The Relation of Initial Methimazole Dose to the Incidence of Methimazole-induced Agranulocytosis in Patients with Graves’ Disease

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Abstract. The relation between the incidence of methimazole (methylmercaptoimidazole; MMI)-induced agranulocytosis and initial MMI dose was evaluated in a group of 514 patients with Graves’ disease who were treated between 1995 and 2005. One hundred and forty-six (28.40%) patients had received an initial dose of 30 mg MMI and 277 (53.89%) patients had been treated with 15 mg MMI. Nine patients (1.75%) developed agranulocytosis due to MMI treatment. Six (4.11%) of 146 patients who received an initial dose of 30 mg MMI, two (4.54%) of 44 patients given an initial dose of 20 mg MMI, and one (0.36%) of 277 patients given an initial dose of 15 mg MMI developed agranulocytosis. There was a statistically significant difference in agranulocytosis incidence between patients receiving an initial dose of 30 mg MMI and those who received an initial dose of 15 mg. Although 8 (4.10%) of 195 patients in the high-dose group (20 mg or higher) developed agranulocytosis, only 1 (0.31%) of 319 patients in the low-dose group (15 mg or lower) did. In conclusion, the incidence of agranulocytosis with low-dose MMI therapy was ten times lower than that of the high-dose regimen.

Key words: Antithyroid-drug, ATD, Agranulocytosis, Graves’ disease, MMI, Methimazole, Methylmercaptoimidazole

AGRANULOCYTOSIS is a potentially fatal side effect of the antithyroid drugs (ATD) that are widely used for the treatment of Graves’ disease. Shirooze et al. [1] and Okamura et al. [2] reported that the effectiveness of low-dose methimazole (methylmercaptoimidazole; MMI) for the treatment of hyperthyroidism was no less than that of 30 mg MMI. In addition, a European prospective randomized study [3] reported that 10 mg and 40 mg MMI regimens were equally effective. Before 1994, when the standard initial dose of MMI was 30 mg, MMI-induced agranulocytosis was a not uncommon, extremely serious, adverse effect.

After implementing a low-dose MMI regimen, patients given an initial dose of 15 mg MMI only rarely developed agranulocytosis. We examined records of patients with Graves’ disease to determine the incidence of MMI-induced agranulocytosis and to identify any association with dose.

Patients and Methods

We analyzed the incidence of MMI-induced agranulocytosis by reviewing the records of patients with Graves’ disease treated at the thyroid clinics of Toho University Oomori Hospital from 1995 to 2005. A diagnosis of Graves’ disease was based on clinical findings, laboratory tests, and the Japan Thyroid Association’s guidelines for the diagnosis of Graves’ disease [4]. Patients who were referred to our clinic after surgery or 131I therapy, some of whom had agranulocytosis,
were excluded from the study. Agranulocytosis was defined as a circulating neutrophil count lower than 500/µL.

Statistical analysis

Analysis of population proportions was performed using Fisher’s exact test. Statistical significance was defined as P<0.05.

Results

A total of 772 patients were diagnosed as having Graves’ disease between 1995 and 2005. Of these, 514 patients with hyperthyroidism were treated with MMI. One hundred and forty-six patients (28.40%) had received an initial dose of 30 mg MMI, and 277 patients (53.89%) had received 15 mg MMI. Nine (1.75%) of these 514 patients developed agranulocytosis due to MMI. Six (4.11%) of the 146 patients who received an initial dose of 30 mg MMI developed agranulocytosis, as did 2 (4.54%) of 44 patients at 20 mg MMI and 1 (0.36%) of 277 at 15 mg MMI. All patients with agranulocytosis had clinical signs and symptoms of infection. Table 1 shows the total number of patients and the number of patients who developed agranulocytosis at each initial dose point. The clinical data of the 9 patients who developed agranulocytosis due to MMI, including the initial dose of MMI, the duration of MMI therapy, leukocyte count (WBC), neutrophil count, and patient outcome, are summarized in Table 2. Of particular importance is that 5 of the 9 patients who developed agranulocytosis had voluntarily interrupted medical treatment (indicated by * in Table 2). There was a statistically significant difference in agranulocytosis incidence between patients receiving 30 mg MMI and those receiving 15 mg MMI. If we define an initial dose of 20 mg or higher as the high-dose group and an initial dose of 15 mg or lower as the low-dose group, 8 (4.10%) of the 195 patients in the high-dose group developed agranulocytosis and only 1 (0.31%) of the 319 patients in the low-dose group developed agranulocytosis. The difference between the high-dose and low-dose groups was statistically significant.

Discussion

Although the incidence of agranulocytosis with low-dose MMI was one-tenth that of the high-dose regimen,
the clinical effectiveness of the regimens was similar
[1–3, 5], suggesting that there is no longer a convincing
erationale for continuing high-dose MMI. Despite con-
vincing evidence for the effectiveness of low-dose
MMI, many patients referred to our clinic had been
placed on high-dose MMI, perhaps because Japanese
reference books recommend an initial dose of 30 mg.
We do not have data for the other major antithyroid
drug, propylthiouracil (PTU), because it is not our first
choice for treatment of Graves’ disease. When fever or
infection develops, many patients who initially receive
treatment at clinics are referred to a general hospital
or medical center such as our university hospital. Our
hospital therefore receives an unrepresentative percent-
age of more serious cases. To avoid such hospital bias,
dropout cases from other clinics were not included in
this report.

ATD-induced agranulocytosis is comparatively rare,
and is less common than other adverse effects, such as
skin rash and itchiness. The Noguchi Thyroid Clinic
and Hospital Foundation [6] reported that the incidence
of agranulocytosis was 0.31% in 13,208 Graves’ dis-
ease cases with a mean dosage of 27.8 ± 8.9 mg/d. Be-
cause a minimum of 1000 to 5000 patients is necessary
to determine the incidence of relatively rare adverse
effects, our sample size was insufficient to calculate
accurately the incidence of agranulocytosis. Tajiri et al.
[7] studied the largest collection of Graves’ disease
cases, 30,798 patients, and found that the incidence
of ATD-induced agranulocytosis was 0.35%; our overall
incidence of 1.75% (9 of 514) was much higher. Al-
though we are unable to explain this relatively high
incidence, we were able to analyze differences between
a high-dose group and low-dose group. It has been
suggested that high doses of MMI are associated with
development of agranulocytosis. ATD-induced agran-
ulocytosis, however, is not a result of dose-related tox-
icity. It might be caused by an immune mechanism
that tends to occur relatively early in the course of med-
cal treatment with drugs to which patients have been
previously exposed. In our experience, voluntary dis-
continuation of medical treatment is not exceptional.
Indeed, in the present study, 5 of the 9 patients who
suffered agranulocytosis had undergone re-treatment
with MMI. We believe that this repeated exposure may
be a risk factor for MMI-induced agranulocytosis.

The mechanisms responsible for the agranulocy-
tosis are unclear, but cellular autoimmunity may be
involved in its development. Positive associations
between HLA class II allele and agranulocytosis were
observed [8], many antibodies such as anti-leukocyte
antibodies and anti-granulocyte antibodies have been
proposed. PTU-induced autoimmune disease was
known as PTU-induced lupus-like syndrome, PTU is
also known as a trigger for antineutrophil cytoplasmic
antibodies (ANCA)-associated vasculitis. Recently,
complement-mediated cytotoxicity was postulated as
a mechanism of PTU-induced ANCA-positive neutro-
penia [9]. ANCA specific for proteinase 3 (PR3) and
myeloperoxidase (MPO) are associated with necrotiz-
ing vasculitis, and ANCA-activated neutrophils con-
tribute to oxidative and proteolytic damage of blood
vessels [10]. Priming (TNF-alpha)-induced transloca-
tion of PR3 and MPO to the cell surface may induce
cytotoxicity [9]. ANCA-associated vasculitis and
ATD-associated ANCA-positive patients in Belgrade
were reported [11]. In this 11-year retrospective
study, they obtained 72 patients with PR3-ANCA or
MPO-ANCA positive, 16/72 (22.3%) patients devel-
oped symptoms of systemic disease during ATD thera-
py. PTU is a very common trigger for ANCA, and 12
of these 16 were induced by PTU. There were only 2
patients showed leukopenia (<3 × 10^9/l) among the
clinically and serologically ANCA-positive ATD-
treated patients [11]. Among the 16 patients, ANCA
developed or was detected after more than a year of
ATD therapy. The duration of ATD therapy in their
study is much longer than that in our cases of MMI-
induced agranulocytosis. In a series of 18 cases, Dai
et al. [12] reported that ATD-induced agranulocytosis
developed 2 to 12 weeks after treatment, which is an
interval similar to the 4 to 10 weeks observed in our
cases.

Slight leukopenia and neutropenia are frequent
events in thyrotoxicosis before treatment with ATD.
Granulocyte colony-stimulating factor (G-CSF) is one
of the hematopoietic cytokines, which stimulates gran-
ulocyte proliferation and activation. Serum G-CSF
levels in untreated patients with Graves’ hyperthyroid-
ism were higher than those of healthy control [13], or
were not different from normal subjects [14]. At least
deficiency of G-CSF does not appear to be a cause of
agranulocytosis by ATD.

Although recombinant human G-CSF (rhG-CSF) is
clinically applicable for patients with agranulocytosis
and GM-CSF use resulted in faster restoration [12], the
recovery time in the G-CSF-treated group did not differ
from that of the untreated group [15].
Cooper et al. [16] reported that patients given an MMI dose of 40 mg or higher had an 8.6-fold higher risk of agranulocytosis than did patients receiving lower doses. Furthermore, they reported that no patients given an MMI dose lower than 30 mg/day developed agranulocytosis. In the present study, no patients given an MMI dose lower than 15 mg/d developed agranulocytosis in the period from January 1995 to September 2004. In October 2004, however, one patient developed agranulocytosis after a 6-week regimen of 15 mg MMI (Case #9 in Table 2). Tajiri et al. [5] reported that MMI dosage at the time patients developed agranulocytosis ranged from 5 to 45 mg. Because we elected to focus on the initial dose of MMI, our results are not directly comparable with those of this earlier study. A European prospective randomized study [3] of 309 patients reported that 10 mg and 40 mg MMI regimens were equally effective; however, the rate of adverse drug reactions was 15.5% in the 10 mg group and 26.0% in the 40 mg group. They reported that one patient in the 10 mg group had granulocytopenia (<2000/µL), and one patient in the 40 mg group had agranulocytosis; however, their sample size was not large enough to determine an association with dose. Our sample size is similar and lacked the statistical power to determine conclusively the incidence of MMI-induced agranulocytosis; one patient who received an initial dose of 15 mg MMI did develop agranulocytosis, and this increased the incidence from zero to 0.36%. Although there are no prospective controlled studies confirming the safety of low-dose MMI therapy with respect to agranulocytosis, our findings strongly suggest that the incidence of agranulocytosis is much lower in a low-dose (15 mg/d or less) MMI regimen than in a high-dose regimen.

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References


