

Medical therapy for thyrotoxicosis

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Abstract

Thyrotoxicosis is a prevalent endocrine disorder. This study reviews the effects and side effects of thionamides in medical therapy for thyrotoxicosis.

Thyrotoxicosis is a prevalent endocrine disorder. Common etiologies include Graves' disease and toxic multinodular goiter.¹ Anti-thyroid drugs (ATD) are the primary treatment modality especially in Graves' disease, or the bridging therapy to stabilize thyroid function prior to definitive treatment with either radioactive iodine or surgery.² With regard to Graves' ophthalmopathy, in contrast to radioactive iodine treatment that confers a definite yet small risk of development or exacerbation of thyroid eye disease, ATD is at least neutral, or may improve, the natural course of the disease by correction of thyrotoxicosis.³ Thionamides, which include methimazole (MMI) and its precursor carbimazole (CMZ), as well as the derivatives of thiouracil, prophyllthiouracil (PTU), are commonly prescribed ATDs.

Thionamides inhibit the thyroid peroxidase-catalyzed iodination of tyrosine residues, thereby decreasing thyroid hormone synthesis. In Graves' disease, thionamides also have an effect on the reduction of intrathyroidal immune dysregulation. Serum concentrations of anti-thyrotropin-receptor antibodies decrease over time in patients prescribed thionamides.⁴ In addition, PTU blocks the peripheral conversion of thyroxine to tri-iodothyronine, and is preferred in the setting of thyroid storm.^{2,4} Under most clinical circumstances, current guidelines recommend MMI/CMZ over PTU in patients who choose medical therapy for Graves' disease.²

Most side effects of MMI/CMZ are dose-related, unlike those of PTU. Minor side effects of thionamides include cutaneous reactions, usually in the form of urticaria or macular eruption (4-6%), gastrointestinal upset and arthralgias (1-5%). Although cross-reactivity exists between MMI/CMZ and PTU, in the case of minor cutaneous

reactions, use of an antihistamine and/or switching from one ATD to another should suffice. Discontinuation of ATD might be necessary for arthralgias and other major side effects.⁴ Arthralgias may precede a severe form of transient migratory polyarthritis.⁴

Agranulocytosis, defined as an absolute granulocyte count $<0.5 \times 10^9/L$, is a rare but life-threatening adverse effect of ATDs. Its estimated frequency is about 0.1-0.5% and it occurs equally among patients receiving MMI/CMZ (0.37%) or PTU (0.35%).⁴ Although mild, transient granulocytopenia might be present in Graves' disease, ATDs are contraindicated if the pre-treatment absolute neutrophil count is $<0.5 \times 10^9/L$.² Agranulocytosis mostly occurs acutely within the first 3 months of treatment. Unless patients develop fever or pharyngitis, routine monitoring of white blood cell count is not recommended.² Nonetheless, a prior uneventful course of ATDs does not preclude the development of agranulocytosis in subsequent treatment courses.⁴

In a genome-wide association study comparing 20 Chinese patients with ATD-induced agranulocytosis with 775 healthy controls, *HLA-B*38:02:01* was identified as the susceptibility locus of MMI/CMZ-related agranulocytosis, with an odds ratio of 265.5 (95% confidence interval = 27.9-2528.0, $p = 2.5 \times 10^{-14}$), a positive predictive value of 0.07, a negative predictive value of 0.999, and the number needed to screen to prevent a single case of MMI/CMZ-related agranulocytosis of 211.⁵ *HLA-B*38:02:01* is common in some Southeast Asian countries and may be a useful pharmacogenetic marker to predict MMI/CMZ-related agranulocytosis.⁵ Although agranulocytosis is thought to be autoimmune mediated, *HLA-B*38:02:01* is not associated with PTU-related agranulocytosis, highlighting the possible differences in genetic risk-markers, as well as mechanisms that underlie the development of agranulocytosis for each ATD.⁵

Hepatotoxicity is another major adverse effect of ATDs estimated to occur in 0.1-0.2% of patients taking thionamides.⁴ Thionamides are contraindicated if liver transaminase level is more than fivefold above the upper limit of the normal reference range prior to drug initiation.² This takes into account the fact that mild hepatic dysfunction

related to thyrotoxicosis itself is not uncommon. Typically, MMI/CMZ-related hepatotoxicity is cholestatic. In a study of serial changes in liver function before and during MMI treatment in 77 newly diagnosed thyrotoxic patients, mild elevation of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels was noted at baseline in approximately one third of patients.⁶ Most had ALT/AST levels around twice the upper limit of normal. In such patients, MMI treatment resulted in a rapid increase in ALT/AST level. In those with normal liver function, MMI treatment also induced mild ALT/AST elevation, usually around twice the upper limit of normal.⁶ In contrast to MMI/CMZ, PTU may cause immunoallergic hepatitis that can deteriorate to fulminant hepatic failure.^{2,4} Although asymptomatic elevation of serum ALT/AST level up to six times the upper limit of normal with spontaneous resolution has been reported, current guidelines recommend discontinuation of PTU if serum transaminase level is elevated to more than two to threefold the upper limit of normal and fail to improve within one week.² After normalization of serum transaminase level, MMI/CMZ can be cautiously initiated with regular monitoring of liver function.

Some adverse effects are shared among all thionamides, although some are more common in one ATD than others or exclusive to MMI/CMZ or PTU. Antineutrophil cytoplasmic antibody positive vasculitis is more commonly associated with PTU than MMI/CMZ.^{2,4} One hypothesis relates to the formation of reactive intermediates from the oxidation of PTU by myeloperoxidase, which might explain the preponderance of this adverse effect in PTU.⁷ In addition, although antineutrophil cytoplasmic antibody positivity occurs more frequently with prolonged exposure to PTU beyond 18 months, the overall risk of developing small vessel vasculitis remains low.⁷ Small vessel inflammation can affect all organs, particularly the kidneys, lungs, and skin. The prognosis after ATD discontinuation is generally good.⁷ MMI/

CMZ-specific adverse events include teratogenic effects such as aplasia cutis, choanal or esophageal atresia. Thus, use of PTU is recommended during the first trimester of pregnancy.²

Current guidelines recommend ATD treatment of 12-18 months for Graves' disease, as prolonged treatment beyond 18 months is not associated with an improved remission rate.⁸ Predictors of relapse in patients with newly diagnosed Graves' disease before the initiation of ATD treatment include young age (<40 years), higher free thyroxine level (≥ 40 pmol/L), higher serum thyrotropin-binding inhibitor immunoglobulin (>6 IU/L), larger goiter at diagnosis, *HLA* subtypes *DQB1*02*, *DQAI*05*, and *DRB1*03*, and *PTPN22* C/T polymorphism.⁹ In general, 50% of patients relapse after the initial remission.¹ Definitive treatment with either radioactive iodine or total thyroidectomy is recommended for relapsed disease. Nonetheless, a prolonged course of low-dose MMI treatment (median follow-up of 71.3 \pm 40.3 months) achieves a better clinical activity score than radioactive iodine does and is a safe and effective alternative, in particular for those with mild Graves' ophthalmopathy.¹⁰

There are many other medications for thyrotoxicosis. Beta-blockers should be considered in all patients with symptomatic thyrotoxicosis, unless contraindicated.² Lugol's iodine and potassium iodide are also important, especially preoperatively or in the setting of thyroid storm.² Lithium, usually given at a dose of 250mg thrice daily, is a useful alternative when thionamides are intolerable or contraindicated.¹¹ Lithium is an effective adjunct to radioactive iodine as it increases radioiodine retention and keeps the radiation dose to a minimum.^{12,13}

To conclude, although monoclonal anti-thyrotropin-receptor antibodies are potential therapeutics for thyrotoxicosis,¹⁴ thionamides and PTU remain inexpensive, tolerable, and simple-to-use ATDs.

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