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Comparison of Methimazole and Propylthiouracil in Patients with Hyperthyroidism Caused by Graves' Disease

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Context: Although methimazole (MMI) and propylthiouracil (PTU) have long been used to treat hyperthyroidism caused by Graves' disease (GD), there is still no clear conclusion about the choice of drug or appropriate initial doses.

Objective: The aim of the study was to compare the MMI 30 mg/d treatment with the PTU 300 mg/d and MMI 15 mg/d treatment in terms of efficacy and adverse reactions.

Design, Setting, and Participants: Patients newly diagnosed with GD were randomly assigned to one of the three treatment regimens in a prospective study at four Japanese hospitals.

Main Outcome Measures: Percentages of patients with normal serum free T_4 (FT4) or free T_3 (FT3) and frequency of adverse effects were measured at 4, 8, and 12 wk.

Results: MMI 30 mg/d normalized FT4 in more patients than PTU 300 mg/d and MMI 15 mg/d for the whole group (240 patients) at 12 wk (96.5 *vs.* 78.3%; $P = 0.001$; and 86.2%, $P = 0.023$, respectively). When patients were divided into two groups by initial FT4, in the group of the patients with severe hyperthyroidism (FT4, 7 ng/dl or more, 64 patients) MMI 30 mg/d normalized FT4 more effectively than PTU 300 mg/d at 8 and 12 wk and MMI 15 mg/d at 8 wk, respectively ($P < 0.05$). No remarkable difference between the treatments was observed in patients with initial FT4 less than 7 ng/dl. Adverse effects, especially mild hepatotoxicity, were higher with PTU and significantly lower with MMI 15 mg/d compared with MMI 30 mg/d.

Conclusions: MMI 15 mg/d is suitable for mild and moderate GD, whereas MMI 30 mg/d is advisable for severe cases. PTU is not recommended for initial use. **(*J Clin Endocrinol Metab* 92: 2157–2162, 2007)**

DESPITE METHIMAZOLE (MMI) and propylthiouracil (PTU) having been used for more than half a century to treat hyperthyroidism caused by Graves' disease (GD), controversy still exists in antithyroid drug (ATD) therapy. For example, according to a survey reported in 1991, MMI was selected as the drug for initial treatment in Japan and Europe, whereas PTU was preferred in the United States (1). Which is more suitable, MMI or PTU, in terms of drug efficacy or adverse effects? In Japan, treatment with MMI 30 mg daily has been "a standard regimen" for GD for a long time, but some reports have insisted that a smaller dosage such as 15 mg daily of MMI is as effective as the standard of 30 mg (2–4). How much should the initial ATD dosage be, a moderate dosage such as 30 mg daily of MMI or a smaller dosage of 15 mg?

The Japan Thyroid Association has been formulating a guideline for the treatment of hyperthyroidism caused by GD, but the data collected on ATD therapy over time were indeterminate on drug selection or suitable starting dosage. Therefore, we undertook this prospective randomized clinical study on initial treatments for thyrotoxic GD to decide the most suitable regimen by comparing the standard treatment of MMI 30 mg/d with PTU 300 mg/d and MMI 15 mg/d in terms of the short-term efficacy and adverse effects.

Patients and Methods

Patients

Only patients with untreated hyperthyroidism due to GD were recruited. GD was diagnosed according to Japan Thyroid Association's diagnosis guidelines (http://thyroid.umin.ac.jp/en/frame.html), defined by clinical findings and the determination of serum free T_4 (FT4), free T_3 (FT3), TSH, TSH receptor antibody (TRAb), and ^{123}I- or ^{99m}Tc-uptake. The following conditions excluded patients from the study: age younger than 16 yr old; pregnancy; relapsed patients after subtotal thyroidectomy or radioiodine therapy; previous treatment with ATD; severe complications, such as heart failure; and patients on glucocorticoid steroids or drugs that may influence thyroid functions.

Study design

This study was conducted as an open prospective randomized trial, with an observation period of 12 wk. Four hospitals in Japan, Ito Hospital

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Abbreviations: ALT, Alanine aminotransferase; AST, aspirate aminotransferase; ATD, antithyroid drug; GD, Graves' disease; MMI, methimazole; PTU, propylthiouracil; RCT, randomized controlled trial; TH, thyroid hormone; TRAb, thyroid stimulating hormone receptor antibody.

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in Tokyo, Kuma Hospital in Kobe, Sumire Hospital in Osaka, and Hamamatsu University Hospital in Hamamatsu, participated in the study. The Ethical Committee of Hamamatsu University School of Medicine and each hospital involved in the study approved the protocol. All eligible patients with untreated GD seen by the four participating hospitals from October 2003 to July 2004 were registered for the trial after obtaining informed consent. To compare the efficiency between MMI 30 mg/d and PTU 300 mg/d or MMI 15 mg/d, patients were distributed at random to the group with MMI 30 mg/d in two divided doses, PTU 300 mg/d in three divided doses or MMI 15 mg/d in a single dose. The necessary sample size was estimated by statistical calculation. For example, when type I error is 0.05, power is 0.8, and efficacy is 60% *vs.* 40%, 82 patients in each group are required. The method of assigning patients to groups was by their admission order at the outpatient clinic in Sumire Hospital and Hamamatsu University Hospital, and by the day of the week when patients first visited the outpatient clinic in Ito Hospital and Kuma Hospital.

A total of 396 patients with untreated GD were initially recruited for the study, with 93 patients excluded from the final analysis of the ATD treatment due to the reasons in Table 1. The percentage of withdrawal was less in the MMI 15-mg group than for other groups due to the significantly less occurrence of early adverse effects. Finally, 303 patients (134 patients at Ito Hospital, 92 at Kuma Hospital, 62 at Hamamatsu University Hospital and 15 at Sumire Hospital) were evaluated. For the adverse event analysis, 371 patients (excluding 25 dropout patients) were examined.

Patients were scheduled to visit the hospitals at 2, 4, 8, and 12 wk after initiation of their treatment. Adverse effects of the drugs were looked for systematically by careful health interview and clinical examinations. Aspirate aminotransferase (AST), alanine aminotransferase (ALT), γ glutamyl transpeptidase, and hematological values were measured for evaluation every visit to the outpatient clinic. Serum FT4 and FT3 with or without TSH were assayed at 4, 8, and 12 wk. When serum FT4 and FT3 were both within normal ranges (FT4, 0.8–1.6 ng/dl; FT3, 3.1–4.9 pg/ml), the dosages of ATD were lessened as follows: MMI from 30 to 15 mg; from 15 to 10 mg; and PTU from 300 to 150 mg. After that, patients were given suitable doses of ATD to maintain normal thyroid hormone (TH) concentrations. When necessary, β-blocker was given concomitantly. The initial dose of ATD was continued without increasing for 12 wk, even if TH did not fall into the normal range. Each of the four hospitals obtained the values for serum FT4 and FT3 within 60 min after taking blood samples at outpatient clinics, and doctors could decide the dose of ATD after checking hormone values.

The number of patients finally analyzed for ATD effectiveness was 98 in the MMI 30-mg, 81 in the PTU 300-mg, and 124 in the MMI 15-mg groups, respectively. The ratio of sex, values for age, and initial TRAb before treatment did not differ between groups (Table 1). Before ATD treatment, all patients had elevated FT4 levels more than 2 ng/dl.

Methods

Serum FT4, FT3, and TSH were measured with a Roche ECLusys kit (Roche, Basel, Switzerland) in Ito Hospital, Sumire Hospital, and Hamamatsu University Hospital, or Architect kits (Abbott Japan Co., Ltd, Osaka 540-0001 Japan) in Kuma Hospital. Although values for the hormones obtained by these two assay kits differed slightly, the data were combined for the analyses because the difference was small (data not shown). The normal values and measurable ranges are as follows: FT4 0.8–1.6 ng/dl (measurable range up to 7 ng/dl), FT3 3.1–4.9 pg/ml (measurable range up to 30 pg/ml). TRAb (normal range 0–10%) was assayed with TRAb-CT (Cosmic Corporation, Tokyo, Japan).

Statistical analysis

Data were analyzed statistically using the χ^2 test for independence and comparison of frequencies. When expected values less than 5 are included in the table of the data, Fisher's exact probability test was used instead of the χ^2 test. For comparison of age and TRAb values among the three groups, ANOVA was used. Calculations were performed using StatView, version 5.0 (SAS Institute Inc., Cary, NC). Statistical significance was defined as $P < 0.05$.

Results

Comparisons of the efficiency of the MMI 30 mg/d treatment with that of the PTU 300 mg/d and MMI 15 mg/d treatment

At 4 wk after initial treatment, serum FT4 levels went down less than 1.7 ng/dl in 52.7%, 38.4%, and 36.7% of the patients treated with MMI 30 mg/d, PTU 300 mg/d, and MMI 15 mg/d, respectively. MMI 15 mg/d was significantly less effective than MMI 30 mg/d ($P = 0.023$). At 8 wk, their ratios were 81.3%, 68.5%, and 70.0%, respectively, and the statistical difference between MMI 30 mg/d with PTU 300 mg/d and MMI 15 mg/d was marginal. At 12 wk, the efficacy was significantly different between them because 96.5% of the patients on MMI 30 mg reached normal FT4, while 78.3% on PTU 300 mg ($P < 0.001$) and 86.2% on MMI 15 mg ($P = 0.023$) (Fig. 1).

Because the severity of hyperthyroidism varied among the patients, we divided the patients into two groups according to their pretreatment serum FT4 values; group A included patients with initial FT4 less than 7 ng/dl and group B with 7 ng/dl or more. There was no difference in the pretreatment FT4 and FT3 values in group A (data not shown), and almost all patients in group B had FT4 above the measurable range. In group A, no difference was found between the treatments at 4 and 8 wk, but at 12 wk, MMI 30 mg/d achieved normal FT4 in every patient, while PTU 300 mg/d and MMI 15 mg/d induced normal FT4 in 87.5% and 92%, respectively, with a statistically significant difference (Fig. 2, *upper*). In group B, MMI 30 mg/d is clearly more effective than PTU 300 mg/d and MMI 15 mg/d in normalizing FT4. At 4 wk after beginning treatment, 38.5% of the patients achieved normal FT4 with MMI 30 mg/d, but only 13.0% with PTU 300 mg/d and 14.3% with MMI 15 mg/d, with both about 35–40% efficiency of MMI 30 mg/d in normalizing FT4. The same tendency was observed at 8 and 12 wk also (Fig. 2, *lower*).

TABLE 1. Patient groupings and data

	No. of patients randomized	No. of patients excluded (%)	No. of side effects (%)	No. of patients not visiting regularly (%)	No. of dropouts (%)	No. of patients analyzed	Male to female ratio	Mean age ± SD (yr)	Initial TRAb values
MMI 30 mg/d	135	37 (27.4)	24 (17.8)	8	5 (3.7)	98	25/73	39.4 ± 13.5	67.8 ± 35.2
PTU 300 mg/d	114	33 (28.9)	20 (17.5)	3	10 (8.8)	81	11/70	40.2 ± 12.9	56.3 ± 23.8
MMI 15 mg/d	147	23 (15.6)	8 (5.4)	5	10 (6.8)	124	26/98	41.0 ± 13.1	61.0 ± 24.9
Total	396	93 (21.8)	52 (13.1)	16 (4.0)	25 (5.9)	303			

A total of 396 patients with untreated GD were initially recruited for the study, with 93 patients excluded from the final evaluation for short-term efficacy of the ATD treatments due to side effects within 4 wk, not visiting a hospital regularly, or dropout. Finally, 303 patients (134 patients at Ito Hospital, 92 at Kuma Hospital, 62 at Hamamatsu University Hospital, and 15 at Sumire Hospital) were analyzed. For the adverse event analysis, 371 patients excluding 25 dropout patients were examined.

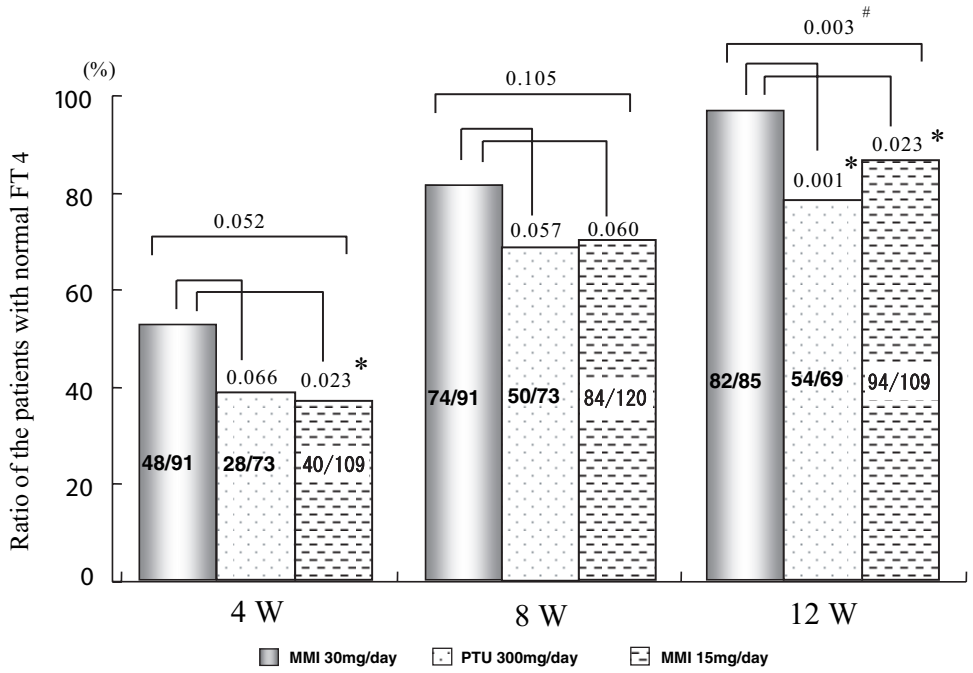

FIG. 1. Comparison of the efficiency of treatment with MMI 30 mg/d and PTU 300 mg/d or MMI 15 mg/d in whole patients with GD in terms of normalizing serum FT4 levels [<1.7 ng/dl (21.9 pmol/liter)]. The *numbers in the columns* show patients with normal FT4/total patients. The *numbers above the columns* are *P* values of χ^2 analyses between MMI 30 mg/d and PTU 300 mg/d or MMI 15 mg/d. #, Significantly different among three treatment groups. *, Statistically significant between MMI 30 mg/d and PTU 300 mg/d or MMI 15 mg/d. W, Weeks.

When the efficiency of these ATD regimens was analyzed in terms of achieving normal FT3 levels (<5 pg/ml), a similar tendency was found, although the difference was less evident (Table 2). For whole patients, MMI 30 mg/d induced normal FT3 more efficiently than PTU 300 mg/d at 8 wk (75.6% *vs.* 57.4%, respectively; $P = 0.021$) and 12 wk (90.0% *vs.* 62.9%, respectively; $P < 0.001$). When the patients in groups A and B were analyzed, there was no difference between the treatments at 4 and 8 wk, but at 12 wk, MMI 30 mg/d was more effective than PTU 300 mg/d and MMI 15 mg/d. The efficiency to achieve normal FT3 level was almost half with PTU 300 mg/d compared with MMI 30 mg/d (66.7 *vs.* 35.0%, respectively; $P = 0.043$) in group B. No relation was found between the efficacy of ATD to normalize TH and age, sex, initial TRAb values, or goiter size (data not shown).

Comparison of adverse events between MMI 30 mg/d and PTU 300 mg/d or MMI 15 mg/d

Table 3 summarizes the incidence of adverse effects in the ATD regimen groups. The incidence was surprisingly high in the PTU group, in which more than half the patients (54 of 104) had some adverse effects. PTU was stopped or changed to MMI for 39 patients. In the MMI 30-mg group, adverse effects occurred in 39 of 130 patients (30%), and the drug was stopped or changed for 28 patients. The difference was statistically significant between the PTU group and the MMI 30-mg group. We found a very high incidence of elevation of transaminase values with PTU. The percentage of patients who showed AST and ALT higher than double the upper range of the normal standard was 26.9% on PTU 300 mg/d, compared with only 6.6% on MMI 30 mg/d ($P < 0.001$). Skin eruption or urticaria similarly occurred in about 22% in either group, but leukocytopenia (less than 1000/μl) was observed in five patients in the PTU group only. One patient treated with MMI 30 mg/d had arthralgia, and the drug was discontinued. Fortunately, no patient experienced serious side effects, such as agranulocytosis.

On the contrary, MMI 15 mg/d caused significantly fewer adverse events than MMI 30 mg/d. The total incidence in the MMI 15 mg group was about half that of the MMI 30-mg group. Although the frequency of mild hepatotoxicity was similar, skin eruption/urticaria induced by MMI 15 mg was only about one third that of MMI 30 mg.

Discussion

There have been only limited studies that compared the effectiveness of MMI and PTU to treat hyperthyroidism caused by GD. Okamura *et al.* (5) reported that MMI 30 mg/d normalized more rapidly TH than PTU 300 mg/d. The mean time required to normalize TH was 6.7 ± 4.6 wk by MMI and 16.8 ± 13.7 wk by PTU ($P < 0.05$). However, their study was retrospective, and it was unclear whether the patients in each group were truly equivalent (5). In fact, only 17 patients were treated with PTU, one fourth that of MMI. There were four prospective randomized controlled trials (RCTs) to compare MMI and PTU (6–9), and the results of these studies indicated the tendency that MMI is somewhat more effective. However, the conclusion should be cautious because of the small number of patients in each group (6, 7, 9). In addition, in one study, both ATDs were given in a single daily usage (8). Because the half-life of PTU is much shorter than that of MMI and a single daily dose regimen is known to be less effective than a divided dose regimen for PTU administra-

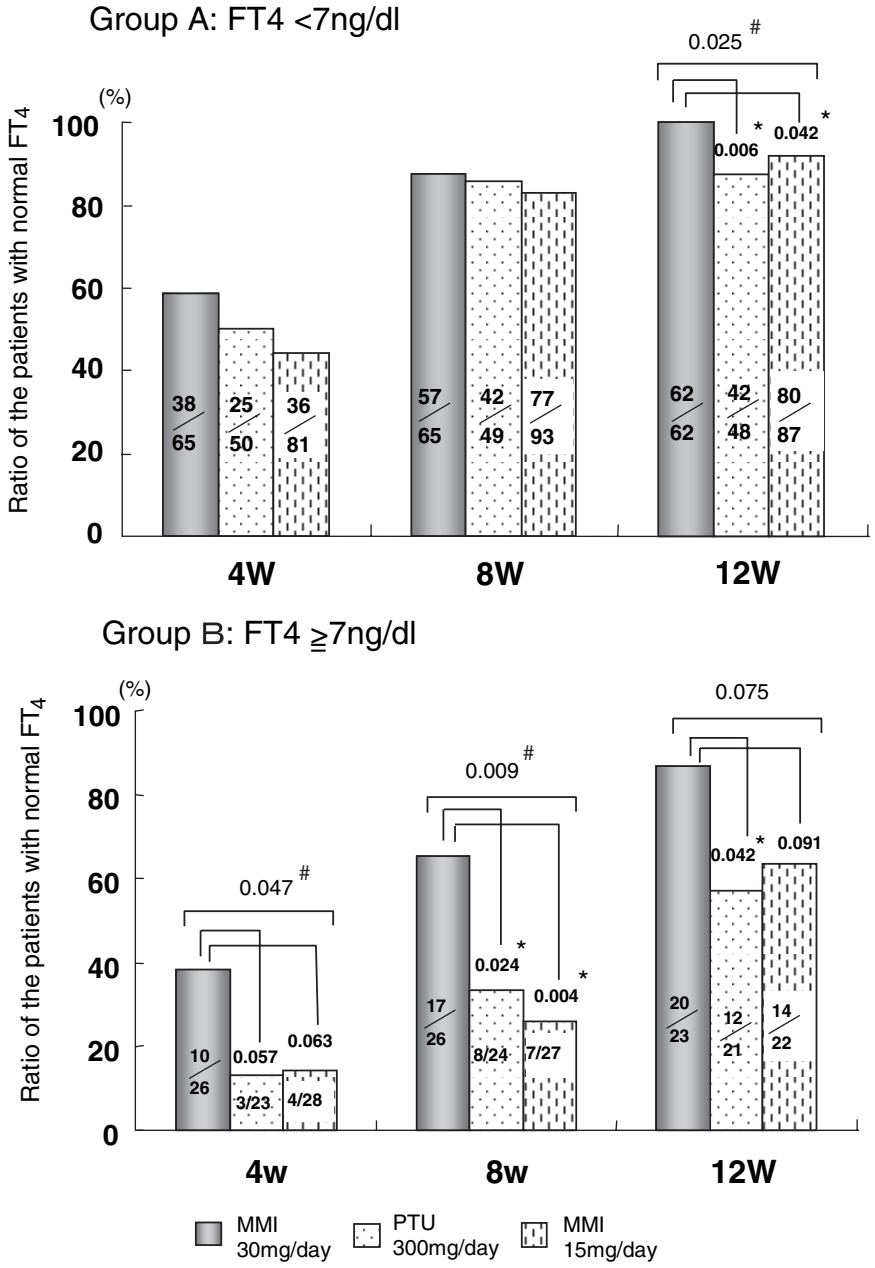

FIG. 2. Comparison of the efficiency of treatment with MMI 30 mg/d and PTU 300 mg/d or MMI 15 mg/d in patients with GD in terms of normalizing serum FT4 levels [<1.7 ng/dl (21.9 pmol/liter)]. The patients were divided into two groups according to their pretreatment serum FT4 values: group A with initial FT4 less than 7 ng/dl (90 pmol/l) (*upper*) and group B with 7 ng/dl or more (*lower*). The *numbers in the columns* show patients with normal FT4/total patients. The *numbers above the columns* are *P* values of χ^2 analyses between MMI 30 mg/d and PTU 300 mg/d or MMI 15 mg/d. #, Significantly different among three treatment groups. *, Statistically significant between MMI 30 mg/d and PTU 300 mg/d or MMI 15 mg/d. W, Weeks.

tion (10), comparison between MMI and PTU in a single daily usage may be unsuitable.

As for the initial dosage of ATD, Benker *et al.* (11) reported that 42.2% of patients became euthyroid within 3 wk on MMI 10 mg/d and 64.8% on 40 mg/d after 3 wk in the European Multicenter Trial Study. At 6 wk, 77.5% and 92.6% of patients became euthyroidism on 10 mg and 40 mg MMI, respectively. In an RCT comparing the effects of 20, 30, 40 mg/d MMI, and 200, 300, 400 mg/d PTU, Kallner *et al.* (7) showed that almost all patients had a normal FT4 level within 12 wk except those who received 20 mg MMI or 200 mg PTU. They concluded that these small doses of ATD were unsuitable due to an unacceptably high incidence of failure to attain euthyroidism within 12 wk. In contrast, Shiroozu *et al.* (2) reported similar effectiveness between MMI 15 mg/d and 30 mg/d, showing that the percentage of patients who became euthyroid and the mean times to achieve it were similar among the groups. Following this report, Mashio *et al.* (3) performed a similar study and confirmed the conclusion of Shiroozu *et al.* (2). The results of both studies are clear, but

TABLE 2. Comparison of the efficiency of treatment with MMI 30 mg/d and PTU 300 mg/d or MMI 15 mg/d in patients with GD in terms of normalizing serum FT3

	No./total no. of patients (%)	No./total no. of patients in group A (%)	No./total no. of patients in group B (%)
At 4 wk			
MMI 30 mg	39/80 (48.8)	34/57 (59.6)	5/23 (21.7)
PTU 300 mg	24/62 (38.7)	24/46 (52.2)	0/16 (0.0)
P value (χ^2)	0.232	0.447	0.066
MMI 15 mg	32/92 (34.8)	30/71 (42.3)	2/21 (9.5)
P value (χ^2)	0.064	0.0498[a]	0.416
P value (χ^2) among three groups	0.166	0.143	0.107
At 8 wk			
MMI 30 mg	62/82 (75.6)	52/61 (85.2)	10/21 (47.6)
PTU 300 mg	35/61 (57.4)	30/42 (71.4)	5/19 (26.3)
P value (χ^2)	0.021[a]	0.090	0.204
MMI 15 mg	62/96 (64.5)	54/72 (75.0)	8/24 (33.3)
P value (χ^2)	0.111	0.139	0.329
P value (χ^2) among three groups	0.064	0.196	0.354
At 12 wk			
MMI 30 mg	72/80 (90.0)	58/59 (98.3)	14/21 (66.7)
PTU 300 mg	39/62 (62.9)	32/42 (76.2)	7/20 (35.0)
P value (χ^2)	<0.001	<0.001[a]	0.043[a]
MMI 15 mg	78/98 (79.6)	66/77 (85.7)	12/21 (57.1)
P value (χ^2)	0.058	0.013[a]	0.525
P value (χ^2) among three groups	<0.001[b]	0.003[b]	0.115

FT3 was considered normalized when it became less than 5 pg/ml (7.68 pmol/liter). Group A patients are those with pretreatment serum FT4 less than 7 ng/dl (90 pmol/liter) and group B with 7 ng/dl or more.

[a] Statistically significant compared with MMI 30-mg group.

[b] Statistically significant among the three groups.

there were some limitations. In the RCT by Shiroozu *et al.* (2), a significant number of patients were considered to be mild because 20–35% of the patients had TRAb values less than 15%. In addition, the dropout ratio was as high as 20%, and a retrospective control group was included. In the study by Mashio *et al.* (3, 4), no information was given about the ratio of dropout patients. Both studies did not pay any attention to the baseline severity of the disease before treatment. Analysis based on the baseline severity of hyperthyroidism is important because it is quite conceivable that a small amount of ATD may be suitable for mild GD but unsuitable for very severe hyperthyroid patients. There has been only one study reporting such an analysis (12), which observed that 20 mg/d carbimazole, a precursor of MMI, was too low for severe Graves' patients (initial $T_4 > 20$ μg/dl) but adequate for less severely hyperthyroid patients. The data are interesting and suggestive, but the number of patients in each group was very small (just seven to nine subjects). Our RCT showed that the MMI 30 mg/d treatment is clearly superior in the effectiveness to achieve normal TH than PTU 300 mg/d and MMI 15 mg/d, especially for patients with severe hyperthyroidism.

Regarding adverse effects, minor ones occurred in as high as 52% of patients treated with PTU 300 mg/d, while 30% and 13.9% with MMI 30 mg/d and MMI 15 mg/d, respectively, in our study. The frequency of minor side effects was reported not to differ between MMI and PTU (13), but this is the first RCT that demonstrated the significantly higher frequency of adverse effects in PTU than MMI. Notably PTU induced mild liver damages four times higher than MMI 30 mg/d. Liaw *et al.* (14) reported that although PTU commonly induces subclinical and asymptomatic liver injury, liver damage is usually transient, and PTU may be continued with caution. However, we stopped the initial medication when AST or ALT elevated more than double the normal level because of the risk of PTU-induced severe hepatotoxicity. Williams *et al.* (15) collected two of their own and 28 cases in the literature of PTU-induced severe hepatic toxicity and reported that seven patients died. MMI 15 mg/d is evidently advantageous over MMI 30 mg/d, with a total incidence less

TABLE 3. Comparison of the incidence of side effects between the MMI 30 mg/d regimen and the PTU 300 mg/d or MMI 15 mg/d regimen

	n	No. of total incidences (%)	No. with changed medication (%)	No. with hepatotoxicity (%)[a]	No. with skin eruption/urticaria (%)	No. with leukocytopenia (%)[b]	No. with other (%)[c]
MMI 30 mg	130	39 (30.0)	28 (21.5)	9 (6.6)	29 (22.3)	0 (0)	1 (0.7)
PTU 300 mg	104	54 (51.9)	39 (37.5)	28 (26.9)	23 (22.1)	5 (4.8)	0 (0)
P value (χ^2)	0.001[d]	0.007[d]	<0.001[d]	0.972	0.016[d]		
MMI 15 mg	137	19 (13.9)	10 (7.3)	9 (6.6)	9 (6.6)	1 (0.7)	0 (0)
P value (χ^2)	0.001[d]	0.001[d]	0.908	<0.001[d]	>0.999		

[a] Elevation of AST and ALT more than double the upper range of the normal standard.

[b] Less than 1000/μl.

[c] Arthralgia.

[d] Statistically significant.

than half and the frequency of skin eruption one third of MMI 30 mg/d. This result was compatible with that of Shiroozu *et al*. (2) and Benker (11) *et al*.

In conclusion, we recommend MMI 15 mg/d for patients with mild and moderate GD. MMI of this dosage can induce euthyroidism as effectively as MMI 30 mg/d, and the frequency of adverse reaction is significantly lower. For severe Graves' patients, MMI 30 mg/d may be advisable to induce euthyroidism within 3 months. PTU is not recommended as an initial ATD because of its high frequency of adverse reactions and rather poor efficacy to decrease TH levels.

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