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Medical Treatment of Graves' Disease: Benzylthiouracil vs. Methimazole, What to Choose?

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Abstract

Introduction: The management of Graves' disease (GD) typically involves the use of synthetic antithyroid drugs (ATDs), primarily Methimazole (MMI) and Carbimazole (BTU), which aim to inhibit thyroid hormone synthesis and restore normal thyroid function. There are uncertainties regarding the choice of the most appropriate synthetic antithyroid drug (ATD) for the treatment of hyperthyroidism related to GD. This study aims to evaluate the efficacy and tolerance of MMI compared to BTU in patients diagnosed with GD. ***Patients and Methods:*** This cross-sectional analytical study included 121 patients diagnosed with GD. The patients were divided into two groups: Group 1 (G1, n=77), consisting of patients treated with Carbimazole (BTU), and Group 2 (G2, n=44), consisting of patients treated with Methimazole (MMI). We compared the efficacy and tolerance of the two drugs. ***Results:*** Adverse effects (AE) related to the ATDs were more frequent with MMI (18.2%) than with BTU (10.4%), but without a significant difference. The decrease in fT4 levels was significantly earlier and more pronounced with MMI compared to BTU. After a standard treatment duration (12 to 18 months), the remission rate was significantly higher with MMI than with BTU (58.3% vs. 31.9%; p=0.012). The relapse rate was comparable between the two groups (14.5% in G1 vs. 11.1% in G2; p=0.76). ***Conclusion:*** MMI is more effective than BTU in reducing fT4 levels and achieving remission in GD after a standard treatment duration. However, its contribution to the occurrence of adverse effects warrants further investigation.

Keywords: Graves' disease, antithyroid drug, adverse effect, remission, Graves' disease (GD), synthetic antithyroid drugs (ATDs), propylthiouracil (PTU), benzylthiouracil (BTU), carbimazole (CBZ), methimazole (MMI), anti-TSH receptor antibody levels (TRAbs)

1. Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism worldwide. Currently, medical treatment with synthetic antithyroid drugs (ATDs) is recommended as the first-line therapy in the majority of cases globally (Ross, D.S., et al., 2016; Kahaly, G.J., et al., 2018). ATDs have been used for approximately 70 years (Cooper, D.S., 2005). The objective of this treatment is to restore euthyroidism as quickly as possible while avoiding potential complications (Laurberg, P., 2006). ATDs are divided into two families sharing thiourea as a common base. The first family consists of thiouracil derivatives represented by Propylthiouracil (PTU) and

Benzylthiouracil (BTU), which appeared in 1946. The second family includes mercaptoimidazole derivatives represented by Carbimazole (CBZ) and Methimazole (MMI), developed since 1952 (Orgiazzi, J., 2011). Currently, MMI is the most widely prescribed ATD worldwide. In Tunisia, only two ATD molecules are available, namely BTU and more recently, MMI (Azizi F, Abdi H, Amouzegar A & HabibiMoeini AS., 2023). Until now, no studies have evaluated or compared these two molecules. There are still uncertainties regarding the choice of the most suitable molecule and whether these two molecules have the same efficacy and tolerance. In this context, we chose to conduct this study aimed at comparing the efficacy and tolerance of radioiodine therapy (BTU) and methimazole (MMI).

2. Patients and Methods

This was a cross-sectional analytical study conducted in the Endocrinology-Diabetology department of the Farhat Hached University Hospital Center in Sousse, Tunisia. We collected 180 medical records of patients who had been followed up at the department for GD over a six-year period, from January 2017 to December 2022. The inclusion criteria were:

- Patients diagnosed with GD and initially followed up at the department,
- Patients whose initial therapeutic choice was medical treatment with antithyroid drugs (ATDs) (radioiodine therapy or MMI),
- Patients with a minimum follow-up of 24 months.

The retained and studied files numbered 121. They were divided into two groups: group G1 (n=77) comprising patients treated with radioiodine therapy and group G2 (n=44) comprising patients treated with methimazole. Data collection on patients and the disease was performed using a pre-established information form. We noted the clinical and biological evolution of patients, as well as the occurrence of any adverse effects at 3, 6, 12, 18, 24, and 30 months from the start of treatment. We defined the following variables as follows:

- Standard treatment duration: The duration recommended by various scientific societies for the treatment of GD with ATDs, which is 12 to 18 months (Ross, D.S., et al., 2016; Kahaly, G.J., et al., 2018).
- Remission: Achieving sustained biological euthyroidism for at least 3 months after discontinuation of ATDs.
- Relapse: Recurrence of biological hyperthyroidism within the year following discontinuation of ATD treatment.
- Failure: Absence of remission.

The collected data were entered and analyzed using SPSS20 software. For comparisons on independent series, we used the $\chi 2$ test for percentages and student's t-test for means. Statistical significance was defined as $p<0.05$.

3. Results

3.1 The Epidemiological, Clinical, and Paraclinical Characteristics of Patients

The two groups were comparable regarding gender ratio, smoking intoxication, presence of a triggering factor, body mass index (BMI), presence of Graves' orbitopathy, initial fT4 levels, initial anti-TSH receptor antibody levels (TRAbs), and average thyroid volume on ultrasound. Furthermore, patients in Group 1 (G1) were significantly younger and had a significantly longer duration of symptom evolution (Table 1).

Table 1. Epidemiological, Clinical, and Paraclinical Characteristics of the Two Groups

	BTU (n=77)	**MMI (n=44)**	***p***
Age (ans), mean±SD	35,1±13	41,7±15	0,02
Gender (Male/Female Ratio)	1,56	2,66	0,22
Tobacco poisoning, n (%)	22 (28,6)	9 (20,4)	0,41
Presence of Trigger Factors, n (%)	22 (28,6)	16 (36,4)	0,43
Duration of Symptoms (months) m±SD	5±4,8	3±2,9	0,01
BMI (kg/m²), m±SD	21,7±3,6	23,2±6,3	0,09
Presence of Graves' Orbitopathy, n (%)	47 (61)	23 (52,3)	0,42

Initial fT4 Levels (pg/ml), m±SD	54 ± 21,8	61,5 ± 24,5	0,09
Initial TRAbs Levels (UI/L), m±SD	25,5±13	24,1±13,7	0,65
Thyroid Volume on Ultrasound (cm^3), m±SD	32,9±13,4	32,6±13,7	0,93

Note: BTU: benzylthiouracil; MMI: methimazole; BMI: Body mass index; TRAbs: anti-TSH receptor antibodies; m: mean; n: frequency; %: percentage; SD: standard deviation, $p<0.05$.

3.2 Adverse Effects

The occurrence of adverse effects (AEs) was not significantly different between the two groups (p=0.26), with 8 patients (10.4%) in G1 and 8 patients (18.2%) in G2 experiencing AEs. These complications are summarized in Table 2. Most of the observed AEs were minor reactions. Notably, there were serious AEs reported, including one case of agranulocytosis associated with Methimazole (MMI) and one case of ANCA-associated vasculitis in each group. The clinical-biological characteristics of patients who developed vasculitis were summarized in a specific Table 3.

Table 2. Adverse Effects Observed in Each Group

Adverse Effect	**BTU (n=77)**	**MMI (n=44)**
Skin Reactions, n (%)	3 (3.9)	3 (6.8)
Neutropenia, n (%)	2 (2.6)	2 (4.5)
Agranulocytosis, n (%)	0	1 (2.3)
Hepatic Cytolysis, n (%)	2 (2.6)	1 (2.3)
ANCA-associated Vasculitis, n (%)	1 (1.3)	1 (2.3)

Note: BTU: benzylthiouracil; MMI: methimazole; n: frequency; %: percentage.

Table 3. Characteristics of Patients Who Developed ANCA-associated Vasculitis

	Age	**Gender**	**ATD**	**Dose (mg/d)**	**Symptomatology**	**Time to Onset (months)**	**Management**
Patient 1	15	Female	BTU	150	AGC, General malaise, impaired renal function, proteinuria	18	- Discontinue ATD - No radical treatment (patient in remission)
Patient 2	38	Female	MMI	15	Diffuse arthralgias, marked fatigue	3	- Discontinue ATD - Acute renal failure

Note: ATD: antithyroid drug; PTU: propylthiouracil; MMI: methimazole; AGC: alteration of the general condition.

3.3 Timing of Adverse Effects

The onset of AEs in relation to the start of treatment with ATS was often around 3 months, particularly for patients treated with Methimazole (MMI) (p=0.02). No further occurrences of AEs were noted beyond 18 months of treatment in both groups (Figure 1).

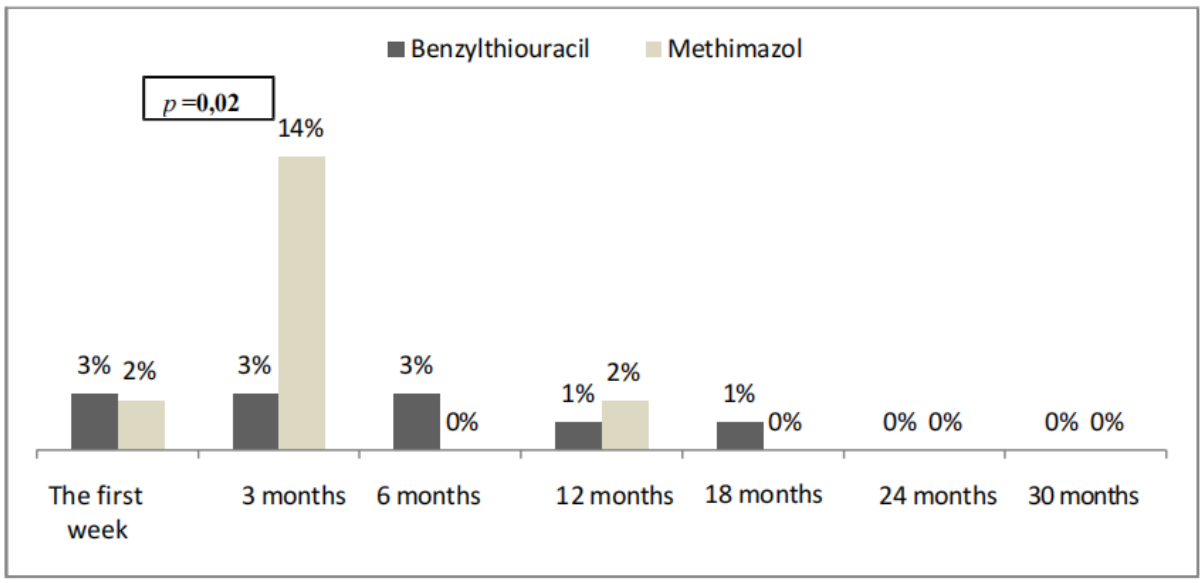

Figure 1. Timeline of Adverse Events in Each Group

3.4 The Evolution of Biological Parameters Under Antithyroid Drugs Summary

The decrease in average fT4 levels was faster and more pronounced with Methimazole (MMI) than with Propylthiouracil (PTU), showing a statistically significant difference starting from the third month of treatment and continuing until the 24th month of follow-up (Figure 2). The percentage of patients who normalized their fT4 levels was also higher with MMI compared to PTU, with a statistically significant difference observed up to the 18th month of treatment. This percentage peaked between the 12th and 18th months of treatment in both groups (Figure 3).

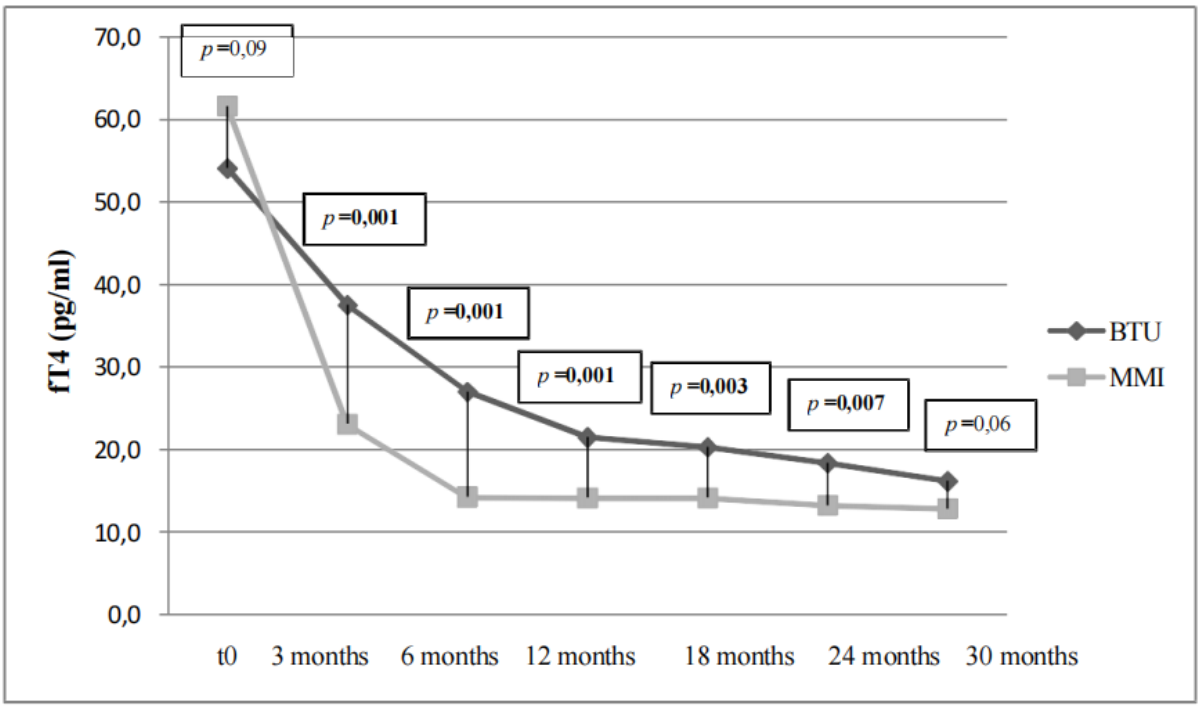

Figure 2. L'évolution de la fT4 au cours du suivi dans les deux groupes

Note: BTU: benzylthiouracil; MMI: methimazole; n: frequency; %: percentage.

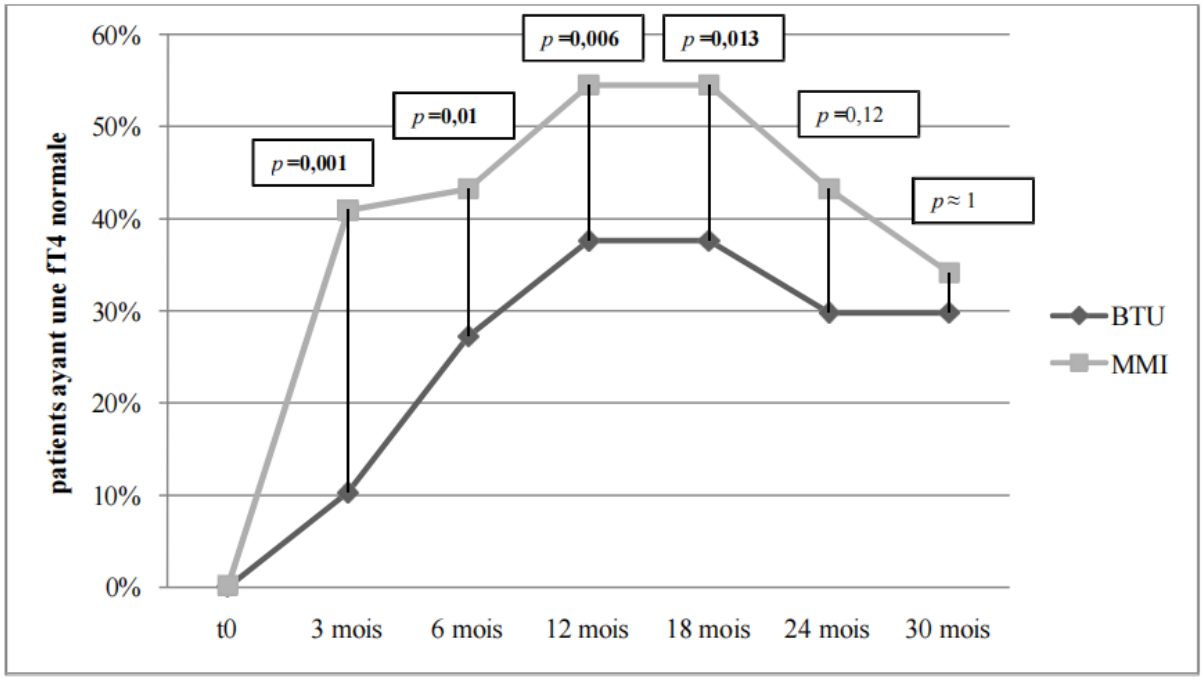

Figure 3. Le pourcentage des patients ayant normalisé leurs fT4 au cours du suivi dans les deux groupes

TRAbs were measured at the end of standard treatment duration in only 15 patients from Group 1 (19.5%) and 10 patients from Group 2 (22.7%). They remained positive in 73.3% of cases in the first group and in only 30% of cases in the second group, with a statistically significant difference (p=0.04).

3.5 Remission and Relapse Rates After Treatment with Antithyroid Drugs Standard Duration Summary

For the study of remission and relapse rates under ATD treatment, we only considered patients who had been treated for at least the recommended standard duration. Their number was 69 patients in Group 1 (G1) and 36 patients in Group 2 (G2).

The remission rate was higher in G2 than in G1 (58.3% vs 31.9%), with a statistically significant difference (p=0.012) (Figure 4).

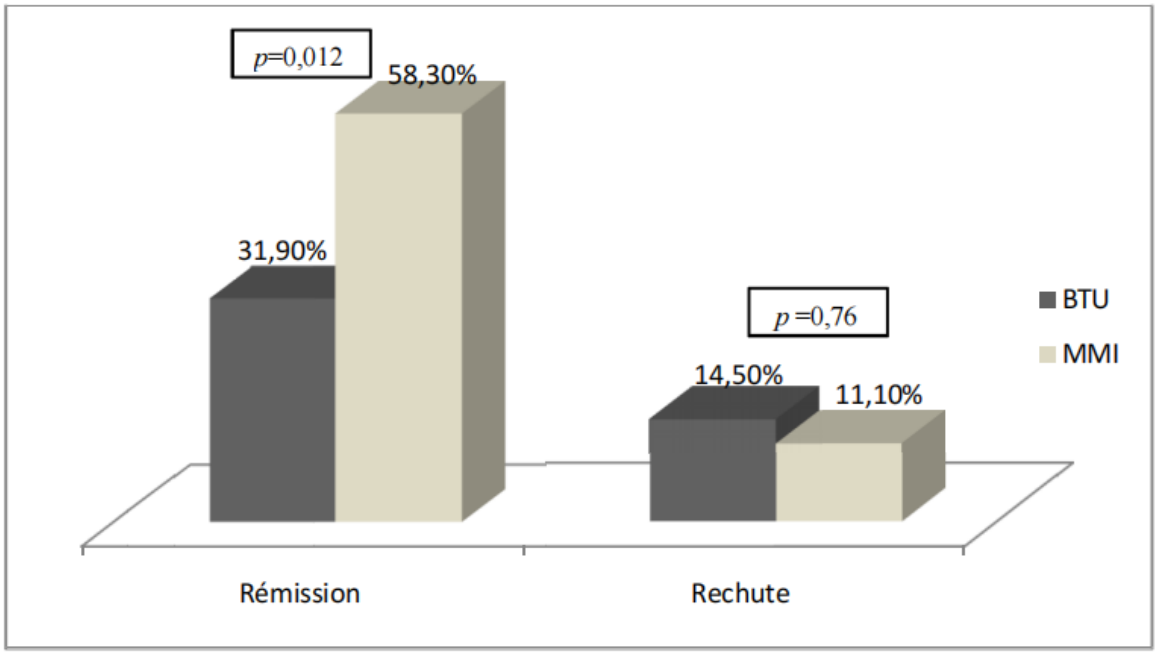

Figure 4. Les taux de rémission et de rechute après traitement de durée standard dans chaque groupe

Among patients who initially achieved remission, 10 patients in G1 (14.5%) and 4 patients (11.1%) in G2 experienced a relapse after treatment discontinuation, with no statistically significant difference (p=0.76) (Figure 4).

4. Discussion

The frequency and mechanisms of antithyroid drug (ATD) toxicity are not perfectly known. “Minor” reactions can cause discomfort that is generally harmless, while a “major” reaction may require discontinuation of treatment. In our study, the majority of observed adverse effects (AEs) were minor reactions (Butt MI, Riazuddin M, Joueidi F & Waheed N., 2023). However, we noted the occurrence of one case of agranulocytosis with methimazole (MMI) and one case of ANCA-associated vasculitis with each molecule. Additionally, the occurrence of AEs was more frequent with MMI than with propylthiouracil (PTU), although the difference was not significant (18.2% vs 10.4%; p=0.26). These results differ from those found in the literature, where it is accepted that PTU is more prone to AEs (Ross, D.S., et al., 2016). Indeed, in a recent historical cohort, Sundaresh et al. reported that the rate of AEs related to PTU was higher than that related to MMI (24.5% vs 13%) and that the majority of AEs related to MMI were seen at daily doses greater than 20 mg (Sundaresh, V., et al., 2017).

Although agranulocytosis is a rare complication, it is serious as it poses a risk to life. In the literature, propylthiouracil (PTU) appears to be more implicated in the occurrence of this complication compared to methimazole (MMI) (Andersohn, F., C. Konzen & E. Garbe, 2007; Takata, K., et al., 2009). Hepatitis is also rare, occurring in 1 to 1.2% of patients treated with PTU (Kim, H.-J., et al., 2001). Fulminant forms are primarily associated with PTU (Ruiz, J.K., et al., 2003). Finally, ANCA-associated small vessel vasculitis can occur during treatment with PTU, or more rarely with MMI (Noh, J.Y., et al., 2009). These vasculitides typically present with arthralgia, fever, skin lesions, and in severe cases, multivisceral failure (Harper, L., et al., 2004). Unlike other adverse effects that generally occur early in treatment, the risk of this complication seems to increase with the duration of treatment. Given the rarity of these adverse effects, regular monitoring of leukocyte counts, liver function, and systematic ANCA testing is not recommended by medical societies (Ross, D.S., et al., 2016; Cooper, D.S., 2005).

Regarding the efficacy of antithyroid drugs (ATDs), few studies have compared the effectiveness of methimazole (MMI) and propylthiouracil (PTU) in the treatment of hyperthyroidism due to Graves’ disease (Nakamura H, Noh JY, Itoh K, Fukata S, Miyauchi A & Hamada N., 2007). Okamura et al. reported that 30 mg/day of MMI normalizes the free T4 (fT4) levels more rapidly than 300 mg/day of PTU (Okamura, K., et al., 1987). Similarly, Nakamura et al. found that the percentage of patients who normalized their fT4 levels was significantly higher with MMI than with PTU (96.5% vs 78.3%; p=0.001). Our results confirmed these findings, as we demonstrated that the decline in fT4 levels was significantly faster and more pronounced with MMI compared to PTU. The percentage of patients who normalized their fT4 levels was also higher with MMI throughout the follow-up period. The remission rates of Graves’ disease under ATD treatment vary from one study to another, ranging from 30% to 70% (Konishi, T., et al., 2011; Jin M, Jang A, Kim CA, Kim TY, Kim WB, Shong YK, Jeon MJ & Kim WG., 2023). However, the most frequently reported rate is approximately 50% (Laurberg, P., 2006). In our study, the remission rate after standard duration medical treatment was significantly higher in the MMI-treated group than in the PTU-treated group (58.3% vs 31.9%, p=0.012). The relapse rate was comparable in both groups and did not vary significantly (p=0.76). These results suggest that MMI may be more effective than PTU for standard duration treatment in terms of achieving remission from Graves’ disease.

5. Conclusion

MMI appears to be superior to PTU in terms of efficacy, as it allows for a more rapid and sustained normalization of fT4 levels. It also leads to better long-term outcomes for Graves’ disease, with a significantly higher remission rate compared to PTU. However, the adverse effects observed with MMI were more frequent than those with PTU, although the difference was not statistically significant. This suggests the need for further studies with larger sample sizes to better substantiate these findings, especially since they contradict some reports in the literature.

References

Andersohn, F., C. Konzen, and E. Garbe, (2007). Systematic review: agranulocytosis induced by nonchemotherapy drugs. *Ann Intern Med*, *146*(9), 657-665.

Azizi F, Abdi H, Amouzegar A, HabibiMoeini AS., (2023, March). Long-term thionamide antithyroid treatment of Graves’ disease. *Best Pract Res Clin Endocrinol Metab.*, *37*(2), 101631.

Butt MI, Riazuddin M, Joueidi F, Waheed N., (2023, March 11). Antithyroid Drugs in the Management of Graves’ Disease: A Friend and Foe. *Cureus*, *15*(3), e36028.

Cooper, D.S., (2005). Antithyroid drugs. *N Engl J Med*, *352*(9), 905-917.

Harper, L., et al., (2004). Propylthiouracil and carbimazole associated-antineutrophil cytoplasmic antibodies (ANCA) in patients with Graves' disease. *Clin Endocrinol*, *60*(6), 671675.

Jin M, Jang A, Kim CA, Kim TY, Kim WB, Shong YK, Jeon MJ, Kim WG., (2023, March 17). Long-term follow-up result of antithyroid drug treatment of Graves' hyperthyroidism in a large cohort. *Eur Thyroid J.*, *12*(2), e220226.

Kahaly, G.J., et al., (2018). European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. *Eur Thyroid J*, *7*(4), 1-20.

Kim, H.-J., et al., (2001). The incidence and clinical characteristics of symptomatic propylthiouracil induced hepatic injury in patients with hyperthyroidism: a single-center retrospective study. *Am J Gastroenterol*, *96*(1), 165-169.

Konishi, T., et al., (2011). Drug discontinuation after treatment with minimum maintenance dose of an antithyroid drug in Graves' disease: A retrospective study on effects of treatment duration with minimum maintenance dose on lasting remission. *Endocr J.*, *58*(2), 95-100.

Laurberg, P., (2006). Remission of Graves' disease during anti-thyroid drug therapy. Time to reconsider the mechanism? *Eur J Endocrinol*, *155*(6), 783-786.

Nakamura H, Noh JY, Itoh K, Fukata S, Miyauchi A, Hamada N., (2007, June). Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. *J Clin Endocrinol Metab.*, *92*(6), 2157-62.

Noh, J.Y., et al., (2009). Clinical characteristics of myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis caused by antithyroid drugs. *J Clin Endocrinol Metab*, *94*(8), 2806-2811.

Okamura, K., et al., (1987). Reevaluation of the effects of methyl mercaptoimidazole and propylthiouracil in patients with Graves' hyperthyroidism. *J Clin Endocrinol Metab*, *65*(4), 719-723.

Orgiazzi, J., (2011). Traitement de la maladie de Basedow: problématiques actuelles. *Presse Med*, *40*(12), 1155-1162.

Ross, D.S., et al., (2016). American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*, *26*(10), 1343-1421.

Ruiz, J.K., et al., (2003). Fulminant hepatic failure associated with propylthiouracil. *Ann Pharmacother*, *37*(2), 224-228.

Smith, T.J. and L. Hegedüs, (2016). Graves' disease. *N Engl J Med.*, *375*(16), 1552-1565.

Sundaresh, V., et al., (2017). Comparative Effectiveness of Treatment Choices for Graves' Hyperthyroidism: A Historical Cohort Study. *Thyroid*, *27*(4), 497-505.

Takata, K., et al., (2009). Methimazole-induced agranulocytosis in patients with Graves' disease is more frequent with an initial dose of 30 mg daily than with 15 mg daily. *Thyroid*, *19*(6), 559-563.