Received: 22 August 2023 | Accepted: 22 January 2024

DOI: 10.1111/fcp.12991

ORIGINAL ARTICLE

Fundamental & Clinical Pharmacology | WILEY

Comparison of agranulocytosis and anti-neutrophil cytoplasmic antibody-associated vasculitis caused by two antithyroid drugs: A pharmacovigilance study using the WHO international database

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Abstract

Background: Methimazole (MMI) and propylthiouracil (PTU) are commonly used for patients with thyrotoxicosis. Agranulocytosis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is associated with high morbidity and mortality, requiring appropriate interventions. In this study, we compared adverse drug effects associated with MMI and PTU using a real-world large pharmacovigilance database.

Abbreviations: AAV, Antineutrophil cytoplasmic antibody-associated vasculitis; ADRs, Adverse drug reactions; ANCA, Antineutrophil cytoplasmic antibody; EGPA, Eosinophilic granulomatosis with polyangiitis; GPA, Granulomatosis with polyangiitis; IC, Information component; ICSR, Individual case safety report; MedDRA, Medical dictionary for regulatory activities; MMI, Methimazole; MPA, Microscopic polyangiitis; PTs, Preferred terms; PTU, Propylthiouracil; rOR, Ratio of odds ratio; UMC, Uppsala monitoring center; WHO, World Health Organization.

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Funding information
This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Methods: We searched all Individual Case Safety Reports reported to be associated with MMI and PTU, from VigiBase between 1967 and June 2, 2021. We conducted disproportionality analysis (case/non-case analysis) to analyze the difference in reported adverse drug reactions (ADRs) between antithyroid drugs (case) and the entire database (non-cases). We further analyzed information for the cases of agranulocytosis and AAV.
Results: Among 11 632 cases of ADRs reported after MMI intake, agranulocytosis occurred in 1633 cases and AAV occurred in 41 cases. For 5055 cases of ADRs reported after PTU intake, agranulocytosis occurred in 459 cases and AAV occurred in 110 cases. Agranulocytosis occurred after a median of 28 days after PTU intake and 33 days after MMI intake. More than 95% of the agranulocytosis cases were classified as serious, but most of them (65.1% for PTU and 70.4% for MMI) were reported to have recovered after dechallenge actions; mostly drug withdrawal. AAV occurred after a median of 668 days after PTU intake, and 1162 days after MMI intake.
Conclusions: This is a pharmacoepidemiological study investigating agranulocytosis and AAV caused by MMI and PTU. Through this research, we could provide more specific insights into a safe prescription of antithyroid drugs in a real-world setting.

KEYWORDS
agranulocytosis, ANCA-associated vasculitis, Antithyroid drugs, methimazole, pharmacovigilance study, propylthiouracil

1 | INTRODUCTION

Thyrotoxicosis is a common systemic disorder caused by excess thyroid hormones with inappropriate activation of the hypothalamic–pituitary–thyroid axis [1]. Excess thyroid hormones have various systemic effects, leading to clinical presentations that include diverse symptoms such as fatigue, anxiety, hair loss, muscle weakness, increased appetite, and weight loss [2]. There is a proposed prevalence of 1.3% in the United States [3], and it is more common in females (2%) than males (0.2%) [4]. Thyrotoxicosis is an important global health problem and warrants a proper understanding of its treatment and medication.

The two most popular antithyroid drugs used for thyrotoxicosis are methimazole (MMI) and propylthiouracil (PTU). Adverse reactions occur in up to 5% of patients using antithyroid drugs, but many are minor; such as fever, rash, urticaria, and arthralgia [2, 5]. However, some major adverse reactions may have considerable impacts, such as agranulocytosis which is the most common and feared reaction [2]. In agranulocytosis, caused by immunological or cytotoxic mechanisms, the neutrophil count is very low leading to an increased vulnerability to various infections [6]. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which is known to be more specific to PTU, is a systemic inflammatory condition affecting small to medium-sized vessels, consisting of three subgroups; granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [7, 8]. Agranulocytosis induced by antithyroid drugs is well known, with clinical presentations of fever and sore throat [9]. AAV caused by PTU has also been demonstrated in several studies [10–12], with clinical presentations of fever, fatigue, and cutaneous vasculitis. However, despite several case reports [13–15], MMI-induced AAV is not well studied. Agranulocytosis and AAV are associated with high morbidity and mortality, requiring appropriate interventions [16, 17].

Several pharmacovigilance studies of PTU and MMI were previously conducted. One pharmacovigilance study from the UK [18] showed the characteristics of a small number of patients (Carbimazole, $n = 45$, and PTU, $n = 9$) suffering from agranulocytosis induced by antithyroid drugs. Another pharmacoepidemiologic study [19] showed that PTU and MMI ranked second and third highest in frequency, respectively, among drugs that induce AAV. While agranulocytosis and AAV induced by the antithyroid drugs MMI and PTU are well known, comparative research on all ADRs caused by these two drugs is limited. Moreover, these studies were conducted with relatively low numbers of patients.

Therefore, in this study, we explored various ADRs associated with antithyroid drugs and identified patients' profiles with adverse reactions of AAV and agranulocytosis using VigiBase; the World Health Organization's (WHO) global Individual Case Safety Report (ICSR) database. We aim to suggest further insight into life-threatening adverse reactions regarding antithyroid drug use.

2 | MATERIALS AND METHODS

2.1 | Study design and data source

This pharmacovigilance study used VigiBase, a WHO global ICSR database [20, 21]. The safety report data was collected from around 140 countries and transferred to VigiBase, which is maintained and managed by the Uppsala Monitoring Center (UMC, Sweden). VigiBase contains information on patient demographics, reported drugs and events, and additional information associated with adverse drug reactions (ADRs). Such information is reported by healthcare professionals, patients, and pharmaceutical companies. The terminology for ADRs was described in the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) [22].

We searched all ICSRs reported to be associated with the two antithyroid drugs, MMI and PTU, from VigiBase between 1967 and June 2, 2021. Additional information was extracted, including patients' characteristics (gender and age), ADR's characteristics (time to onset, dose, reaction duration, seriousness, and outcome), regions, reporters, and reporting years. This study was approved by the institutional review board of Yonsei University Severance Hospital (IRB number: 4-2021-002).

2.2 | Variables

Information component (IC) was calculated as $\log_2((n_{observed} + 0.5)/(n_{expected} + 0.5))$; $n_{observed}$ = actual number of case reports for the combination of drug-effect; $n_{expected} = (n_{drug} * n_{effect})/n_{total}$; n_{drug} = number of case reports for the drug, regardless of effects; n_{effect} = number of case reports for the effect, regardless of drug [23]. IC_{025} was defined as the lower bound of the 95% CI for IC, and statistical significance was considered when $IC_{025} > 0$ [24].

2.3 | Comparison of adverse effects

Through disproportionality analysis (case/non-case analysis) with our data from VigiBase and comparison of the ratio of odds ratios (rOR) for major ADRs [2], we narrowed down our focus to agranulocytosis and ANCA. The ratio of odds ratios between MMI and PTU for severe but uncommon adverse reactions were listed in order of frequency reported for PTU; 95% CI (p-value) has been described for the analysis. Univariable logistic regression was performed to analyze rOR to compare ADRs between MMI and PTU, using the Chi-squared test or Fisher's test [25]. Statistical significance was defined as two-tailed p-values less than 0.05. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R software (version 3.1.1; R Foundation, Vienna, Austria).

2.4 | Analysis of agranulocytosis and ANCA-associated vasculitis

Among the major ADRs, we further analyzed the following information for the cases of agranulocytosis and AAV. Descriptive epidemiological data of the patients reported with each adverse reaction after MMI or PTU were used, with variables including gender, age, region reporting, reporters, reporting years, time to onset (of adverse reactions), dose, and reaction duration, with subcategories according to the classification used in the VigiBase reporting system. Categorical variables were described as number count (percentage), and continuous variables were expressed as median (interquartile range). Dechallenge actions and outcomes according to each action were also described as number count (percentage).

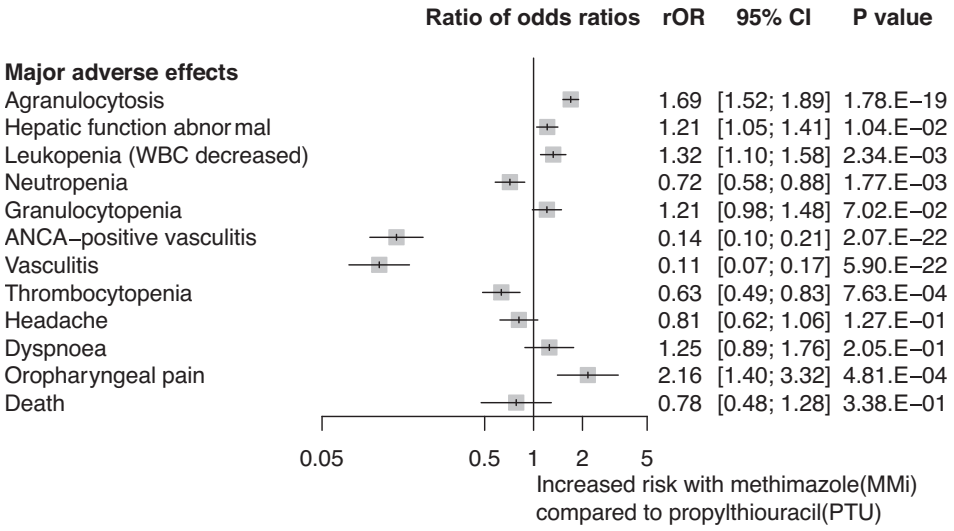

FIGURE 1 Comparison of major adverse drug reactions between propylthiouracil and methimazole in order of incidence by propylthiouracil. rOR, ratio of odds ratios; 95% CI, 95% confidential interval; WBC, white blood cell; ANCA, anti-neutrophil cytoplasmic antibody.

3 | RESULTS

3.1 | Comparison of adverse drug reactions

We compared MMI and PTU's reported major adverse drug reactions (Figure S1). Agranulocytosis ranked third highest ($n = 459$) in PTU users and first highest ($n = 1633$) in MMI users. While most major ADRs showed similar ranks between the 2 drugs, AAV showed 14th and 82nd rank in PTU and MMI users, respectively.

We analyzed the rOR between MMI and PTU for major adverse drug reactions (Figure 1). While agranulocytosis, hepatic function abnormality, leukopenia, and oropharyngeal pain showed higher odds ratios of MMI

TABLE 1 Descriptive epidemiologic data of the patients reported with an agranulocytosis after PTU ($n = 459$, $IC_{0.25} = 5.86$) or MMI ($n = 1633$, $IC_{0.25} = 6.61$) use.

Characteristics	PTU n(%) *Data availability n(%)*		MMI n(%) *Data availability n(%)*	
Gender		452 (98.5%)		1585 (97.1%)
Male	74 (16.4%)		224 (14.1%)	
Female	378 (83.6%)		1361 (85.9%)	
Age		440 (95.9%)		1536 (94.1%)
0–17	13 (3.0%)		37 (2.4%)	
18–44	194 (44.1%)		686 (44.7%)	
45–64	139 (31.6%)		547 (35.6)%)	
65–74	45 (10.2%)		151 (9.8%)	
75 ~	49 (11.1%)		115 (7.5%)	
Region reporting		459 (100.0%)		1633 (100.0%)
America	47 (10.2%)		145 (8.9%)	
Europe	209 (45.5%)		632 (38.7%)	
Oceania	23 (5.0%)		0 (0.0%)	
Asia	180 (39.2%)		856 (52.4%)	
Reporters		362 (78.9%)		1230 (75.3%)
Health professionals	357 (98.6%)		1209 (98.3%)	
Non-health professionals	5 (1.4%)		21 (1.7%)	
Reporting years		459 (100.0%)		1633 (100.0%)
2016 ~	118 (25.7%)		654 (40.0%)	
2011–2015	107 (23.3%)		445 (27.3%)	
2006–2010	37 (8.1%)		143 (8.8%)	
2001–2005	47 (10.2%)		90 (5.5%)	
~ 2000	150 (32.7%)		301 (18.4%)	
Time to onset		324 (70.6%)		1176 (72.0%)
Median days (25–75%)	28 (17–58)		33 (23–56)	
Dose		325 (70.8%)		945 (57.9%)
Median mg (25–75%)	300 (150–400)		20 (15–30)	
Reaction duration		67 (14.6%)		352 (21.6%)
Median days (25–75%)	7 (5–12)		10 (7–16)	
Serious		190 (41.4%)		1192 (73.0%)
Yes	182 (95.8%)		1157 (97.1%)	
No	8 (4.2%)		35 (2.9%)	
Outcome		355 (77.3%)		1315 (80.5%)
Died	6 (1.7%)		15 (1.1%)	
Fatal	9 (2.5%)		61 (4.6%)	
Not recovered/resolved	41 (11.5%)		90 (6.8%)	
Recovered/resolved	299 (84.2%)		1149 (87.3%)	

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; IC, information component; MMI, methimazole; PTU propylthiouracil.

compared to that with PTU, AAV, and vasculitis showed lower odds ratios of MMI (AAV rOR 0.14, 95% CI 0.10–0.21; vasculitis rOR 0.11, 95% CI 0.07–0.17).

3.2 | Analysis of agranulocytosis and ANCA-associated vasculitis

Among the major adverse reactions, we further analyzed agranulocytosis and AAV.

3.2.1 | Agranulocytosis

Despite differences in the number of reported cases, agranulocytosis after PTU and MMI showed similar tendencies (Table 1), mostly reported in middle-aged subjects, from 18 to 44 years of age (PTU 44.1% and MMI 44.7%), and females (PTU 83.6% and MMI 85.9%). Agranulocytosis after PTU intake occurred after a median of 28 days and lasted for a median of 7 days. On the other hand, agranulocytosis upon MMI intake occurred after a median of 33 days and lasted for a median of 10 days. Among PTU reports, 95.8% of the cases were classified as serious events, but 65.1% of all cases were reported to have recovered, resolved, or undergone recovery. This observation was similar to reports after MMI intake, with 97.1% classified as serious and 70.4% reported to be recovered, resolved, or undergoing recovery.

After the adverse reaction, the drug was mainly withdrawn in both cases; 62.3% of the cases after PTU and 68.2% after MMI initiation. Most patients had a favorable long-term outcome, but few cases were reported to have significant clinical impact; 1.3% death and 2.0% fatal outcomes were reported for PTU, and 0.9% death and 3.7% fatal outcomes were reported for MMI, respectively (Table 2).

TABLE 2 Dechallenge actions & outcomes of the patients reported with an agranulocytosis after PTU ($n = 459$, $IC_{0.25} = 5.86$) or MMI ($n = 1633$, $IC_{0.25} = 6.61$) use.

Dechallenge action	**PTU n(%)**		**MMI n(%)**	
Data availability n(%)	***114 (24.8%)***		***1139 (69.7%)***	
	Action	**Outcome**	**Action**	**Outcome**
Dose increased	0 (0.0%)		3 (0.3%)	
Reaction abated		-		3 (100%)
Drug withdrawn	71 (62.3%)		777 (68.2%)	
Reaction abated		51 (71.8%)		663 (85.3%)
No effect observed		4 (5.6%)		28 (3.6%)
Effect unknown		15 (21.1%)		74 (9.5%)
Fatal		1 (1.4%)		12 (1.5%)
Dose reduced	4 (3.5%)		1 (0.1%)	
Reaction abated		4 (100.0%)		1 (100%)
Dose not changed	5 (4.4%)		4 (0.4%)	
Reaction abated		4 (80.0%)		2 (50.0%)
Effect unknown		1 (20.0%)		0 (0.0%)
Fatal		0 (0.0%)		1 (25.0%)
Not applicable		0 (0.0%)		1 (25.0%)
Not applicable	10 (8.8%)		20 (1.8%)	
Reaction abated		7 (70.0%)		5 (25.0%)
No effect observed		1 (10.0%)		1 (5.0%)
Effect unknown		1 (10.0%)		4 (20.0%)
Fatal		1 (10.0%)		10 (50.0%)
Unknown	24 (21.1%)		334 (29.3%)	
Reaction abated		13 (54.2%)		101 (30.2%)
No effect observed		0 (0.0%)		5 (1.5%)
Effect unknown		11 (45.8%)		65 (19.5%)
Fatal		0 (0.0%)		3 (0.9%)
Not applicable		0 (0.0%)		160 (47.9%)

Abbreviations: IC, information component; MMI methimazole; PTU propylthiouracil.

3.2.2 | ANCA-associated vasculitis

One hundred and ten cases of AAV after PTU and thirty-nine AAV upon MMI treatment were reported (Table 3). PTU was mostly reported in middle-aged subjects, from 18 to 44 years of age (47.6%), and females (88.2%), whereas most reports with MMI treatment were among older subjects from 45 to 64 years of age (43.6%), and females (84.6%). AAV after PTU intake occurred after a median of 668 days and lasted for a median of 66.3 days. On the other hand, AAV after MMI intake occurred after a median of 1162 days and lasted for a median of 144.5 days.

After the adverse reaction, the drug was mainly withdrawn in both cases; 65.5% of the cases after PTU and 80.5% after MMI intake. Usually, the reaction

TABLE 3 Descriptive epidemiologic data of the patients reported with an ANCA-associated vasculitis after PTU ($n = 110$, $\boldsymbol{Ic_{0.25}} = 7.13$) or MMI ($n = 41$, $\boldsymbol{Ic_{0.25}} = 5.15$) use.

Characteristics	PTU n(%) *Data availability n(%)*		MMI n(%) *Data availability n(%)*	
Gender		110 (100.0%)		39 (95.1%)
Male	13 (11.8%)		6 (15.4%)	
Female	97 (88.2%)		33 (84.6%)	
Age		105 (95.5%)		39 (95.1%)
0–17	7 (6.7%)		3 (7.7%)	
18–44	50 (47.6%)		11 (28.2%)	
45–64	30 (28.6%)		17 (43.6%)	
65–74	11 (10.5%)		5 (12.8%)	
75 ~	7 (6.7%)		3 (7.7%)	
Region reporting		110 (100.0%)		41 (100.0%)
America	11 (10.0%)		12 (29.3%)	
Europe	15 (13.6%)		0 (0.0%)	
Oceania	1 (0.9%)		0 (0.0%)	
Asia	83 (75.5%)		29 (70.7)	
Reporters		105 (95.5%)		41 (100.0%)
Health professionals	104 (99.0%)		40 (97.6%)	
Non-health professionals	1 (1.05)		1 (2.4%)	
Reporting years		110 (100.0%)		41 (100.0%)
2016 ~	46 (41.8%)		23 (56.1%)	
2011–2015	59 (53.6%)		17 (41.5%)	
2006–2010	5 (4.5%)		1 (2.4%)	
2001–2005	0 (0.0%)		0 (0.0%)	
~ 2000	0 (0.0%)		0 (0.0%)	
Time to onset		37 (33.6%)		10 (24.4%)
Median days (25–75%)	668 (77–2044)		1162 (263.25–2730.125)	
Dose		50 (45.5%)		20 (48.8%)
Median mg (25–75%)	100 (100–200)		12.5 (5–20)	
Reaction duration		30 (27.3%)		12 (29.3%)
Median days (25–75%)	66.25 (36–142.75)		144.5 (95.75–235.25)	
Serious		109 (99.1%)		41 (100.0%)
Yes	106 (97.2%)		41 (100.0%)	
No	3 (2.8%)		0 (0.0%)	
Outcome		76 (69.1%)		34 (82.9%)
Died	0 (0.0%)		0 (0.0%)	
Fatal	3 (3.9%)		5 (14.7%)	
Not recovered/resolved	5 (6.6%)		1 (2.9%)	
Recovered/resolved	68 (89.5%)		28 (82.4%)	

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; IC, information component; MMI, methimazole; PTU propylthiouracil.

subsided, and about 2.9% of PTU, and 12.2% of the MMI cases were fatal (Table 4).

4 | DISCUSSION

To the best of our knowledge, this is an international pharmacovigilance study that compared and analyzed ADRs associated with MMI and PTU, the most prescribed antithyroid drugs. Our comparison of ADRs induced by MMI and PTU revealed that most of them were not severe in nature. However, among them, agranulocytosis and AAV are severe conditions, which led us to analyze descriptive epidemiological data of 2092 cases of agranulocytosis and 151 cases of AAV associated with MMI and PTU use. Based on our analysis, we were able to introduce some precautions clinicians should consider when prescribing antithyroid drugs.

While guidelines for thyrotoxicosis do not recommend routine white blood cell monitoring [26, 27], Tajiri et al reported that routine white blood cell count monitoring was necessary to check agranulocytosis when initiating antithyroid drugs [28]. Our result shows that the onset of agranulocytosis usually took less than 60 days, suggesting the need for routine monitoring within the first 2 to 3 months after antithyroid drug initiation. Moreover, the immediate action after the occurrence of agranulocytosis was drug withdrawal, generally resulting in recovery of agranulocytosis.

AAV onset after antithyroid drugs is well-described but has not been reported in large cohorts. Physicians must pay close attention especially when prescribing PTU. The median time to onset of AAV after PTU use was 668 days, which is consistent with a single-center study [29]. While some case reports describe AAV after MMI [30, 31], our study specifically showed that the median onset time was 1162 days. However, the

TABLE 4 Dechallenge actions and outcomes of the patients reported with an ANCA-associated vasculitis after PTU ($n = 110$, $IC_{0.25} = 7.13$) or MMI ($n = 41$, $IC_{0.25} = 5.15$) use.

Dechallenge action	PTU n(%)		MMI n(%)	
Data availability n(%)	*104 (94.5%)*		*41 (100.0%)*	
	Action	**Outcome**	**Action**	**Outcome**
Dose increased	0 (0.0%)		0 (0.0%)	
Reaction abated		-		-
Drug withdrawn	72 (65.5%)		33 (80.5%)	
Reaction abated		51 (70.8%)		26 (78.8%)
No effect observed		4 (5.6%)		1 (3.0%)
Effect unknown		16 (22.2%)		2 (6.1%)
Fatal		1 (1.4%)		4 (12.1%)
Dose reduced	1 (0.9%)		1 (2.4%)	
Reaction abated		1 (100%)		1 (100%)
Dose not changed	5 (4.5%)		1 (2.4%)	
Reaction abated		4 (80.0%)		0 (0.0%)
Effect unknown		1 (20.0%)		1 (100%)
Fatal		0 (0.0%)		0 (0.0%)
Not applicable		0 (0.0%)		0 (0.0%)
Not applicable	4 (3.6%)		2 (4.9%)	
Reaction abated		2 (50.0%)		0 (0.0%)
No effect observed		0 (0.0%)		0 (0.0%)
Effect unknown		1 (25.0%)		1 (50.0%)
Fatal		1 (25.0%)		1 (50.0%)
Unknown	22 (20.0%)		4 (9.8%)	
Reaction abated		11 (50.0%)		1 (25.0%)
No effect observed		0 (0.0%)		0 (0.0%)
Effect unknown		11 (50.0%)		3 (75.0%)
Fatal		0 (0.0%)		0 (0.0%)
Not applicable		0 (0.0%)		0 (0.0%)

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; IC, information component; MMI, methimazole; PTU propylthiouracil.

range of 25–75% was large, implying that the time to onset of AAV is highly variable, from less than a week to more than 10 years. This suggests that, unlike agranulocytosis, clinicians must be aware of AAV as a possible ADR during the entire time of antithyroid drug use.

Severe ADRs should be considered when changing antithyroid drugs. AAV and vasculitis showed the lowest ratio of odds ratio for MMI compared with PTU. MMI being a well-known first-choice drug for thyrotoxicosis, PTU may be used for patients in 1st trimester of pregnancy or with previous history of ADRs associated with MMI use [1, 32]. Our result suggests that when clinicians change the drugs from MMI to PTU in such conditions, it is necessary to pay careful attention to clinical manifestations of vasculitis, especially AAV.

The major strength of our study is that we used global data from more than 130 countries worldwide, thereby investigating large numbers of cases of ADRs compared with previous studies. Health professionals reported about 98% of the data, making our analyses reliable. Moreover, through our analysis, we were able to provide more specific insights into ADRs associated with the prescription of antithyroid drugs.

However, our study has some limitations. First, we could not obtain some information – time to onset, reaction duration, and specific actions made by the physicians were not reported in many cases, potentially causing statistical error. Second, the terms we used may lack clarity. For each reporter, the terms of ADRs varied. Vasculitis was reported in 102 cases after PTU and 27 cases after MMI, and there is a possibility that some cases reported as 'vasculitis' were actually ANCA-associated vasculitis. Agranulocytosis also showed similar ambiguity, with reports under 'leukopenia', 'decreased WBC', and 'granulocytopenia'. This indicates possible miscommunication between case reporters and the data users. However, for our analyses, we limited and clarified the term of ADRs only to "agranulocytosis" and "ANCA-associated vasculitis" to overcome confusion on these vague terms. Third, there is possible reporting bias for ADRs. Reporters might tend to over-report severe cases and under-report mild cases. Lastly, patients' history before ADRs – such as comorbidities, were not reported. As each patients' condition might affect their adverse drug reactions, further studies considering the conditions are needed.

In conclusion, we investigated how MMI and PTU, the most used antithyroid drugs, are associated with several ADRs. MMI and PTU have a high risk of inducing agranulocytosis. PTU, compared with MMI, has a higher risk of inducing AAV, alerting clinicians to be aware of such possibilities. We also analyzed agranulocytosis and AAV, associated with MMI and PTU; their characteristics, and how such patients were treated. Our findings may help clinicians to use drugs safely while treating thyrotoxicosis in a real-world setting.

AUTHOR CONTRIBUTIONS

SY Jung, **DK Yeon,** and **JI Shin** designed the research. **SY Jung**, **JY Han,** and **JM Lee** performed the analysis. **JY Han** and **JM Lee** drafted the manuscript. **MS Kim and SW Lee** prepared illustrated figures. **Andreas Kronbichler, Kalthoum Tizaoui, Ai Koyanagi, EY Kim, KC Song, HW Chae, MS Kim,** and **SW Lee** revised the manuscript for important intellectual content. All authors read and approved the final manuscript. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

ACKNOWLEDGMENTS

We appreciate members of the custom search team at the Uppsala Monitoring Centre (Uppsala, Sweden) research section, who were invaluable to the successful performance of this study. The supplied data from VigiBase was obtained from various sources and the likelihood of a causal relationship was not the same in all reports. Finally, the results and conclusions of this study do not represent the opinion of the WHO.

CONFLICT OF INTEREST STATEMENT

Authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Han JY, Lee JM, Jung SY, et al. Comparison of agranulocytosis and anti-neutrophil cytoplasmic antibody-associated vasculitis caused by two antithyroid drugs: A pharmacovigilance study using the WHO international database. *Fundam Clin Pharmacol*. 2024;1-9. doi:10.1111/fcp.12991