Characteristics of Korean Patients with Antithyroid Drug-Induced Agranulocytosis: A Multicenter Study in Korea

Hee Kyung Kim[1], Jee Hee Yoon[1], Min Ji Jeon[2], Tae Yong Kim[2], Young Kee Shong[2], Min Jin Lee[3], Bo Hyun Kim[3], In Joo Kim[3], Ji Young Joung[4], Sun Wook Kim[4], Jae Hoon Chung[4], Ho-Cheol Kang[1]

[1]Department of Internal Medicine, Chonnam National University Medical School, Gwangju; [2]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul; [3]Department of Internal Medicine, Pusan National University School of Medicine, Busan; [4]Division of Endocrinology and Metabolism, Department of Medicine, Thyroid Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: Antithyroid drugs (ATDs) can lead to the development of agranulocytosis, which is the most serious adverse effect. Characteristics of ATD-induced agranulocytosis (AIA) have seldom been reported due to the rarity. In this study, we characterized the clinical features for AIA in Korean patients.

Methods: We retrospectively reviewed data from patients with AIA diagnosed between 1997 and 2014 at four tertiary hospitals. Agranulocytosis was defined as an absolute neutrophil count (ANC) below 500/mm^3.

Results: The mean age of the patients (11 males, 43 females) was 38.2±14.9 years. Forty-eight patients (88.9%) with AIA had fever and sore throat on initial presentation, 20.4% of patients developed AIA during the second course of treatment, and 75.9% of patients suffered AIA within 3 months after initiation of ATD. The patients taking methimazole ($n=39$) showed lower levels of ANC and more frequent use of granulocyte-macrophage colony-stimulating factor than propylthiouracil ($n=15$) users. The median duration of agranulocytosis was 5.5 days (range, 1 to 20). No differences were observed between the long (≥6 days) and short recovery time (≤5 days) groups in terms of age, gender, ATDs, duration of ATDs, or initial ANC levels. Four patients (7.4%) who were taking ATDs for less than 2 months died of sepsis on the first or second day of hospitalization.

Conclusion: The majority of AIA incidents occur in the early treatment period. Considering the high fatality rate of AIA, an early aggressive therapeutic approach is critical and patients should be well informed regarding the warning symptoms of the disease.

Keywords: Graves disease; Antithyroid agents; Agranulocytosis

INTRODUCTION

Graves' disease is the most common cause of hyperthyroidism. In Korea, the overall incidence is 0.72 per 1,000 persons/year (males 0.40 and females 1.03), and its prevalence is 3.40/1,000 persons (males 2.09 and females 4.70) [1]. The treatment mo-

dalities involve antithyroid drugs (ATDs), radioactive iodine therapy (RAI), and total thyroidectomy. ATDs are used as an initial treatment for Graves' disease in 97.1% of patients in Korea and are generally well-tolerated agents [2]. ATDs can cause transient and minor adverse reactions such as benign leukopenia, urticaria, rash, arthralgia, and arthritis in 1% to 5% of pa-

tients, and agranulocytosis, severe toxic hepatitis, vasculitis, and lupus-like syndrome are very rare but fatal. Agranulocytosis, which is defined as a granulocyte count below 500/mm^3, is a life-threatening adverse reaction of ATDs [3]. Reports on the characteristics of agranulocytosis are limited because its incidence is rare, occurring in 0.1% to 0.5% of patients [4,5]. Several studies have shown that ATD-induced agranulocytosis (AIA) occurs more frequently in elderly patients and within the first 3 months of treatment [6-8]. In Korea, the largest AIA study included 13 patients in a single center [9], and other studies consisted only of several case reports [10-15]. Therefore, in the present study, we reviewed data from AIA patients at four tertiary hospitals in Korea and investigated their clinical characteristics.

METHODS

Patients and methods

Data from fifty-four patients (43 females and 11 males) with Graves' disease who developed AIA and were treated at Chonnam National University Hwasun Hospital, Asan Medical Center, Samsung Medical Center, and Pusan National University Hospital between 1997 and 2014 were retrospectively evaluated. Only 37% of patients (20/54) were diagnosed and treated for Graves' disease at the hospital where they were admitted. The remaining 34 patients were referred from primary physicians after being diagnosed with AIA. Agranulocytosis was defined as a granulocyte count below 500/mm^3. Patients were admitted to the hospitals due to symptoms such as fever or sore throat or agranulocytosis detected incidentally on routine laboratory follow-up tests. ATDs were stopped immediately and antibiotics and/or granulocyte-macrophage colony-stimulating factor (GM-CSF) treatment started. We defined the resolution of AIA as recovery of granulocyte counts to 500/mm^3 or more. We reviewed and compared the clinical and laboratory reports according to the type of ATD and the recovery time from AIA.

Ethics statement

This study was reviewed and approved by the Institutional Review Board of each participating hospital.

Statistical analyses

SPSS version 21 (IBM Co., Armonk, NY, USA) was used for all statistical analyses. Continuous variables are shown as median values (the smallest variable and the largest variable) and mean±standard deviation. Categorical variables are expressed as rates and proportions. The unpaired Student *t* test, Mann-Whitney *U* test (nonparametric test), chi-square test, and Fisher exact test were used for statistical analyses. A *P*<0.005 was considered to indicate statistical significance.

RESULTS

Characteristics of 54 patients with AIA

The mean age of the 54 patients was 38.2±14.9 years (range, 9 to 72). Fever and sore throat occurred in 48 patients during the median of 4 days (range, 1 to 23) before diagnosis, and the remaining six patients without any symptoms were diagnosed during a routine complete blood count (CBC) test during a checkup. The six asymptomatic patients had the CBC performed within 1 month of AIA onset, and the white blood cell (WBC) counts showed lower normal range levels (range, 2,000 to 4,100/mm^3) except in one patient (5,710/mm^3). Among the 48 patients with fever, 16 patients had the CBC test performed within 1 month, and 68.8% of them (11/16) showed mild leukocytopenia (range, 1,100 to 4,000/mm^3). In five patients who had their WBC levels measured within 5 days before AIA onset, the absolute neutrophil count (ANC) levels were less than 1,000/mm^3. AIA developed during the first course of treatment in 43 patients (79.6%), and 11 patients experienced adverse events during the treatment for relapsed Graves' disease, with a prior uneventful course of the same ATD treatment. Thirty-nine patients (72.2%) were taking methimazole (MMI) and 15 patients (27.8%) were taking prophylthiouracil (PTU). The median ATD treatment duration before AIA was 44 days (range, 4 to 3,808), and the numbers of interval days between the two drugs were similar. The onset time distribution was: within 30 (27.8%), 60 (64.8%), and 90 days (75.9%). Eight patients (14.8%) developed AIA over 3 years while taking ATD. The average doses of MMI and PTU given at the onset of AIA were 23.0±10.8 mg/day (range, 5 to 60) and 282.1±114.1 mg/day (range, 75 to 450), respectively. No patient experienced other adverse effects, including skin eruptions or pruritus. All patients stopped taking ATDs immediately and were treated with broad-spectrum antibiotics. GM-CSF was used in 44 patients for 1 to 17 days. ANC counts were elevated above 500/mm^3 between 1 and 20 days (median, 5.5) after the treatment. Of the 48 patients with available follow-up records, RAI was administered to 40 patients, thyroidectomy was performed in four patients, ATD was changed to another drug in two patients, and the remaining two patients received no additional treatment.

Table 1. Characteristic of Patients with AIA according to the ATD

Characteristic	MMI (*n*=39)	PTU (*n*=15)	*P* value
Age, yr	35.6±14.6	45.1±13.8	0.033
Male sex	6 (15.4)	5 (33.3)	0.142
ATD duration, day	48 (4–3,808)	32 (10–2,173)	0.997
Daily dose at the time of diagnosis, mg/day	23.0±10.8	282.1±114.1	
First therapy/relapsed cases	33/6	10/5	0.142
Febrile episodes	36 (92.3)	12 (80.0)	0.197
Fever duration, day	4.5 (1–23)	4 (1–21)	0.837
ANC at the time of diagnosis, /mm^3	10 (0–440)	190 (0–480)	0.001
Recovery period, day	6 (1–19)	2.5 (1–20)	0.401
GM-CSF	36 (92.3)	8 (53.3)	0.003
Duration of GM-CSF, day	4.5 (1–16)	2 (1–17)	0.489
Death	3 (7.7)	1 (6.7)	0.897

Values are expressed as mean±SD or number (%).
AIA, ATD-induced agranulocytosis; ATD, antithyroid drug; MMI, methimazole; PTU, propylthiouracil; ANC, absolute neutrophil count; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Incidences of AIA

All of the 12 enrolled patients at Samsung Medical Center were newly diagnosed with Graves's disease, and prescribed ATD at the hospital where they were admitted. During the same study period, 9,855 patients were newly diagnosed with Graves' disease, and treated with ATD. The estimated incidence of AIA was 0.12%.

Characteristics of patients according to the ATD and treatment duration

The patients treated with PTU were older than patients treated with MMI (45.1±13.8 vs. 35.6±14.6, *P*=0.033). Differences in gender, duration of treatment, and duration of fever between the two drugs were not observed. The patients taking MMI showed lower ANC levels and higher frequency of GM-CSF use than PTU users. The recovery time was similar between the two groups (Table 1). There were no differences in age, gender, type of ATD used, initial ANC levels, recovery time, and fatality according to the duration of ATD treatment (≤30 days vs. >30 days; ≤60 days vs. >60 days; and ≤3 years vs. >3 years).

Characteristics of patients according to the recovery time

The mean recovery time was 6.3±4.7 days (median, 5.5; range, 1 to 20). We divided the subjects into two groups on the basis of the median recovery time (5.5 days); a short recovery group consisting of patients who recovered within 5 days and a long recovery group of patients requiring 6 days or more to recover from AIA. The risk factors for the delayed recovery

group were not identified. No differences were observed in age, gender, type of ATD used, duration of treatment, or initial ANC levels between the two groups.

Fatal cases

Among 54 patients with AIA, four patients (one male, three female) died from sepsis on the 1st and 2nd day of hospitalization. The mean age was 41.0±19.9 years (range, 21 to 62). The patients were admitted to the hospitals with septic shock 4 to 7 days after the onset of fever. Three patients were taking MMI for 2 months, the dosages of which were 15 mg in two patients, and 30 mg in one patient before disease presentation, and one patient was started on 300 mg PTU 27 days before admission. All of the patients had bacteremia, and cultured bacteria were positive for *Pseudomonas aeruginosa, Enterobacter cloacae*, and *Streptococcus pneumonia*.

DISCUSSION

In the present study, which is to date the largest in Korea, we analyzed 54 AIA patients. AIA occurred within the first 3 months after initiation of ATDs in 76% of patients, but complications developed even after 3 years of treatment or in relapse cases treated with the same drugs in previously unaffected patients. Five patients with fever and mild neutropenia (ANC, 500 to 1,000/mm^3) developed AIA within 5 days and their ANC and febrile symptoms were recovered after ATDs were discontinued. The patients treated with MMI showed lower

ANC levels, but their recovery times from AIA did not differ.

ATDs are the common treatment modality for Graves' disease in Korea [2]. ATDs are associated with a variety of minor adverse effects including urticaria, arthralgia, and gastrointestinal upset in 1% to 5% of patients as well as life-threatening complications such as agranulocytosis and hepatitis. AIA risk factors are not well established because of its low incidence of occurrence. Recently, Nakamura et al. [7] analyzed 754 AIA patients, the largest study to date. The results showed that AIA tends to occur abruptly within 3 months after initiation of therapy, and elderly patients and females are more susceptible to AIA. In our study, 76% of patients were diagnosed with AIA within the first 90 days of treatment, similar to the observations in other published reports [7,9]. Importantly, AIA can occur even 3 years or more after the initiation of ATD therapy or in relapse patients with a previously uneventful course of the same drug therapy [4,16]. Although controversial, several studies have reported that elderly patients are susceptible to agranulocytosis [6,7], and have a higher rate of death [17]. In our study, the mean age of AIA patients and fatal cases were 38 years and 41 years, respectively. The mean onset age of Graves' disease was 44 years according the Medicare claims data provided by the Health Insurance Review and Assessment Service in Korea [1]. Therefore, it was difficult to make conclusions regarding the use of age as a risk factor of AIA. Other risk factors for AIA include the types and dose of ATDs. Several studies reported that patients with low-dose MMI therapy showed a lower risk of agranulocytosis compared with a high-dose MMI or PTU [4,6,18,19]. We could not determine an association with the dose of drugs because various dosages were initiated in patients with AIA. In our study, 72% patients of AIA were given MMI. Although, it is difficult to make conclusions on the basis of this study, it is considered that MMI is a much more common prescription than PTU; for example, from 2007 to 2011, MMI was prescribed to 54.8% with Graves' disease, whereas PTU was prescribed to 42.9% patients with Graves' disease in Korea [1]. Patients taking MMI showed more severe agranulocytosis, but the recovery time was not different than in patients taking PTU. There are no studies directly comparing PTU and MMI; thus, it is difficult to interpret the meaning of more severe agranulocytosis in patients taking MMI. Five febrile patients with mild neutropenia (ANC, 500 to 1,000/mm³) developed agranulocytosis within 5 days. During the same study period, two patients with mild neutropenia without symptoms of fever or sore throat were taking MMI for 5 and 42 months. One patient who developed AIA 5 months after the initiation of drug therapy showed recovered ANC levels 3 months later without any treatment change and another patient had persistent mild neutropenia without any symptoms and signs despite continuing MMI. Therefore, cessation of ATDs should be considered in symptomatic neutropenic patients.

Eighty percent of patients (43/54) with agranulocytosis presented with fever and sore throat due to nasopharyngeal bacterial infection. Broad-spectrum antibiotic therapy is essential with cessation of the causative drug for the treatment of agranulocytosis [16]. The usefulness of G-CSF or GM-CSF has been controversial; several reports showed their effectiveness in shortening the recovery time of agranulocytosis and reducing morbidity and mortality [20-22]. Because this study was performed retrospectively, we could not determine the effects of GM-CSF on shortening the recovery time from AIA. Agranulocytosis is an autoimmune-mediated response as demonstrated by anti-granulocyte and anti-neutrophil cytoplasmic antibodies present in immunofluorescence and cytotoxicity assays [23,24]. Therefore, steroid therapy is occasionally employed for the treatment of AIA, although the effects are questionable.

Development of sepsis increases mortality when the occurrence of AIA is not recognized and therapy is delayed, and mortality was higher in elderly patients [17]. Since AIA develops suddenly and prevention is difficult, providing adequate information to patients is important. Patients need to understand the early signs and symptoms of AIA and should visit the hospital immediately if they occur. The WBC and ANC of patients should be monitored once symptoms occur and the ATDs discontinued immediately until test results are available, especially for elderly patients. In the present study, 50% of the patients recovered 6 days after ATDs were discontinued, but the risk factors for delayed recovery could not be determined. The four fatality cases developed sepsis 4 to 7 days after fever, but the risk factors for fatality could not be determined due to the small number of patients.

In most cases, agranulocytosis occurs abruptly with very low incidence, and various guidelines exist for the treatment of Graves' disease related to regular monitoring of WBC counts [5,25-27]. Nakamura et al. [7] reported that the time interval between the last day with normal WBC levels and onset of agranulocytosis was 33 days in most patients, although some patients showed a gradual decline in granulocyte count; therefore, routine WBC measurement is not recommended. However, Tajiri et al. [3] suggested that asymptomatic patients can be detected through routine CBC monitoring and rescued by discontinuing ATD therapy, and regular monitoring of WBC every

2 weeks for the first 2 months of therapy was recommended in Japan. In our study, six patients without any symptoms were diagnosed with agranulocytosis using routine WBC tests, and WBC levels were low compared with the normal range at 1 month prior to the onset of agranulocytosis. Therefore, although routine monitoring of WBC counts has not been considered cost-effective in all patients, but monitoring WBC for 3 months after the initiation of ATDs can be helpful for predicting and detecting agranulocytosis in asymptomatic patients. If low or declining WBC levels are observed in patients receiving ATD therapy, WBC counts should be monitored to prevent the development of more severe agranulocytosis.

There were several limitations to this study. First, we were unable to show the cumulative incidence of AIA according to duration of taking ATD. We could only estimate the incidence at one center (Samsung Medical Center), which was 0.12%. This incidence is in agreement with other published reports [4,5]. Another limitation of the study is that we did not determine changes in WBC before AIA development, which is a limitation of retrospective studies. In total, 67% patients (16/24) showed mild leukocytopenia within 1 month before AIA onset. Infrequently, patients showed a tendency to have declining leukocyte counts before the onset of AIA. Therefore, CBC monitoring in the early treatment phase could be beneficial. Third, we could not determine the cause of the difference in ANC levels between patients taking MMI and PTU. A study with a larger number of patients is necessary to determine the cause of the difference.

In conclusion, agranulocytosis tends to occur within 3 months after starting ATDs, with the majority of patients experience fever and sore throat. In clinical practice, physicians should be aware of AIA and inform patients of the side effects of ATDs, and consider routine CBC monitoring during the early treatment period. Patients with fever and mild neutropenia were regarded as having agranulocytosis and had to discontinue taking ATDs and undergo close follow-up.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

REFERENCES

1. Seo GH, Kim SW, Chung JH. Incidence & prevalence of hyperthyroidism and preference for therapeutic modalities in Korea. J Korean Thyroid Assoc 2013;6:56-63.
2. Yi KH, Moon JH, Kim IJ, Bom HS, Lee J, Chung WY, et al. The diagnosis and management of hyperthyroidism consensus: report of the Korean Thyroid Association. J Korean Thyroid Assoc 2013;6:1-11.
3. Tajiri J, Noguchi S. Antithyroid drug-induced agranulocytosis: special reference to normal white blood cell count agranulocytosis. Thyroid 2004;14:459-62.
4. Cooper DS. Antithyroid drugs. N Engl J Med 2005;352:905-17.
5. Brent GA. Clinical practice. Graves' disease. N Engl J Med 2008;358:2594-605.
6. Cooper DS, Goldminz D, Levin AA, Ladenson PW, Daniels GH, Molitch ME, et al. Agranulocytosis associated with antithyroid drugs. Effects of patient age and drug dose. Ann Intern Med 1983;98:26-9.
7. Nakamura H, Miyauchi A, Miyawaki N, Imagawa J. Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. J Clin Endocrinol Metab 2013;98:4776-83.
8. Tajiri J, Noguchi S, Murakami T, Murakami N. Antithyroid drug-induced agranulocytosis. The usefulness of routine white blood cell count monitoring. Arch Intern Med 1990; 150:621-4.
9. Song YS, Kang SM, Ahn CW, Cha BS, Chang HS, Chung WY, et al. A case of PTU (propylthiouracil)-induced agranulocytosis in Graves' disease: additional cases of antithyroid drug-induced agranulocytosis in Yonsei University Hospital last 10 years. Korean J Med 2001;60:398-403.
10. Lee SJ, Chung ES, Kim YC, Bae YK, Chang HS, Jung JW, et al. A case of necrotizing colitis and perforation in agranulocytosis secondary to methimazole therapy. Korean J Intern Med 1980;23:161-6.
11. Oh MH, Lee JK, Kim HS, Kim HM. A case of agranulocytosis and Stevens-Johnson syndrome after propylthiouracil therapy in Graves' disease. Korean J Intern Med 1990;39:700-4.
12. You KH, Son SS, Song SY, Park MS, Lee YG, Cho CG. The effect of granulocyte colony stimulating facto(G-CSF) in a patient with propylthiouracil-induced agranulocytosis. J Korean Soc Endocrinol 1993;8:347-50.
13. Lee KW, Chung YS, Kim HM, Choi SY, Song MK, Kim HS, et al. A case of methimazole induced agranulocytosis treated with granulocyte colony stimulating factor (G-CSF).

J Korean Soc Endocrinol 1997;12:68-74.

14. Park SY, Chun SW, Kim YJ, Kim SJ. A case of agranulocytosis and soft tissue abscess after increasing methimazole dose in a patient with Graves disease under long-term maintenance therapy. J Korean Thyroid Assoc 2011;4:54-7.

15. Jeong GH, Kim SK, Myung DS, Chung JO, Cho DH, Chung DJ, et al. Agranulocytosis due to secondary exposure to antithyroid drugs in a relapsed Graves' disease patient. Korean J Med 2008;75:362-6.

16. Weetman AP. Graves' disease. N Engl J Med 2000;343:1236-48.

17. Pearce SH. Spontaneous reporting of adverse reactions to carbimazole and propylthiouracil in the UK. Clin Endocrinol (Oxf) 2004;61:589-94.

18. Takata K, Kubota S, Fukata S, Kudo T, Nishihara E, Ito M, et al. 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 2009;19:559-63.

19. Wiberg JJ, Nuttall FQ. Methimazole toxicity from high doses. Ann Intern Med 1972;77:414-6.

20. Balkin MS, Buchholtz M, Ortiz J, Green AJ. Propylthiouracil (PTU)-induced agranulocytosis treated with recombinant human granulocyte colony-stimulating factor (G-CSF). Thyroid 1993;3:305-9.

21. Fukata S, Kuma K, Sugawara M. Granulocyte colony-stimulating factor (G-CSF) does not improve recovery from antithyroid drug-induced agranulocytosis: a prospective study.

Thyroid 1999;9:29-31.

22. Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. Ann Intern Med 2007;146:657-65.

23. Toth EL, Mant MJ, Shivji S, Ginsberg J. Propylthiouracil-induced agranulocytosis: an unusual presentation and a possible mechanism. Am J Med 1988;85:725-7.

24. Fibbe WE, Claas FH, Van der Star-Dijkstra W, Schaafsma MR, Meyboom RH, Falkenburg JH. Agranulocytosis induced by propylthiouracil: evidence of a drug dependent antibody reacting with granulocytes, monocytes and haematopoietic progenitor cells. Br J Haematol 1986;64:363-73.

25. Franklyn JA, Boelaert K. Thyrotoxicosis. Lancet 2012;379:1155-66.

26. Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 2011;21:593-646.

27. Vanderpump MP, Ahlquist JA, Franklyn JA, Clayton RN. Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. The Research Unit of the Royal College of Physicians of London, the Endocrinology and Diabetes Committee of the Royal College of Physicians of London, and the Society for Endocrinology. BMJ 1996;313:539-44.