Analysis of 754 Cases of Antithyroid Drug-Induced Agranulocytosis Over 30 Years in Japan

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Background: Agranulocytosis is a rare but serious complication of antithyroid drug (ATD) therapy. Characteristics of agranulocytosis have been reported in only a small number of patients.

Method: We studied 754 cases of ATD-induced agranulocytosis reported over 30 years. The age distribution and sex ratio were compared with those in 12 503 untreated Graves' patients at Kuma Hospital. The annual number of new Graves' patients in Japan was estimated from the Japan Medical Data Center Data Mart-Pharmacovigilance health insurance receipt database.

Results: Agranulocytosis developed within 90 days after starting ATD therapy in most patients (84.5%). The methimazole dose given at onset was 25.2 ± 12.8 mg/d (mean ± SD). The mean age was 43.4 ± 15.2 years, and the male to female ratio was 1:6.3. When compared with patients at Kuma Hospital, patients with agranulocytosis were older ($P < .001$) and more females ($P < .0001$). Of 211 patients with more than 1 granulocyte measurement before onset, 131 (62%) showed normal counts (>1000/μL) within 2 weeks before onset, demonstrating real sudden onset of agranulocytosis. In contrast, some of the 20 patients with more than 4 measurements showed gradual decreases in granulocyte counts. Analysis of physician reports for 30 fatal cases revealed that some deaths might have been prevented. The number of new Graves' patients treated with ATD was estimated at about 35 000 per year, and the incidence rate of agranulocytosis was 0.1% to 0.15% in Japan.

Conclusion: This is the largest study of agranulocytosis. Agranulocytosis tends to occur abruptly within 3 months after initiation of ATD therapy, although it develops gradually in some patients. Providing every patient with sufficient information on agranulocytosis is critical. (***J Clin Endocrinol Metab* 98: 4776–4783, 2013**)

Antithyroid drug (ATD) therapy is associated with a variety of adverse reactions. Urticaria (or skin rash), low-grade liver dysfunction, and arthralgia are common minor side effects, whereas agranulocytosis, myeloperoxidase antineutrophil cytoplasmic antibody-related vasculitis, and severe hepatotoxicity are rare but serious complications (1). Among them, agranulocytosis, defined as a granulocyte count below 500/μL, is the most serious life-threatening event. It can occur abruptly, and prediction and prevention are very difficult. Agranulocytosis is a rare event, occurring in 0.1% to 0.5% of Graves' patients receiving ATD therapy (2–4). Because of the low incidence and abruptness of agranulocytosis, controversy exists over the value of regularly monitoring white blood cell (WBC) counts in Graves' patients receiving ATD therapy. From the standpoint of cost-effectiveness and usefulness, the American Thyroid Association guidelines and some review articles recommend against regular monitoring (3–5). On the other hand, the methimazole (MMI) package insert in Japan includes a strong warning to check blood counts every 2 weeks for the first 2 months of therapy, and Tajiri et al (6) reported that they successfully identified

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Abbreviations: ATD, antithyroid drug; JDM-PV, Japan Medical Data Center Data Mart-Pharmacovigilance; MMI, methimazole; PTU, propylthiouracil; WBC, white blood cell.

78% of granulocytopenia cases before onset of symptoms by periodically checking blood counts.

Although agranulocytosis is generally believed to occur suddenly, more commonly in elderly patients, and in the early treatment period after starting ATD therapy, no studies have demonstrated the characteristics of agranulocytosis in a large number of patients because of its low incidence. Under the Pharmaceutical Affairs Law of Japan, physicians should report adverse drug reactions to pharmaceutical companies. In response, the companies should collect detailed information from the medical institutions, including age, sex, time to onset of adverse reaction, type and severity of adverse reaction, dose at onset, test results, treatment details, and outcome. We studied 754 reports of ATD-induced agranulocytosis.

Materials and Methods

Analysis of the reports of patients with agranulocytosis

A total of 754 patients with Graves' disease who developed ATD-induced hematologic complications were reported to Chugai Pharmaceutical Co, Ltd. from January 1981 to April 2011. Among them, 725 patients were treated with MMI, 28 patients with propylthiouracil (PTU), and 1 patient with both MMI and PTU. Agranulocytosis was diagnosed in 670 patients (88.9%), whereas 84 patients (11.1%) were reported with pancytopenia or aplastic anemia. Agranulocytosis was defined as a granulocyte count below 500/μL, but the basis for pancytopenia or aplastic anemia diagnoses was not clear in the reports. When any degree of thrombocytopenia or anemia was present together with agranulocytosis, diagnoses of pancytopenia or aplastic anemia were made completely on the basis of the physicians' judgment. Because the distinction between diagnoses is not necessarily clear, we have used agranulocytosis as a diagnostic term including other hematologic complications. We analyzed age, sex, and other medical information from physician reports. Reported cases included 30 fatal cases. Six patients with insufficient data were excluded from detailed analysis. We then extracted 211 patients who had more than 1 measurement of WBC and granulocyte counts in the 90 days before the onset of agranulocytosis. The number of days between the last examination and onset of the event was studied.

Patients with Graves' disease at Kuma Hospital

The age distribution and sex ratio of patients reported with agranulocytosis were compared with those of 12 503 patients with untreated Graves' disease (9864 females, 2639 males; mean age, 40.4 ± 15.2 years) who visited Kuma Hospital from 2005 to 2012 (Kuma patients). Most of the patients who visited Kuma Hospital were treated with MMI.

Estimation of the number of new patients with Graves' disease in Japan

The annual number of new patients with Graves' disease under MMI treatment in Japan was calculated using the Japan Medical Data Center Data Mart-Pharmacovigilance (JDM-PV) health insurance receipt database (approximately 980 000 insurance subscribers; October 2009 to March 2011; age 0–74 years) from Japan Medical Data Center Co, Ltd. New Graves' disease patients in the database were defined as cases in health insurance receipt data from April 2010 to March 2011 that met the following three conditions: 1) diagnosis of thyrotoxicosis with diffuse goiter (E-050) per the International Classification of Diseases, 10th revision; 2) prescription of MMI or PTU in the same month as diagnosis; and 3) no diagnosis of this disease or prescription of these drugs in the 12 months preceding the first diagnosis and prescription during the period studied. The number of patients obtained was divided by the database population (insurance subscribers) to calculate the estimated ratio of new Graves' patients in the database population. The number of patients with Graves' disease who started ATD treatment per year in Japan was estimated by extrapolating the ratio in the database to the entire Japanese population based on the October 2010 census (database patients). We excluded patients older than 65 years, because the number of insurance subscribers older than 65 was small enough to cause a large error in the estimated number of Graves' patients in this age group.

Statistical analysis

The age distribution of patients with agranulocytosis was compared with that of Kuma patients using Student's unpaired *t* test. The sex ratio between patients with agranulocytosis and Kuma patients was analyzed using the χ^2 test. Calculations were performed using JMP version 6.0 (SAS Institute Inc). Statistical significance was defined as $P < .05$.

Results

Analysis of physician reports of 754 patients with ATD-induced agranulocytosis

We studied 754 cases of ATD-induced agranulocytosis reported to Chugai Pharmaceutical until April 2011. The number of reports increased every year until 2003, probably due to a rise in physician awareness of drug complications. An average of 43 patients per year was reported during the most recent 8 years (see Supplemental Figure 1, published on The Endocrine Society's Journals Online website at http://jcem.endojournals.org). Patients overall comprised 619 females and 98 males (sex was not specified for 37 patients). Most patients (96.2%) were given MMI, reflecting that MMI is much more common than PTU as an ATD treatment in Japan. The average dose of MMI given at onset of agranulocytosis was 25.2 ± 12.8 mg/d (mean ± SD) in 514 patients (MMI dose was uncertain in 211 patients). PTU was used for only 29 patients, and the mean dose at onset was 216.7 ± 116 mg/d in 15 patients (information was not given in 14 patients). Patient age ranged from 7 to 81 years, and the mean age was 43.4 ± 15.2 years (mean ± SD; exact age not given in 51 cases). Patients in their 40s and 50s were the most common, accounting for nearly 45% of all patients (Figure 1). The

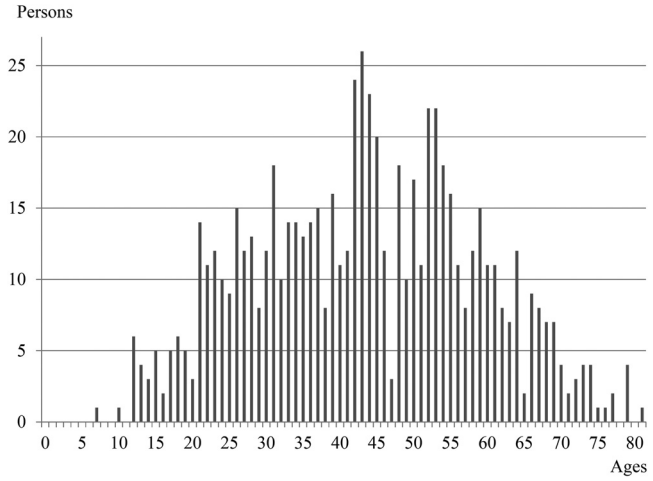

Figure 1. The age distribution of patients with agranulocytosis. The mean age was 43.4 ± 15.2 years (mean ± SD) in 703 patients (exact age not given in 51 cases).

female to male ratio was 6.3:1. We compared the age distribution and sex ratio with those of 12 503 untreated Graves' patients who visited Kuma Hospital from 2005 until 2012, where the mean age was 40.4 ± 15.2 years and the female to male ratio was 3.7:1. Patients with agranulocytosis were older ($P < .001$) than patients at Kuma Hospital, and there were more females ($P < .0001$). Days to onset of agranulocytosis after initiation of ATD therapy is shown in Figure 2 (n = 461; excluding patients with an unclear date of onset or start date for ATD therapy). Agranulocytosis developed in more than 71.6% of patients within 60 days and in 84.6% within 90 days. However, it is notable that 55 patients developed agranulocytosis after 4 months. Several patients were reported to have developed agranulocytosis more than 2 years after starting ATD treatment, but most of them had been re-exposed after a discontinuation period. However, information was insufficient in some cases.

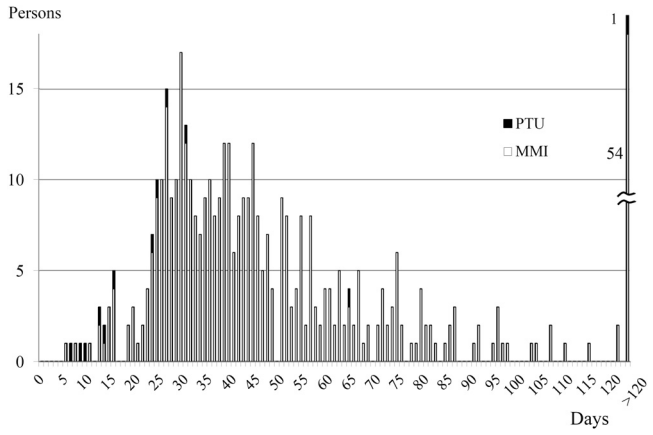

Figure 2. Time to onset of agranulocytosis after initiation of ATD therapy in 458 patients. Patients were excluded if the date of agranulocytosis onset or date of initiation of ATD therapy were unclear. Agranulocytosis occurred in 26.5%, 71.6%, and 84.6% within 30, 60, and 90 days, respectively. After 4 months, 54 patients developed agranulocytosis, and most patients who developed agranulocytosis 2 years after initiation of ATD therapy had periods of treatment discontinuation.

Calculation of the number of new patients with Graves' disease per year in Japan

Because there have been no reliable reports on the number of new patients with Graves' disease each year who start ATD treatment in Japan, we tried to estimate this number using the JDM-PV health insurance receipt database. We excluded patients older than 65 years from calculation to avoid a large error due to this age group as described in Materials and Methods. About 33 500 new patients developed Graves' disease and received ATD treatment in the 1-year period from April 2010 to March 2011 (see Supplemental Table 1). Patients in their 30s were the most common, followed by patients in their 40s. The female to male ratio was 2.8:1, which is similar to that at Kuma Hospital. If we consider that among approximately 35 000 new Graves' patients treated with ATD, 40 to 50 patients developed agranulocytosis each year (43 patients per year during the most recent 8 years), the incidence is estimated to be around 0.1% to 0.15%.

Analysis of fatal agranulocytosis in patients with Graves' disease

Among 754 patients with ATD-induced agranulocytosis, 30 patients died (Figure 3). We studied physician reports of these cases, excluding 5 cases with insufficient data for analysis. One patient was excluded because the cause of death might not have been agranulocytosis. Among the remaining 24 patients, agranulocytosis was reported in 17 patients and pancytopenia in 7 patients

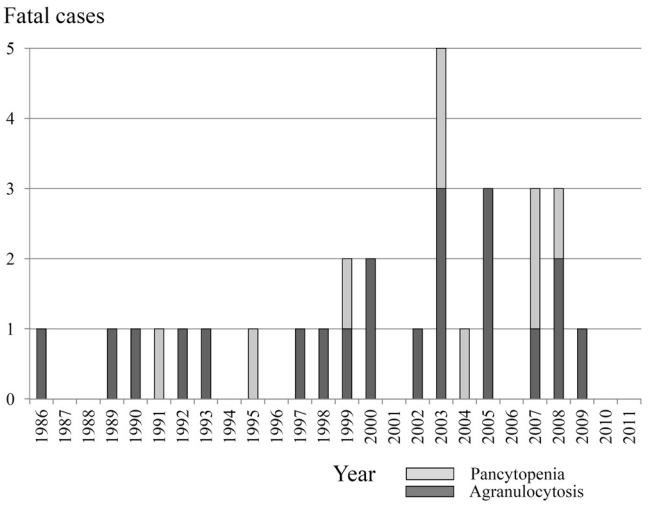

Figure 3. Fatal cases due to agranulocytosis or pancytopenia reported since 1986 in Japan. Twenty-one cases were reported as agranulocytosis and 9 cases as pancytopenia/aplastic anemia. Data were poor and could not be further analyzed in 5 cases. It was uncertain whether death was caused by agranulocytosis in 1 patient.

(Table 1). There were 19 females and 5 males, and the mean age was 49 ± 16 years. One female patient started MMI 30 mg, changed to PTU 300 mg 6 weeks later in response to urticaria, and developed pancytopenia 26 days afterward. The other 23 patients were treated with MMI, and the mean dose of MMI at onset of agranulocytosis was 24 mg/d (5–45 mg).

Analysis of the period from initiation of ATD therapy to onset of agranulocytosis showed that agranulocytosis developed within 2.5 months in most patients but after 5

Table 1. Analysis of Fatal Cases

Sex	Age, y	Diagnosis	ATD Dose, mg/d	Symptoms	Days A	Days B	Days C
M	39	Agranulocytosis	20	Fever, pharyngitis, unconsciousness	54	1	11
F	58	Agranulocytosis	30	Fever, dyspnea	11	5	2
M	35	Agranulocytosis	30	Fever, pharyngitis	24	1	6
F	31	Agranulocytosis	10	Fever, pharyngitis	447	3	5
M	41	Agranulocytosis	30	Fever, unconsciousness	23	0	1
F	24	Agranulocytosis	30	Pharyngitis, dyspnea	150	3	11
F	54	Agranulocytosis	30	Fever, pharyngitis	36	4	4
F	50	Agranulocytosis	15	Fever, dyspnea	32	1	15
M	30	Agranulocytosis	40	Fever, septic shock	42	2	3
F	50	Agranulocytosis	30	Fever	38	0	10
F	36	Agranulocytosis	20	Fever, pharyngitis	40	3	7
F	69	Agranulocytosis	25	Fever, pharyngitis	43	2	19
F	21	Agranulocytosis	15	Fever, pharyngitis	56	1	23
F	73	Agranulocytosis	30	Fever, pharyngitis	36	3	16
F	73	Agranulocytosis	5	Fever, pharyngitis	61	3	11
F	37	Agranulocytosis	20	?[b]	67	?[b]	2
F	58	Agranulocytosis	30	Fever, unconsciousness	49	1	4
F	66	Pancytopenia	15	Bleeding	42	3	52
M	62	Pancytopenia	45	Bleeding	43	0	9
F	46	Pancytopenia	30	Pharyngitis, vomiting	39	2	1
F	43	Pancytopenia	20	Bleeding	96	2	?[c]
F	65	Pancytopenia	20	Fever, pharyngitis	37	2	14
F	66	Pancytopenia	20	Fever	36	1	8
F	53	Pancytopenia	300[d]	Fever, pharyngitis	26	Several	61

Abbreviations: F, female; M, male.

[a] Mean age was 49 ± 16 years, and mean MMI dose was 24 mg/d. Days A represents days between initiation of ATD treatment and onset of agranulocytosis or pancytopenia. Days B represents days between onset of symptoms and diagnosis. Days C represents days between diagnosis of agranulocytosis or pancytopenia and death.

[b] Because this patient had tetanus, symptoms due to agranulocytosis were not clear.

[c] This patient was transferred to another hospital, and the date of death was not clear.

[d] PTU 300 mg/d.

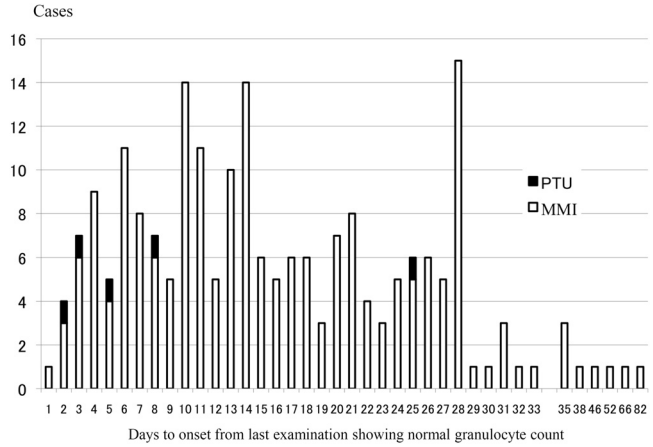

Figure 4. Duration between last examination confirming granulocyte count >1000/μL and onset of agranulocytosis in 211 patients with more than 1 measurement in the 90 days before onset. Normal granulocyte counts were confirmed in 45 (21.3%) and 111 (52.6%) patients within 1 and 2 weeks before onset, respectively.

months in one patient and after 15 months in another patient. From a therapeutic point of view, early diagnosis of agranulocytosis and initiation of therapy are critical. Of 23 patients (excluding 1 for whom agranulocytosis symptoms were unclear), 9 were diagnosed with agranulocytosis or pancytopenia on the day of or after onset of symptoms, but diagnosis in other patients took 3 days (6 patients), 4 days (1 patient), or even 5 days (2 patients) from the onset of symptoms (Table 1). The main reason for delayed diagnosis may be insufficient knowledge of agranulocytosis among patients. Four patients did not visit a medical institution despite symptoms, 2 patients mistook the symptoms for a common cold, and 2 other patients did not consider their symptoms to be serious. Five patients did visit a clinic for high fever and pharyngitis, but their doctors did not examine WBC or granulocyte counts, having presumably been given no information about the patients' ATD therapy.

After admission, every patient received intensive therapy, but 5 of 23 patients (excluding 1 who died in a different hospital and had an unspecified date of death) died within 3 days (Table 1). Based on physician reports, therapeutic procedures could have been improved by stopping MMI immediately when agranulocytosis was suspected and administering granulocyte colony stimulating factor as soon as possible. However, 10 patients would have been very difficult to save because their conditions deteriorated very rapidly without responding to prompt intensive care.

Analysis of 211 patients with more than 1 granulocyte measurement in the 90 days before onset of agranulocytosis

Some patients developed agranulocytosis suddenly and deteriorated very rapidly. Among 754 patients, we found that 211 had more than 1 granulocyte measurement, usually at a regular hospital visit, in the 90 days before onset. Figure 4 shows days to onset of agranulocytosis from last examination a patient had showing normal granulocyte count (>1000/μL). For example, 1 day means that a patient had a normal granulocyte measurement on the previous day before the onset. The interval was from 1 to 82 days, being continuous up to 33 days. To our surprise, granulocyte counts greater than 1000/μL were confirmed in 1 week before onset in 21.3% of patients (45 of 211 patients). In the 2 weeks before onset, 52.6% of patients (111 of 211 patients) had normal granulocyte counts. Although the data are dependent on the interval between blood examinations in each patient and do not represent the real time interval for development of agranulocytosis, this demonstrates how agranulocytosis developed abruptly.

On the other hand, agranulocytosis seemed to develop more slowly in some patients with a gradual decline in granulocyte count. There were 20 patients with more than 4 granulocyte measurements, including the pre-ATD measurement, in the 30 days before onset. Granulocyte count tended to decrease gradually until onset of agranulocytosis in 11 patients (Figure 5A), although all of the counts were in the normal range, whereas it did not decline steadily in 9 of these patients (Figure 5B).

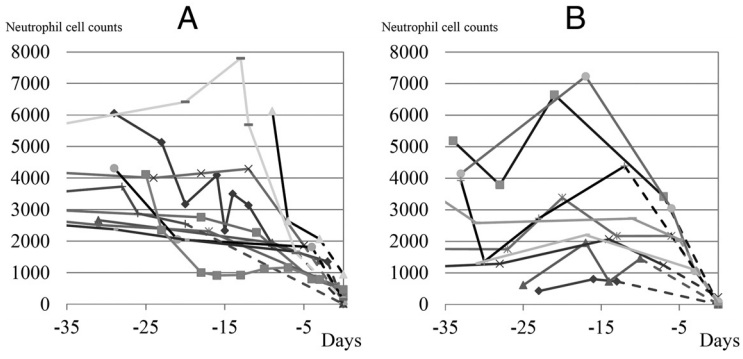

Figure 5. Change in granulocyte count in 20 patients with more than 4 granulocyte measurements, including the pre-ATD measurement, from the 30 days before onset. Granulocyte counts in 11 patients tended to decline before development of agranulocytosis (A), whereas it did not show a steady decline in 9 patients (B).

Discussion

In this study, we analyzed physician reports of 754 cases of ATD-induced agranulocytosis in Japan and obtained several important findings. First, we confirmed that agranulocytosis most commonly occurs within a few months after initiation

of ATD treatment. More than 70% of patients developed agranulocytosis within 60 days and nearly 85% within 90 days. The risk of developing agranulocytosis in the early treatment stage has been reported in studies with a relatively small number of patients (6–9), and this was also demonstrated in this study using a larger sample of 754 cases. In this study, 55 patients developed agranulocytosis 4 months after starting treatment (Figure 2). Therefore, although continual vigilance for agranulocytosis is necessary, particular caution is needed in the first 3 months. Vigilance is also necessary during re-exposure to ATD after a period of discontinuation.

Second, we directly demonstrated that agranulocytosis develops suddenly by extracting 211 patients who had more than 1 measurement of granulocyte count before onset. One patient showed a normal granulocyte count just 1 day before onset. The time interval between the last examination day with normal granulocyte counts and onset of agranulocytosis was continuous to 33 days (Figure 4). Although the data do not represent the real time interval for agranulocytosis development, to our knowledge, this is the first demonstration of abruptness of onset in a large sample. Periodic measuring of WBC count is not recommended by many doctors because it is of little value in predicting agranulocytosis (3–5), but in Japan, periodic monitoring of Graves' patients at 2-week intervals in the first 2 months is recommended. Our findings give strong warning against overdependence on blood tests every 2 weeks. In fact, more than half of the patients with agranulocytosis exhibited normal granulocyte counts in the 2 weeks before onset.

Third, despite the sudden onset of agranulocytosis in many cases, some patients showed a gradual decline in granulocyte count. Among 20 patients with more than 4 granulocyte measurements including the pretreatment measurement, granulocyte counts tended to decrease gradually in 11 patients, but all of the counts were above 1000/μL (Figure 5). Agranulocytosis develops more slowly in these patients, so careful monitoring of blood tests may help predict its onset. Tajiri et al (6) reported that only 12 in 55 patients with ATD-induced agranulocytosis manifested signs and symptoms of infection at the time of diagnosis, whereas the other 43 patients were asymptomatic and diagnosed by routine monitoring of WBC counts. We studied cases of agranulocytosis and granulocytopenia over the past 5 years at Kuma Hospital, where about 1500 new Graves' patients start ATD treatment annually, and found that nearly half of the patients were diagnosed with asymptomatic conditions by routine monitoring of granulocyte counts, supporting Tajiri's observation (manuscript in preparation).

The mechanism of agranulocytosis is uncertain, but 2 types of pathogenesis are possible: an immune-mediated process and direct intoxication. In terms of an immune process, Guffy et al (10) reported the existence of complement-dependent IgM antibodies against granulocytes in the serum of a patient who was receiving PTU and suddenly developed agranulocytosis. Antibody-mediated cytotoxicity was evident only against granulocytes taken from 2 of the 8 donors, suggesting that only a subset of patients receiving ATD may be susceptible to agranulocytosis. Fibbe et al (11) demonstrated the presence of circulating antibodies to differentiated granulocytes, monocytes, and myeloid and erythroid progenitor cells. Similar findings regarding an immunogenic process were also reported by Bilezikian et al (12) and Wall et al (13). These immunogenic abnormalities that underlie drug sensitivity may be genetic, and some patients may be susceptible as Guffy et al (10) suggested. In general, the immune-mediated destruction of circulating neutrophils proceeds rapidly. On the other hand, destruction of granulocytes by direct or indirect drug intoxication takes a few weeks. Our study supports the presence of 2 types of pathogenesis in ATD-induced agranulocytosis.

Fourth, analysis of fatal cases showed the importance of providing every patient with adequate information about agranulocytosis. A considerable number of patients may have not known that agranulocytosis is a serious, life-threatening complication that can be induced by ATD. Some patients did not visit clinics immediately after onset of the initial symptoms of agranulocytosis, and others did visit a physician but may have not mentioned ATD. These physicians did not consider the possibility of agranulocytosis and prescribed only cold medicine. Because agranulocytosis develops suddenly and prevention is difficult, it is critical that patients understand the early signs and symptoms of agranulocytosis, such as sore throat and high fever. If agranulocytosis is suspected, the patient should immediately discontinue ATD until test results are available. It cannot be overemphasized that physicians prescribing ATD should give patients adequate information about agranulocytosis, its possible symptoms, and how to deal with suspected cases.

We confirmed that elderly patients are susceptible to agranulocytosis, as reported previously (6, 7). Patients with agranulocytosis were significantly older than the 12 503 untreated Graves' patients at Kuma Hospital. Although the exact mean age of patients in the database was unknown because patients over 65 years old were excluded, most patients were in their 30s, whereas agranulocytosis was most common among those in their 40s and 50s. Our study also confirmed that agranulocytosis is more likely to occur in females than in males, as Tajiri et

al (6) reported. To assess the risk factors for patients who develop agranulocytosis vs those who do not, a very large comparison group would be necessary, considering that the incidence of agranulocytosis is very low. We should be aware that even the 12 503 patients at Kuma Hospital may not be enough for comparison.

The MMI dose at onset of agranulocytosis was 25.2 ± 12.8 mg/d (mean ± SD) in 514 patients, which was not different from the dose in patients who died (24 mg/d). Previously, we undertook the prospective randomized clinical study on initial treatments for thyrotoxic Graves' disease and found that MMI 15 mg/d is suitable for most patients (14). MMI 15 mg/d has also been reported to be safer than MMI 30 mg/d in terms of agranulocytosis development (15). Based on these studies, the guidelines for the treatment of Graves' disease issued by the Japan Thyroid Association recommend MMI 15 mg/d as an initial treatment (16). Hopefully, the number of agranulocytosis patients will be on the decline as use of smaller amounts of MMI becomes more common in Japan.

Finally, it is interesting to estimate the incidence of agranulocytosis in Japan. When the number of patients newly prescribed ATD in the JDM-PV database was extrapolated to the entire Japanese population, it was estimated that approximately 35 000 patients were treated. The number of agranulocytosis reports reached around 40 to 50 cases per year after 2003. Assuming that about 40 to 50 cases of agranulocytosis occur in 35 000 Graves' patients newly treated with ATD, the incidence of agranulocytosis in Japan is around 0.1% to 0.15%. The number of agranulocytosis reports from medical institutions is, however, considered to be lower than the actual incidence. In their systematic literature search, Hazell and Shakir (17) reviewed 37 studies from 12 countries to determine the extent to which adverse drug reactions are underreported to spontaneous reporting systems. The median underreporting rate across the 37 studies was 94%; that is, only 6% of events were reported. The extent to which agranulocytosis is underreported in Japan is unknown, but it can be assumed that cases of agranulocytosis without severe or fatal outcomes may not be reported. Yamada et al (18) studied factors associated with spontaneous reporting of adverse drug reactions in Japan and found that the launch lag of a drug was negatively associated with the reporting number of its adverse reactions. Both MMI and PTU have been used for more than 50 years, and their adverse reactions may have a tendency to not be reported compared with new drugs.

Comparison of the incidence of agranulocytosis between MMI and PTU is not possible in this study, because there are no data showing the number of untreated Graves' patients who started therapy with MMI or PTU from January 1981 to April 2011. However, in the study of Tajiri et al (6) in Japan with 15 398 patients, no difference was found in the incidence of agranulocytosis between the two drugs.

Limitations of this study are that data are completely dependent on physician reports, and necessary data are missing in a considerable number of reports. The distinction between agranulocytosis and pancytopenia was not necessarily rigorous, and in some cases, it was unclear whether symptoms or even death were due to agranulocytosis. Despite these limitations, we believe that this study, the largest to date in patients with agranulocytosis, provides important and thought-provoking information.

Acknowledgments

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