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Review Paper

Management Of Hyperthyroidism: From Antithyroid Drugs to Novel Agents

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ABSTRACT

The medical field deals with hyperthyroidism which occurs when the body produces excessive thyroid hormones because it creates a major worldwide health problem. The most common cause of the condition remains Graves' disease but older people who lack adequate iodine treatment show high rates of toxic multinodular goiter and toxic adenoma. Current treatment methods which include antithyroid drugs and radioactive iodine and thyroidectomy, deliver effective results but the treatment methods struggle to achieve permanent results which maintain safety and restore thyroid function. The existing review updates the current understanding of hyperthyroidism through examination of its disease mechanisms and available treatment options. The study investigates how standard drug treatments function which requires different approaches to administer methimazole and propylthiouracil for special groups including pregnant women. The study investigates how cholestyramine functions as an additional treatment for patients who do not respond to standard methods. The research focuses on new biological treatments such as teprotumumab which treats thyroid eye disease and rituximab which treats recurrent Graves' disease, because these treatments start a new trend of using biological medicine to target essential disease causes. The research team showed their future research plans which include developing small molecule inhibitors and implementing tailor-made healthcare solutions through precision medicine.

INTRODUCTION

Hyperthyroidism arises when the thyroid gland produces and secretes excessive amounts of triiodothyronine and thyroxine. The medical condition of thyrotoxicosis develops when there is an abundance of thyroid hormones in the bloodstream which can originate from multiple sources, including thyroiditis and exogenous intake of thyroid hormones. The worldwide

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occurrence of hyperthyroidism affects between 0.2 and 1.3 percent of people who lack sufficient iodine according to research studies. In India, thyroid disorders are highly prevalent, with recent estimates suggesting hyperthyroidism affects approximately 1.9% of the population, which shows a female preponderance. The primary cause of the disease occurs because Graves' disease (GD) which is an autoimmune disorder while toxic multinodular goiter (TMNG) and toxic adenoma (TA) complete the list of causes. The American Thyroid Association (ATA) and European Thyroid Association (ETA) established new guidelines that improve existing treatment methods which have not changed for many years. This review aims to synthesize current evidence on standard management while highlighting the transition toward novel targeted therapies. [1,2,3,4,5,6]

2. Pathophysiology and Therapeutic Targets

The hypothalamic-pituitary-thyroid axis controls the process of thyroid hormone production. In Graves' disease (GD) the presence of thyroid-stimulating immunoglobulins (TSI) and TSH receptor antibodies (TRAb) enables these antibodies to bind with TSH receptors (TSHR) located on thyrocytes [7]. This continuous stimulation process results in follicular cell growth through both hypertrophy and hyperplasia while producing excessive amounts of hormones.

The TMNG and TA conditions develop through the activation of somatic mutations which affect TSHR and GNAS genes to create continuous cAMP signaling activity that does not require TSH [8]. The distinct mechanisms must be understood because B-cell immunomodulatory therapies that use rituximab and IGF-1 receptor treatments which use teprotumumab show effectiveness against autoimmune Graves' disease but fail to treat nodular autonomous disease [9].

3. Conventional Pharmacological Management (Antithyroid Drugs)

Thionamides remain the first-line therapy for GD in children, pregnancy, and adults desiring remission [6].

Thionamides: Methimazole (MMI) and Propylthiouracil (PTU) The two medications both function as thyroid peroxidase TPO inhibitors which stop the organification process of iodine and the iodotyrosine coupling mechanism [10]. PTU has an additional effect of inhibiting type 1 deiodinase, thereby blocking the peripheral conversion of T4 to T3 [11].

Dosing and Efficacy: MMI is preferred due to its longer half-life (allowing once-daily dosing) and superior side-effect profile [6]. The starting doses of the medication begin at 10 to 30 mg which patients should take every day. The first trimester of pregnancy and thyroid storm represent the only situations in which clinicians should use PTU because it poses severe hepatotoxicity risks [12].

Adverse Effects:

• **Mino**r: Rash, urticaria, and arthralgia occur in up to 5% of patients [13].

• **Major:** The most serious risk of agranulocytosis occurs at a rate between 0.2 and 0.5 percent. Patients need to receive education which teaches they must stop their medication and seek emergency healthcare when they develop fever or sore throat [14]. MMI causes cholestasis while PTU results in fulminant hepatic necrosis as the two drugs produce different levels of liver damage [15].Patients with GD achieve remission between 12 and 18 months after starting ATD treatment according to research which shows their remission rates at 30 to 50 percent [16]. The diagnosis of high TRAb levels together with the presence of a large

goiter indicates which patients will experience a relapse of their condition [17].

4. Non-Pharmacological Definitive Therapies

A.Radioactive Iodine (RAI) Therapy RAI (I-131) provides an affordable everlasting solution for treatment. The sodiumiodide symporter (NIS) takes up the substance which emits beta particles that lead to follicular cell death [18]. • Indications: The treatment applies to patients who have relapsed GD or TMNG or TA or who have medical conditions that make them unfit for surgery [19]. • Contraindications: The treatment stands as an absolute prohibition during pregnancy and lactation periods. The treatment generally gets avoided for patients with moderate-to-severe Graves' orbitopathy (GO) because it worsens their eye condition [20]. • Outcomes: The medical professionals aim to induce hypothyroidism as the primary result in GD which happens to more than 80 percent of patients [21]. B. Surgical Management (Thyroidectomy) The surgical procedure establishes an instant solution for hyperthyroidism The medical guidelines recommend surgery to treat patients who have large compressive goiters or suspected malignancy or moderate-to-severe GO that needs RAI treatment or who prefer this option [22]. The medical team should choose total or near-total thyroidectomy instead of subtotal resection because it offers better results for preventing cancer recurrence [23]. The procedure carries dangers which include transient or permanent hypoparathyroidism that leads to hypocalcemia and a less than 1 percent chance of recurrent laryngeal nerve injury that occurs in high-volume medical facilities [24].

5. Adjunctive and Symptomatic Therapies

- The use of beta-blockers requires Propranolol or atenolol to provide immediate relief from symptoms which include palpitations and tremor until ATDs become effective [25].
- The use of Inorganic Iodine (Lugol's solution/SSKI) for preoperative procedures decreases gland vascularity while it stops hormone release through the Wolff-Chaikoff effect during thyroid storm [26].
- Cholestyramine functions as a bile acid sequestrant which blocks the enterohepatic pathway that carries thyroid hormones. It serves as an essential treatment during severe thyrotoxicosis or thyroid storm to quickly decrease hormone production levels [27].
- The use of high-dose glucocorticoids causes steroid hormones to stop peripheral T4-to-T3 conversion which makes them essential treatment methods for both thyroid storm and severe GO cases. [28]

6. Management in Special Populations

Pregnancy

Hyperthyroidism affects 0.1–0.4% of pregnancies [29]. HCG-mediated gestational thyrotoxicosis must be differentiated from GD.

- **Therapy:** The medical guidelines recommend PTU as the first trimester treatment option which prevents MMI-related embryopathy effects of aplasia cutis and choanal atresia [30]. The patients must transition to MMI during their second trimester because it reduces liver toxic effects on mothers [6].
- The target achievement requires maintaining maternal free T4 levels at their highest normal level because this prevents fetal hypothyroidism [31].

Thyroid Storm

A life-threatening emergency requires multiple treatment methods which include beta-blockers PTU (the preferred drug) and inorganic iodine

(given after PTU) and corticosteroids and cooling methods for patient support [32].

7. Emerging and Novel Therapeutic Agents

The development of biologics and small molecules emerges from the restrictions which conventional therapies present to doctors. The development of biologics which specifically target the insulin-like growth factor 1 receptor (IGF-1R) between 2019 and 2021 results from the requirements which modern medical systems impose on new treatment options. Teprotumumab functions as a monoclonal antibody which blocks the insulin-like growth factor-1 receptor (IGF-1R) from receiving signals. The human body establishes a physical and functional connection between IGF-1R and TSHR which exists on orbital fibroblasts that develop in GD. Teprotumumab demonstrated its ability to decrease proptosis and clinical activity scores in active TED during its testing in Phase 2 and 3 clinical studies. The treatment produces muscle spasms plus hyperglycemia and hearing damage. Rituximab functions as a monoclonal antibody which targets the anti-CD20 protein. Doctors use the treatment to help patients who have active GO and who experience recurrent GD after stopping their anti-thyroid medication. The treatment eliminates B cells from the body which leads to decreased TRAb production and reduced ability to present antigens. Researchers study TSHR antagonists which are small molecules that prevent TSH/TRAb binding and researchers study peptide immunotherapy which creates immune tolerance to the TSH receptor. The two treatments together create a potential cure which preserves the thyroid. [9,33,34,35]

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