), and neonatal Fc receptor (FcRn) antagonists—have demonstrated potential in reducing thyrotropin receptor antibody (TRAb) titers and improving remission rates in refractory GD. TSH receptor (TSHR) blocking antibodies and small-molecule antagonists represent promising etiological treatment strategies. **Conclusion:** GD pharmacotherapy is transitioning from empirical immunosuppression to precision-targeted interventions. Future therapeutic paradigms should emphasize individualized treatment protocols and discontinuation strategies guided by dynamic TRAb monitoring.

Keywords

Graves' Disease, Antithyroid Drugs, Methimazole, Thyrotropin Receptor Antibody, Rituximab, Targeted Therapy

1. Introduction

Graves' disease (GD) is an organ-specific autoimmune disorder and the predominant cause of hyperthyroidism in iodine-sufficient regions, accounting for ap-

*First author.
#Corresponding author.

proximately 80% of all hyperthyroidism cases [1]. The global prevalence of GD ranges from 0.5% to 2.0%, with an annual incidence of 20 - 30 cases per 100,000 individuals. Epidemiological data from China indicate an adult prevalence (≥18 years) of 0.53%, with significant female predominance (0.69% vs. 0.38% in males) [2]. Although GD may present at any age, peak incidence occurs between 30 and 50 years.

The pathogenesis of GD involves complex interactions between genetic susceptibility and environmental triggers. Polymorphisms in genes encoding HLA-DR3, CTLA-4, and PTPN22 confer increased disease risk, while environmental factors—including smoking, excessive iodine intake, psychological stress, and infections—can disrupt immune homeostasis. The central pathophysiological mechanism involves loss of immune tolerance [3] to the thyroid-stimulating hormone receptor (TSHR), resulting in the production of TSHR antibodies (TRAbs). Thyroid-stimulating antibodies (TSAbs), a subset of TRAbs, mimic TSH activity by activating the TSHR-cAMP signaling pathway, thereby stimulating thyroid follicular cell proliferation and excessive thyroid hormone (TH) synthesis. This process ultimately culminates in hyperthyroidism, goiter, and Graves' orbitopathy (GO) [3] [4].

Current therapeutic modalities for GD include antithyroid drugs (ATDs), radioactive iodine (^{131}I) therapy, and thyroidectomy. [3] ATDs represent the preferred initial treatment across most of Asia and Europe due to their non-invasive nature and capacity to preserve thyroid function. Recent advances in understanding the immunopathogenesis of GD have catalyzed the development of novel targeted therapeutic agents directed against B cells, TSHR, and antibody metabolism pathways, offering new treatment avenues for patients with refractory or recurrent disease [4] [5].

2. Traditional Antithyroid Drugs (ATDs)

2.1. Classification and Mechanisms of Action

ATDs are categorized into two primary classes: thioureas and imidazoles. Thioureas include propylthiouracil (PTU) and methylthiouracil (MTU), whereas imidazoles comprise methimazole (MMI) and its prodrug carbimazole (CMZ) [1].

Pharmacological Mechanisms: Both classes inhibit thyroid peroxidase (TPO) activity, thereby blocking iodine organification and coupling reactions required for TH synthesis. Additionally, ATDs exert immunomodulatory effects by reducing intrathyroidal lymphocyte infiltration and TRAb titers, potentially through inhibition of HLA-DR antigen expression on thyroid follicular cells and modulation of regulatory T cell (Treg) function [6].

Pharmacokinetic Considerations: PTU exhibits a relatively short half-life (approximately 1.5 hours), necessitating dosing every 8 hours. In contrast, MMI possesses a longer half-life (6-8 hours), permitting once-daily administration. A distinctive advantage of PTU is its capacity to inhibit type I deiodinase in peripheral tissues, thereby reducing the conversion of T4 to T3—an effect that proves partic-

ularly beneficial during thyroid storm management.

2.2. Treatment Strategies and Dosing Regimens

2.2.1. Initial Treatment Approaches

Two primary therapeutic strategies guide ATD administration: the titration regimen and the block-replace regimen. The titration approach involves dynamic dose adjustments based on serial thyroid function assessments to identify the minimum effective dose maintaining euthyroidism. Conversely, the block-replace regimen employs high-dose ATDs to completely suppress endogenous TH synthesis, supplemented with levothyroxine (L-T4) to maintain hormonal balance. Although the block-replace strategy may accelerate biochemical normalization, current evidence demonstrates no superiority regarding long-term remission rates. Furthermore, the higher ATD doses required increase the risk of adverse effects, rendering this approach unsuitable for routine clinical practice.

Initial Dose Selection: Dosing should be individualized based on hyperthyroidism severity:

Mild (FT4 1.0 - 1.5× upper limit of normal [ULN]): MMI 5 - 10 mg/day;

Moderate (FT4 1.5 - 2.0× ULN): MMI 10 - 20 mg/day;

Severe (FT4 2.0 - 3.0× ULN): MMI 30 - 40 mg/day.

Thyroid function should be monitored every 3 - 4 weeks during the initial treatment phase. As biochemical control is achieved, the MMI dose should be progressively tapered to a maintenance dosage (5 - 10 mg/day) [7].

2.2.2. Treatment Duration and Discontinuation Criteria

The standard treatment duration ranges from 12 to 18 months. Discontinuation criteria include:

Completion of the full therapeutic course (≥12 months);

Restoration of biochemical euthyroidism with normalized TSH levels;

Seroconversion of TRAb to negative (a critical predictive indicator) [8].

Significant reduction or seroconversion to negative of thyrotropin receptor antibodies (TRAbs), as measured by third-generation binding assays (e.g., electrochemiluminescence immunoassays). *While functional assays differentiating thyroid-stimulating antibodies* (*TSAbs*) *from blocking antibodies provide deeper pathophysiological insight, current clinical guidelines and the majority of evidence supporting TRAb-guided therapy are based on serial measurements of total TRAb binding activity.*

Studies demonstrate that patients achieving negative TRAb status at discontinuation exhibit 1-year remission rates approaching 50%, whereas those with persistently positive TRAb face relapse risks as high as 80% [9]. Practical clinical application involves a defined monitoring cadence: TRAb levels should be assessed at baseline, at 6 - 12 months of therapy, and again prior to considering ATD withdrawal. In patients who are biochemically euthyroid on a low maintenance dose of ATD (e.g., MMI 5 - 10 mg/day), TRAb trends should guide decision-making. For patients with a significant and sustained decline in TRAb titers (e.g., >50%

reduction from baseline or titers falling into the low-positive range), continuation of ATD therapy for an extended period (18 - 24 months or longer) is recommended to maximize the chance of eventual seroconversion and lasting remission. For patients with persistently high or stable positive TRAb titers after 12 - 18 months of treatment, the likelihood of remission upon ATD withdrawal is low. In this scenario, clinicians should discuss definitive treatment options (radioactive iodine or thyroidectomy) with the patient. Alternatively, long-term low-dose MMI therapy represents a viable alternative for those wishing to avoid ablative procedures. Extending ATD therapy beyond 2 - 5 years can increase remission rates to 60% - 80% [10], particularly in patients with mild-to-moderate disease. Consequently, for patients failing to achieve remission, long-term low-dose MMI therapy represents a viable alternative to immediate transition to ^{131}I or surgical intervention.

2.2.3. Relapse and Retreatment

Relapse following ATD discontinuation most commonly occurs within the first 6 months, with an overall relapse rate of 40% - 60% [11]. Established risk factors for relapse include: Young age (<40 years); Male sex; Cigarette smoking; Large goiter (>80 g); Elevated TRAb titers; T3-predominant hyperthyroidism [12]. For patients experiencing first relapse, treatment options include a second ATD course or definitive therapy (radioactive iodine or surgery). When selecting a second ATD course, anticipated remission rates remain comparable to initial therapy.

2.3. Adverse Effects: Monitoring and Management

Adverse effects occur in approximately 5% of patients [6], ranging from mild allergic reactions to severe organ toxicity.

***Mild Reactions* (5% - 10%):** These include pruritic rash, urticaria, arthralgia, and gastrointestinal discomfort. Symptomatic management with antihistamines or switching to an alternative ATD may be considered (cross-reactivity between MMI and PTU occurs in approximately 50% of cases) [13].

***Agranulocytosis*:** This represents the most serious adverse effect, with an annual incidence of 0.1% - 0.3%, typically manifesting within the first 90 days of treatment. Classic presentation includes sudden-onset high fever, pharyngitis, and mucosal ulceration. Management requires:

Immediate ATD discontinuation and complete blood count evaluation (diagnosis confirmed by absolute neutrophil count < 500/μL);

Permanent avoidance of all ATD rechallenge;

Prompt initiation of broad-spectrum antibiotics and granulocyte colony-stimulating factor (G-CSF) therapy;

Protective isolation for critically ill patients [14].

Hepatotoxicity: Occurring in 0.1% - 0.2% of patients [6], hepatotoxicity manifests differently with specific agents—MMI typically causes cholestatic injury, whereas PTU is associated with hepatocellular necrosis and, rarely, fulminant hepatic failure [15]. Liver function should be assessed pretreatment and monitored

if symptoms such as jaundice, dark urine, or abdominal pain develop [16].

ANCA-Associated Vasculitis: A rare but serious complication, predominantly associated with long-term PTU therapy, presenting with fever, arthralgia, and renal or pulmonary involvement [17].

Monitoring Strategy: Current ATA/AACE guidelines recommend baseline complete blood count and liver function testing prior to therapy initiation but do not mandate routine monitoring during treatment. Instead, emphasis is placed on patient education regarding immediate drug discontinuation and urgent medical evaluation should fever or sore throat develop.

2.4. Special Populations

Pregnancy: ATD use during the first trimester (particularly weeks 6 - 10) requires careful consideration due to teratogenic risks—MMI is associated with embryopathy (aplasia cutis, choanal atresia), whereas PTU carries a risk of hepatotoxicity [18]. Clinical recommendations include:

Prioritizing PTU during the first trimester (lower teratogenic risk) with close hepatic monitoring [19]; Transitioning to MMI by the end of the first trimester to minimize hepatotoxicity risk;

Utilizing the lowest effective dose to maintain FT4 at the upper limit of the trimester-specific reference range [20].

Children and Adolescents: MMI constitutes first-line therapy, with an initial dose of 0.15 - 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$. Remission rates with ATDs in pediatric populations are lower than in adults (approximately 30%). However, given the long-term risks associated with ^{131}I and surgery, extending ATD therapy beyond 2 years is recommended. PTU is contraindicated in children due to an FDA black box warning regarding hepatic failure risk [21].

3. Adjunctive Therapies

3.1. Beta-Blockers

Beta-adrenergic blockade effectively controls symptoms of sympathetic overactivity (palpitations, tremor, anxiety). Propranolol (40 - 160 mg/day) or selective β1-blockers such as atenolol (25 - 100 mg/day) may be employed. High-dose propranolol (>160 mg/day) inhibits peripheral T4-to-T3 conversion, though this effect is rarely necessary. Contraindications include asthma, severe bradycardia, and decompensated heart failure [16].

3.2. Glucocorticoids

Glucocorticoids are indicated for thyroid storm, moderate-to-severe active GO, and severe thyrotoxicosis. Their mechanisms include inhibition of T4-to-T3 conversion and broad immunosuppression. Standard regimens include oral prednisone (40 - 60 mg/day) or intravenous methylprednisolone pulse therapy (0.5 - 1.0 g weekly for 6 weeks). Monitoring for hypertension, hyperglycemia, and infectious complications is essential [22].

4. Emerging Targeted Biologics and Small-Molecule Therapies

4.1. B-Cell Targeted Therapy

4.1.1. Anti-CD20 Monoclonal Antibody: Rituximab (RTX)

RTX induces depletion of $CD20^+$ B cells, thereby attenuating TRAb production. Evidence from several exploratory trials demonstrates its potential, though study populations and designs vary [23].

El Fassi *et al.*: In a study of newly diagnosed GD patients, a single-course RTX (500 mg × 2 doses) combined with MMI demonstrated a 1-year relapse rate of 40% after ATD withdrawal, compared to 100% in the MMI monotherapy control group. This suggests RTX may delay relapse in early disease [24];

Heemstra *et al.* observed biochemical remission in 9 of 13 patients with recurrent GD following RTX treatment, with significant TRAb reduction at 26 weeks [25];

Cheetham *et al.* An exploratory trial in adolescent GD demonstrated that RTX combined with ATD increased the 2-year remission rate to 48% (vs. expected rates of 20% - 30%).

The variation in remission rates across studies (40% to ~69%) is likely influenced by disease stage (newly diagnosed vs. relapsing), concomitant ATD use, and follow-up duration. RTX shows promising signals, but its definitive clinical role requires larger, controlled trials.

4.1.2. Anti-CD40 Monoclonal Antibody: Iscalimab (CFZ533)

Iscalimab is a non-depleting anti-CD40 monoclonal antibody that blocks the CD40-CD40L co-stimulatory signal, thereby inhibiting B-cell activation. A phase II proof-of-concept study involving 15 newly diagnosed GD patients demonstrated that 47% achieved biochemical remission (normalized FT4 without additional ATD) following 12 weeks of treatment, with a mean TRAb reduction of 66% [26]. However, relapse in some patients by week 24 suggests the necessity for maintenance therapy protocols.

4.1.3. Anti-BAFF Monoclonal Antibody: Belimumab

B-cell activating factor (BAFF) is elevated in GD patients and correlates positively with TRAb levels [27]. Belimumab inhibits B-cell maturation through BAFF antagonism. Open-label studies have reported a high incidence of adverse effects (predominantly nasopharyngitis) during long-term follow-up, though serious adverse events remained manageable [28]. Crucially, robust evidence from randomized controlled trials with clear primary efficacy endpoints (e.g., TRAb reduction, remission rate) in a defined GD population is currently lacking. Therefore, its role remains investigational.

The neonatal Fc receptor (FcRn) protects immunoglobulin G (IgG) from lysosomal degradation, thereby maintaining its prolonged half-life. FcRn blockade accelerates clearance of pathogenic IgG, including TRAbs. Rozanolixizumab has demonstrated capacity to reduce IgG levels by 70% in conditions such as myas-

thenia gravis and immune thrombocytopenia. For GD, a phase II clinical trial evaluating the FcRn antagonist RVT-1401 is currently underway [29]. As of this review, no published efficacy or safety data from controlled trials in GD populations are available, making this a pre-clinically supported but clinically unproven approach [29].

4.2. Direct TSHR-Targeted Therapies

4.2.1. TSHR-Blocking Antibody: K1-70

K1-70 is a fully human monoclonal antibody functioning as a TSHR antagonist. A first-in-human, non-controlled Phase I trial in patients with GD and Graves' orbitopathy demonstrated that a single dose of K1-70 induced transient hypothyroidism (primary pharmacodynamic effect) in 100% of patients and improved hyperthyroid symptoms [30]. These findings confirm the feasibility of TSHR as a therapeutic target, suggesting potential applications in thyroid storm or acute GO management.

4.2.2. TSHR Tolerogenic Peptide: ATX-GD-59

ATX-GD-59 is a TSHR peptide vaccine designed to induce TSHR-specific Treg cells [31]. A small, non-controlled Phase I study involving 10 GD patients reported that after 18 weeks of subcutaneous ATX-GD-59 administration, 50% achieved normalized FT3 levels. This early exploratory signal supports the feasibility of antigen-specific immunotherapy but requires validation in larger, controlled trials with longer follow-up to assess sustained immune tolerance [32].

4.3. Small-Molecule TSHR Antagonists

Small-molecule compounds (e.g., ANTAG-3, VA-K-14, S37a) modulate TSHR signaling through allosteric mechanisms, offering the convenience of oral administration. Neumann *et al.* reported that NCGC00229600 can block TSHR activation by patient serum IgG in vitro. No clinical trial data in human GD populations have been reported for any small-molecule TSHR antagonist. They represent a promising future avenue for oral targeted therapy but remain in the discovery and preclinical development stage [33].

4.4. Targeted Immunotherapy for Graves' Disease: Core Safety Management

I. Pre-Treatment Essentials

Screening: Test for Hepatitis B, Hepatitis C, HIV, and Tuberculosis.

Vaccination: Administer all necessary vaccines at least 4 weeks before starting therapy.

Baseline Tests: Blood tests (CBC, liver/kidney function, immunoglobulins), and pregnancy test for women.

II. Key Points During Treatment

Prevent Reactions: Infusion reactions are common with the first dose, requiring pre-medication and monitoring.

Prevent Infection: The primary risk. Patients must report symptoms like fever; monitor CBC and immunoglobulin levels regularly.

Specific Monitoring: Belimumab: Monitor for mood changes and proteinuria. FcRn antagonists: Watch for headaches and IgG levels.

III. Discontinuation Criteria

Stop treatment in case of severe hypersensitivity, life-threatening infection, serious neurological events, or symptomatic hypogammaglobulinemia.

5. Clinical Decision-Making and Stepwise Therapy Selection

1. New Diagnosis

Step 1-Initiate Antithyroid Drug (ATD): Methimazole (MMI) is the first-line therapy for most patients. The initial dose is titrated based on disease severity (e.g., 10 - 20 mg/day for moderate hyperthyroidism).

Step 2-Add Adjunctive Therapy: Initiate a beta-blocker (e.g., propranolol) for rapid symptom control of tachycardia, tremor, and anxiety.

Step 3-Monitor and Titrate: Assess thyroid function every 3 - 4 weeks, tapering the MMI to a maintenance dose (5 - 10 mg/day) once euthyroidism is achieved.

Step 4-Plan Duration & Discontinuation: Aim for a standard treatment course of 12 - 18 months. The key criterion for considering ATD withdrawal is the seroconversion of thyrotropin receptor antibody (TRAb) to negative, which is a strong predictor of sustained remission.

2. First Relapse after ATD Course

Step 1-Reassess Options: Discuss the choice between a second course of ATD or definitive therapy (radioactive iodine [^{131}I] or thyroidectomy). A second ATD course has a similar anticipated remission rate as the initial therapy.

Step 2-Favor Definitive Therapy if High-Risk: Consider definitive therapy strongly if the patient has risk factors for relapse (e.g., young age, large goiter, high TRAb titers).

Step 3-Consider Extended ATD Course: If opting for a second ATD course, plan for a longer duration (e.g., 18 - 24 months or more) to maximize the chance of remission, as extending therapy to 2 - 5 years can increase remission rates to 60-80%.

3. Persistent Disease after Prolonged ATD (e.g., >18 - 24 months)

Step 1-Evaluate TRAb Status: If TRAb titers remain persistently high or stable despite prolonged therapy, the likelihood of drug-free remission is low.

Step 2-Discuss Definitive Therapies: Counsel the patient on the benefits and risks of ^{131}I therapy or thyroidectomy.

Step 3-Offer Long-term Low-dose ATD: For patients who wish to avoid ablative procedures, long-term low-dose MMI therapy is a viable and effective alternative to control hyperthyroidism.

4. Contraindication or Severe Adverse Reaction to ATDs

Step 1-Discontinue ATD Immediately: This is mandatory for severe reactions like agranulocytosis or significant hepatotoxicity. Patients must be educated to stop the drug and seek urgent care for symptoms like fever or sore throat.

Step 2-Initiate Alternative Definitive Treatment: Radioactive iodine (^{131}I) or thyroidectomy becomes the primary treatment option.

Step 3-Consider Emerging/Biologic Therapy (Investgational Context): For patients unsuitable for both ATDs and definitive therapies, targeted biologics like rituximab (anti-CD20) may be considered as a clinically viable option based on exploratory trials, though larger controlled studies are needed to define its role.

5. Pregnancy Planning or Early Pregnancy

Step 1-Preconception Counseling: Aim for stable euthyroidism on the lowest possible ATD dose before conception.

Step 2-First Trimester Management: Use Propylthiouracil (PTU) preferentially during the first trimester (weeks 6 - 10) due to its lower teratogenic risk compared to MMI, with close monitoring for hepatotoxicity.

Step 3-Second/Third Trimester Management: Transition from PTU to MMI by the end of the first trimester to minimize the risk of PTU-induced hepatotoxicity.

Step 4-Dose & Monitoring: Use the lowest effective ATD dose to maintain maternal Free T4 at the upper limit of the trimester-specific reference range. PTU is contraindicated in children but can be used in pregnancy with vigilance.

6. Conclusion and Future Perspectives

Pharmacotherapy for Graves' disease is undergoing a critical paradigm shift. Traditional ATDs remain the cornerstone of treatment for most newly diagnosed patients, yet therapeutic strategies require optimization: extending treatment duration (>18 months), guiding discontinuation decisions through dynamic TRAb monitoring, and identifying low-risk populations can significantly enhance outcomes. For patients with recurrent or refractory disease, biologics such as rituximab have transitioned from "experimental" to "clinically viable" options, and their combination with ATDs holds promise for increasing permanent remission rates while avoiding thyroid ablation. Future research directions include: 1. Developing personalized treatment decision models based on TRAb epitope specificity and HLA genotyping; 2. Optimizing the timing and duration of biologic therapies (e.g., RTX); 3. Advancing small-molecule TSHR antagonists through clinical trials; 4. Investigating combined immunotolerance strategies (e.g., ATX-GD-59 with low-dose ATDs) to achieve "immune reconstitution" rather than mere immunosuppression. 5. The therapeutic goal for GD is evolving from "controlling hyperthyroidism" to "curing immune dysregulation." Through precise patient stratification and targeted interventions, the ultimate objective of curing hyperthyroidism while preserving thyroid function and avoiding lifelong hormone replacement therapy is becoming increasingly attainable.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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