

## Prevention of Relapse of Graves' Disease by Treatment with an Intrathyroid Injection of Dexamethasone

Xiao-Ming Mao, Hui-Qin Li, Qian Li, Dong-Mei Li, Xiao-Jing Xie, Guo-Ping Yin, Peng Zhang, Xiang-Hong Xu, Jin-Dan Wu, Song-Wang Chen, and Shu-Kui Wang

Departments of Endocrinology (X.-M.M., H.-Q.L., Q.L., D.-M.L., X.-J.X., G.-P.Y., P.Z., X.-H.X., J.-D.W.), Ultrasonography (S.-W.C.), and Central Laboratory (S.-K.W.), Affiliated Nanjing First Hospital, Nanjing Medical University, Nanjing 210006, China

**Introduction:** Antithyroid drugs are widely used in the treatment of Graves' disease (GD), but the relapse rate is very high after therapy withdrawal. We evaluated the reduction effects of intrathyroid injection of dexamethasone (IID) on the relapse rate of hyperthyroidism in patients with newly diagnosed GD.

**Patients and Methods:** A total of 191 patients with GD completed the study. After 6 months of treatment with methimazole (MMI), the patients were randomly assigned to receive either MMI (96 patients) alone or MMI combined with IID (MMI+IID; 95 patients) treatment for 3 months, followed by continuing a dose of MMI that would maintain euthyroidism for the next 9 months in all of the patients. After withdrawal of the medical therapy, patients were followed for 24 months, and the relapse rate of hyperthyroidism was evaluated.

**Results:** No statistical difference was observed in the levels of serum  $FT_4$ , TSH, or TSH receptor antibodies (TR-Ab), the thyroid volume, or the TR-Ab positive rate between the two groups at month 6. After the next 3 months of treatment with MMI+IID or MMI alone, the levels of TSH increased significantly, and the levels of serum TR-Ab, the TR-Ab positive rate, and thyroid volume decreased significantly in the MMI+IID group compared with the MMI group. Seven patients (7.4%) experienced a relapse of overt hyperthyroidism in the MMI+IID group and 49 patients (51%) in MMI group during the 2-yr follow-up period ( $P < 0.001$ ).

**Conclusions:** MMI+IID treatment is helpful to prevent relapse of hyperthyroidism in GD after medical therapy withdrawal. (*J Clin Endocrinol Metab* 94: 4984–4991, 2009)

Graves' disease (GD) is one of the most common organ-specific autoimmune diseases affecting humans, and it is caused by autoantibodies that induce thyrotoxicosis by mimicking the action of TSH and activating the TSH receptor. However, the exact pathogenesis remains poorly understood. Currently, the main treatment strategies for GD include antithyroid drugs (ATD), thyroid ablation with radioiodine, or surgery (1). Conservative therapy with ATD is the first choice treatment in China and Europe, with methimazole (MMI) being most commonly used. A long-term therapy of about 12–18 months is

usually adopted (2, 3), which requires careful monitoring of patients for side effects of rash, joint pain, liver inflammation, and agranulocytosis (3, 4). After therapy withdrawal, the relapse rate is very high (40–60%), and many patients need further treatment. Therefore, doctors, particularly in the United States, favor thyroid ablation with radioiodine treatment in most instances. However, thyroid ablation with radioiodine is not devoid of unwanted side effects such as subsequent hypothyroidism and the possibility of secondary neoplasia. Surgical thyroidectomy is the least often used therapy.

Thyroid surgery entails postoperative hypothyroidism and hospitalization costs.

GD is characterized by persistent infiltration of the thyroid parenchyma by lymphocytes composed mainly of CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes. These lymphocytes can secrete certain cytokines and induce inflammatory processes, which may partially participate in the pathogenesis of GD (3, 5, 6). The pathological characteristics of thyroid tissue in GD are similar to that of orbital tissue in Graves' ophthalmopathy and can be characterized by diffuse infiltration by lymphocytes, the release of cytokines, and active inflammatory status that are involved in the pathogenesis (7–9).

Glucocorticoids have antiinflammatory, immunomodulatory, and immunosuppressive effects that have long been used in the treatment of Graves' ophthalmopathy and are one of the most effective medicines (10, 11). Several reports have shown that glucocorticoids can decrease the release of some cytokines and reduce inflammation (12, 13) and some thyroid specific antibodies, such as TSH receptor antibodies (TR-Ab), antithyroperoxidase antibodies, and antithyroglobulin antibodies (13–15). Those effects might affect the autoimmune process of GD. Moreover, glucocorticoids have been used for the treatment of GD in several early reports in which serum free T<sub>3</sub> and free T<sub>4</sub> (FT<sub>4</sub>) or total T<sub>3</sub> and total T<sub>4</sub> levels decreased after 8-d or 3-wk treatment with glucocorticoids (16, 17). In a case report, Peter (18) treated a patient with GD with a combination of glucocorticoids (for 8 months) and ATD (10 months). After cessation of therapy, the patient continued to be euthyroid for the next 3 yr. However, the number of selected patients was small, and the duration of the therapy was relatively short in those studies, so they might not confirm the effects of glucocorticoids on GD.

The aim of this trial was to evaluate the potential effects of treatment by MMI combined with intrathyroid injection of dexamethasone (IID) on clinical outcomes in GD.

## Patients and Methods

### Study protocol

The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Nanjing Medical University and health authorities according to their regulations. Written informed consent was obtained from subjects before the study began.

### Patients

A total of 216 consecutive Chinese patients with newly diagnosed GD were screened from the Endocrine Clinic of Nanjing First Hospital Affiliated to Nanjing Medical University between June 2004 and July 2005. Among them, 206 eligible patients were enrolled. All of the patients, aged 20 to 63 yr, were diag-

nosed based on commonly accepted clinical and laboratory criteria: hyperthyroidism, diffuse goiter without nodular formation at ultrasound, uniform pattern of uptake on scan with Tc-99m, and the presence of TR-Ab in the serum. The diagnosis of hyperthyroidism was based on signs and symptoms of thyrotoxicosis and on the basis of raised FT<sub>4</sub> levels with low TSH. Exclusion criteria were as follows: pregnancy, allergy to ATD, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels more than two times the upper normal range, noncompliance because of psychiatric or other serious diseases, or unwillingness to participate in the study.

### Study design

This study was conducted in four phases: 1) all of the patients received MMI (Merck & Co., Inc., Darmstadt, Germany) treatment with a titration regimen for 6 months; 2) patients were randomly assigned to receive either MMI treatment alone (MMI group) or MMI combined with IID (MMI+IID group) (dexamethasone sodium phosphate injection, 5 mg/ml; Shandong Xinhua Pharmaceutical Co., Ltd., Zibo City, China) treatment for 3 months; 3) all of the patients continued to receive MMI treatment for the next 9 months; and 4) follow-up for 2 yr.

During phase 1, all of the patients received a daily starting dose of 20 mg MMI with control visit at 2 wk and 1, 2, 3, 4, and 6 months. A careful medical examination and laboratory assessment of FT<sub>4</sub>, TSH, and total white blood cell count levels were performed at each visit, and ALT and AST were measured at 3-month intervals. If a condition of euthyroidism was achieved (euthyroidism was defined as the elimination of most symptoms of hyperthyroidism and serum levels of TSH and FT<sub>4</sub> in the normal range), pharmacological therapy was adjusted gradually, and a continuing dose of MMI was given to maintain euthyroidism. If subclinical thyrotoxicosis occurred (subclinical thyrotoxicosis was defined as the suppression of serum TSH levels with simultaneously normal serum FT<sub>4</sub> values), MMI treatment was continued until euthyroidism was achieved.

After 6 months of MMI titration treatment, the FT<sub>4</sub>, TSH, and TR-Ab levels and thyroid volume were measured, and the patients were randomly assigned to one of the two groups, i.e. the MMI group or the MMI+IID group. Patients in the MMI group were treated with MMI alone for 3 months. Patients in the MMI+IID group were treated with MMI combined with IID. The MMI therapy strategy was the same as that of MMI group. The IID therapy was started at month 7, and the course of treatment lasted for 3 months. The IID therapy was performed using a 25-gauge (0.25-mm) needle under ultrasound guidance. When the needle reached the thyroid, the syringe plunger was pulled back to check for bleeding. If there was no bleeding, the drug was injected slowly into the thyroid (which lasted about 0.5 min). When the needle was pulled out, pressure was applied to the injection sites with cotton for 5 min to prevent bleeding and leakage of drug. The injection was performed in both lobes of the thyroid. The dosage of dexamethasone was 5 mg (1.0 ml) in each lobe, twice a week during the first month of the treatment. The treatment strategy was changed to once a week in the second month and twice a month in the third month; the dosage of dexamethasone was the same as in the first month. The cumulative dosages of dexamethasone in each 4-wk period were 80 mg, 40 mg, and 20 mg, respectively. Side effects of the treatment were evaluated and treated carefully in this period. After 9 months, FT<sub>4</sub>, TSH, and TR-Ab levels and thyroid volume were measured.

At the third stage of treatment, all of the patients were maintained on MMI alone for the next 9 months with control visits at 3-month intervals. At the end of this stage, FT<sub>4</sub>, TSH and TR-Ab levels and thyroid volume were measured.

After 18 months, the medical therapy was discontinued, and patients were followed up for another 2 yr. Follow-up visits were every 6 months. In addition, patients were reviewed immediately, outside scheduled follow-up visits, if they felt they might be suffering a disease relapse. Each follow-up visit consisted of clinical assessment of thyroid status and measurement of serum FT<sub>4</sub> and TSH levels.

### Laboratory measurements

Blood cells were quantified in a Coulter Gen S System 2 analyzer (Coulter Corp., Hialeah, FL). Agranulocytosis was defined as a total granulocyte count of less than  $1 \times 10^9$  granulocytes per liter of blood. ATD treatment was immediately discontinued in all patients with agranulocytosis, and the patients were excluded from the study. Serum TSH (reference range, 0.34–5.60  $\mu$ U/ml) and FT<sub>4</sub> (reference range, 0.61–1.22 ng/dl) levels were measured by chemiluminescence assay (Unicel DXI 800; Beckman Coulter, Fullerton, CA). TR-Abs were assessed by RIA with a commercial kit (TSH Rezak; Medipan GmbH, Berlin, Germany). (Solubilized TSH receptor was obtained from porcine thyroid tissue, and the tracer was <sup>125</sup>I-TSH.) TR-Ab was defined as positive above 14 U/liter; intra- and interassay coefficients of variation were less than 4.8% and 4.6–7.6%, respectively. Serum ALT and AST levels were determined by enzymatic procedures on an automated autoanalyzer (Olympus AU 2700 Chemistry Analyzer; 1st Chemical Ltd., Tokyo, Japan). The thyroid volume was estimated by ultrasonography (GE Medical Systems, Milwaukee, WI) using a 7.5-MHz linear array transducer (19). All examinations were performed and interpreted by the same experienced radiologist. Thyroid volume was obtained by computing the volumes of both lobes [lobe (ml) = length (mm)  $\times$  width (mm)  $\times$  depth (mm)  $\times$  0.479]. Nodules and/or cystic areas were included in the thyroid volume (reference values, 18 ml for females, and 25 ml for male patients).

### Statistical analysis

We assumed that the long-lasting recurrence rate in the MMI group would be 50% (2) and that MMI+IID treatment should lead to a 20% decrease in recurrence rate, and we estimated that an overall recurrence rate would be 30%. To achieve a power of 0.8 with an  $\alpha$  of 0.05, we needed 71 patients in each group of the trial. We aimed to enroll 86 patients per group to allow for exclusions based on an estimated dropout rate of 20%.

A total of 191 patients completed the trial. Only the patients who completed the four-phase study were included into the relapse and the efficacy analyses. Normally distributed and continuous variables are presented as mean  $\pm$  sd. Clinical characteristics of the patients at baseline are given as proportions in Table 1. Comparability of the two randomized groups with respect to clinical characteristics was investigated using parametric and nonparametric analysis as appropriate.

To analyze the effects of the two therapy strategies on thyroid volume, the patients with thyromegaly, 47 patients in the MMI group and 44 in the MMI+IID group, were included in statistical analysis.

Relapse was defined by unequivocal evidence of recurrent clinical and biochemical thyrotoxicosis, *i.e.* symptoms or signs of

**TABLE 1.** Baseline characteristics of patients with GD before treatment with MMI

	MMI group	MMI+IID group	P value
n	96	95	
Age (yr)	34.7 $\pm$ 11.3	35.3 $\pm$ 10.1	NS
Sex (% of females)	86.5	85.3	NS
FT <sub>4</sub> (ng/dl)	3.12 $\pm$ 1.04	3.01 $\pm$ 0.98	NS
TR-Ab (U/liter)	51.30 $\pm$ 61.58	49.93 $\pm$ 62.33	NS
TR-Ab positive (%)	87.4	89.5	NS
Thyroid volume (ml)	24.40 $\pm$ 12.87	23.47 $\pm$ 2.72	NS
Goiter (%)	48.9	46.3	NS

NS, Not significant.

thyrotoxicosis in the presence of suppressed serum TSH and simultaneously elevated serum FT<sub>4</sub> (all defined according to the laboratory reference range). The recurrence of Graves' hyperthyroidism during follow-up in the IID and MMI treatment groups was analyzed using Kaplan-Meier curves and compared by the  $\chi^2$  test between groups. *P* values of less than 0.05 were considered significant.

### Results

A total of 216 patients with GD underwent screening. Of those patients, 206 were eligible and received the first stage of treatment with MMI. In this stage, three patients were excluded: two developed agranulocytosis, and one had increased concentrations of ALT (more than two times the upper normal range). The remaining 203 patients were randomly assigned to one of the two groups: MMI group (*n* = 101) or MMI+IID group (*n* = 102). Of those patients, five (two in the MMI group and three in the MMI+IID group) discontinued the study (one was withdrawn by the investigator, two were unwilling to accept treatment with MMI, and two were unwilling to accept treatment with IID). Of the remaining 198 patients who completed 18 months of treatment, 191 completed the 2-yr follow-up and seven (3.5%; three in the MMI group, and four in the MMI+IID group) dropped out because of emigration or loss to follow-up (Fig. 1).

Clinical characteristics, FT<sub>4</sub>, TR-Ab, TR-Ab-positive rate, and thyroid volume at baseline were similar between the two groups (Table 1). Thyroid enlargement by ultrasound examination was found in 91 of 191 the patients, including 47 in the MMI group (48.9%) and 44 in the MMI+IID group (46.3%) (*P* > 0.05) (Table 1).

### Treatment outcomes and MMI dosages

After 6 months of treatment with MMI, 174 patients achieved euthyroidism. Of those patients, 88 were in the MMI group (91.7%), and 86 were in the MMI+IID group (90.5%). The rate of euthyroidism was not significantly different between the two groups (*P* > 0.05). The remain-

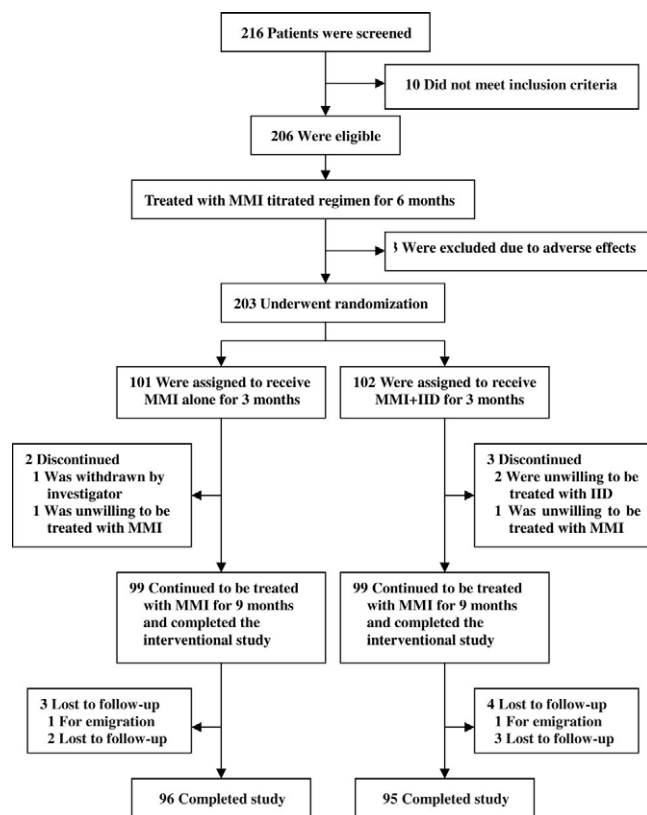


FIG. 1. Enrollment and outcomes.

ing 17 patients achieved subclinical thyrotoxicosis (eight in MMI group and nine in MMI+IID group). After 9 months of treatment, 186 patients achieved euthyroidism. Of those patients, 93 were in the MMI group (96.7%) and 93 in the MMI+IID group (97.9%). The remaining five patients (three in the MMI group and two in the MMI+IID group) still suffered subclinical thyrotoxicosis. After 18 months of treatment, all of the patients achieved euthyroidism.

The average dosages of MMI in the MMI and MMI+IID groups were  $5.08 \pm 3.74$  and  $5.37 \pm 3.99$  mg, respectively ( $P > 0.05$ ), at month 6;  $3.28 \pm 3.28$  and  $3.26 \pm 1.71$  mg, respectively ( $P > 0.05$ ), at month 9; and  $2.94 \pm 0.96$  and  $2.89 \pm 0.91$  mg, respectively ( $P > 0.05$ ), at month 18.

### Change of thyroid hormone, TSH, serum TR-Ab, and goiter size

Patient data were collected over an 18-month treatment period (Fig. 2). Figure 2, A and B, shows the course changes of the levels of serum FT<sub>4</sub> and TSH in the two groups. As expected, the levels of serum FT<sub>4</sub> of patients in the two groups were markedly reduced after 6 months of MMI treatment compared with baseline (MMI group,  $3.12 \pm 1.04$  vs.  $0.88 \pm 0.20$  ng/dl,  $P < 0.001$ ; MMI+IID group,  $3.01 \pm 0.98$  vs.  $0.87 \pm 0.23$  ng/dl,  $P < 0.001$ ). No statistically significant difference was

observed in the levels of serum FT<sub>4</sub> between the two groups at months 6, 9, and 18 ( $P > 0.05$ ) (Fig. 2A). No difference was seen in the levels of TSH between the two groups at month 6 ( $2.24 \pm 1.83$  vs.  $2.85 \pm 2.63$  mIU/liter;  $P > 0.05$ ). However, after 9 and 18 months of treatment, the levels of TSH increased significantly in the MMI+IID group compared with the in MMI group (at month 9,  $3.38 \pm 1.87$  vs.  $2.71 \pm 2.06$  mIU/liter,  $P < 0.05$ ; at month 18,  $3.96 \pm 1.46$  vs.  $2.87 \pm 1.99$  mIU/liter,  $P < 0.001$ ) (Fig. 2B).

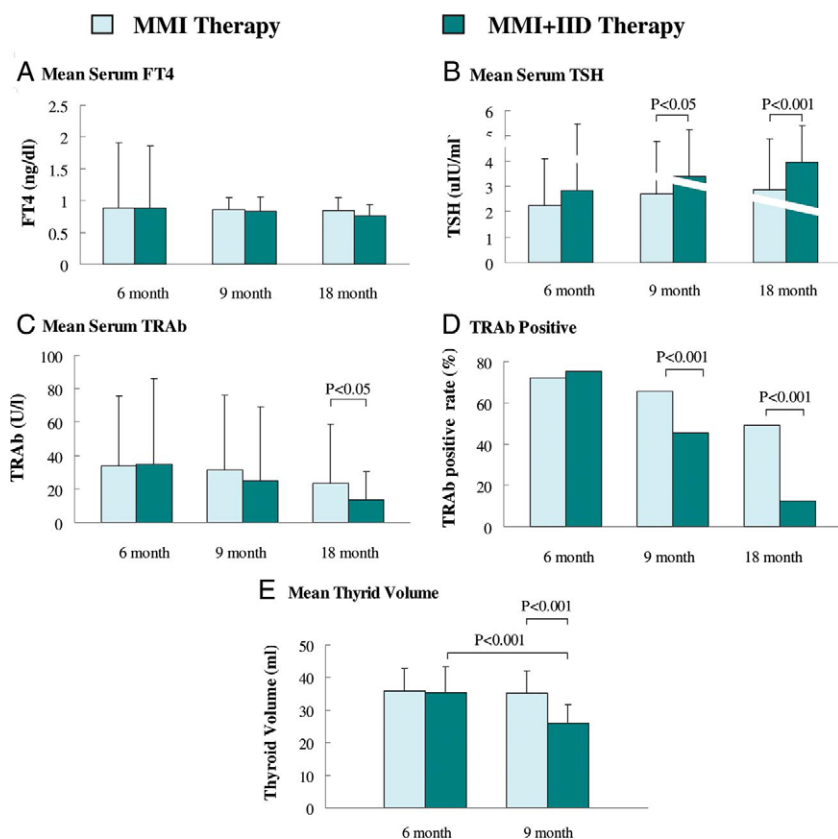
Figure 2, C and D, shows the course changes of the levels of serum TR-Ab and the TR-Ab positive rate. No difference was seen in the levels of serum TR-Ab between the two groups at months 6 and 9 ( $P > 0.05$ ). However, at month 18, the level of serum TR-Ab was significantly lower in the MMI+IID group than in the MMI group ( $13.5 \pm 17.05$  vs.  $23.54 \pm 34.95$  U/liter;  $P < 0.05$ ) (Fig. 2C). No statistically significant difference was observed in the TR-Ab positive rate between the two groups at month 6 ( $P > 0.05$ ). However, at months 9 and 18, the TR-Ab positive rates were significantly lower in the MMI+IID group than in the MMI group (at month 9,  $45.3$  vs.  $65.6\%$ ,  $P < 0.001$ ; at month 18,  $12.6$  vs.  $48.9\%$ ,  $P < 0.001$ ) (Fig. 2D).

Figure 2E shows the course change of thyroid volume. After 6 months of MMI treatment, there were still 47 patients (48.9%) with a thyroid goiter in the MMI group and 44 (46.3%) in the MMI+IID group. No difference was seen in thyroid volume between the two groups ( $35.96 \pm 6.86$  vs.  $35.38 \pm 7.76$  ml;  $P > 0.05$ ). At month 9, the thyroid volume decreased significantly in the MMI+IID group compared with month 6 ( $25.98 \pm 5.72$  vs.  $35.38 \pm 7.76$  ml;  $P < 0.001$ ) and was significantly lower than the MMI group ( $35.14 \pm 6.93$  ml;  $P < 0.001$ ). No statistically significant difference was observed in thyroid volume at month 9 compared with month 6 in the MMI group ( $P > 0.05$ ).

### Relapse of hyperthyroidism

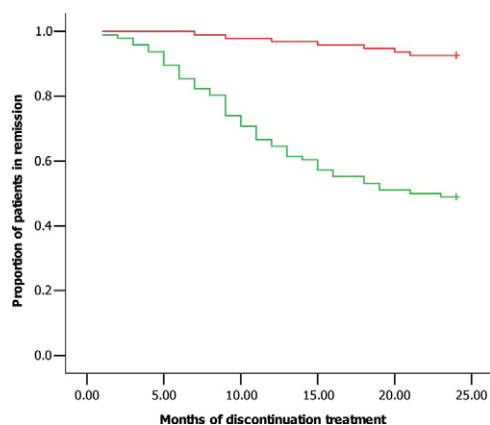
Two years after withdrawal of antithyroid therapy, 49 patients (51%) experienced relapse of overt hyperthyroidism in the MMI group, whereas only seven patients (7.2%) in the MMI+IID group did ( $P < 0.001$ ). There were five patients in MMI group and four patients in MMI+IID group who experienced subclinical hyperthyroidism during the 2-yr follow-up period. In the MMI group, relapse occurred in 14 patients (14.5%) within 6 months after withdrawal of the ATD, in 34 patients (35.4%) within the first year, and in 15 patients (15.6%) during the second year of follow-up. The mean time of relapse was 10.2 months. In the MMI+IID group, none of the patients experienced relapse within 6 months after withdrawal of the





**FIG. 2.** Changes of FT<sub>4</sub>, TSH, TRAb, and goiter size. A–C, Results of mean ( $\pm$ SD) for FT<sub>4</sub>, TSH, and TRAb levels during 18 months of treatment with MMI or IID+IMM in patients with GD. Bars correspond to SD of the mean. D, Results of the TRAb-positive rate during 18 months of treatment. E, Results of mean ( $\pm$ SD) value for thyroid volume after 6 and 9 months of treatment (47 patients with thyromegaly in MMI group and 44 in MMI+IID group).

ATD. The relapse occurred in three patients (3.1%) within the first year, and in four (4.2%) patients during the second year of follow-up. The mean time of relapse was 14.6 months (Fig. 3).



**FIG. 3.** Kaplan-Meier curves depicting the proportion of patients in the MMI group (red line;  $n = 96$ ) and in the MMI+IID group (green line;  $n = 95$ ) remaining in remission at various time intervals during the 2-yr follow-up period after discontinuation of treatment.

## Treatment side effects

ATD reactions were not common and were usually not severe enough to require discontinuation from the study. Seven patients developed a rash and/or itching, four patients complained of joint or muscle discomfort, seven patients noted a metallic taste, five patients had gastrointestinal complaints thought to be related to the medication, one developed jaw pain, two developed agranulocytosis, and four developed drug-induced hepatitis (one was severe, and the other three increased liver enzymes, but not more than two times the upper normal range). Of the three patients who discontinued due to drug reactions, two did so due to agranulocytosis, and one did so because of hepatitis.

Adverse reactions of intrathyroid injection were mild, and none of the patients were discontinued from the study. Most of the patients complained of mild pain and swelling in the site of injection, and these sensations usually lasted only for a few minutes. No severe bleeding, such as hematoma, was observed after the injection.

No overt systemic adverse reactions were found that were severe enough to require discontinuation from the study after IID therapy. Seven patients complained of headache, and three patients complained of dizziness after IID treatment. These symptoms usually lasted for 10 to 30 min, and it was difficult to differentiate whether they were caused by medication or intrathyroid injection. The level of fasting blood glucose did not increase significantly after IID treatment ( $5.14 \pm 0.71$  vs.  $5.31 \pm 0.82$  mmol/liter;  $P > 0.05$ ). None of the patients developed obvious manifestations of Cushing's syndrome after IID therapy or during the follow-up period.

## Discussion

GD affects nearly 0.5% of the population and is the underlying cause of 50 to 80% of cases of hyperthyroidism (20). ATD are still the main therapy for Graves' hyperthyroidism in a lot of regions, but the relapse rate is very high (51–68%) after withdrawal of antithyroid treatment (2). To reduce the relapse rate, some studies have tried to prescribe replacement T<sub>4</sub> either with the ATD treatment or after completion of antithyroid treatment. However, there

is no clear evidence supporting the efficacy of thyroid hormone supplementation after the initial treatment of GD with antithyroid medication (4, 21, 22). Therefore, the optimal medical therapy for Graves' hyperthyroidism remains a subject of debate. The objective of the present study was to explore an innovative regimen to decrease the relapse rate of hyperthyroidism after withdrawal of antithyroid therapy.

The present trial shows that the treatment with MMI combined with IID markedly reduced the relapse rate of hyperthyroidism after withdrawal of antithyroid therapy. The 2-yr cumulative relapse rate obtained in our study was 7.4% in the MMI+IID regimen and 51% in the MMI-alone regimen. The relapse rate in the MMI-alone treatment group was similar to some previous studies at 54–58%, with a follow-up of 2–4.3 yr after 12–18 months of treatment (23, 24).

The exact reason why glucocorticoid therapy can effectively decrease the relapse rate of hyperthyroidism is not known. ATD used in the treatment of hyperthyroidism due to GD possess an immunosuppressive effect in addition to its effect on thyroperoxidase (25, 26). After ATD therapy, some patients with GD achieved a long-term remission, and the mechanism behind the remission was suggested to be a direct immunosuppressive action of the ATD (27). On the other hand, many patients still experienced relapse after withdrawal of ATD. If immunosuppressive effects of ATD play an important role in remission of GD, the effects of ATD might be feeble. Glucocorticoid injection into the thyroid in our study might strengthen the immunosuppressive effects of MMI and induce a significant reduction in the relapse of GD.

In our trial, we selected a titration regimen for 18 months because longer follow-up data (2 to 5 yr after the completion of ATD therapy) showed no evidence to suggest that the block-replace therapy could reduce the relapse rate of GD when compared with the standard titration regimen. Furthermore, there was a significantly higher rate of drug withdrawal due to side effects in the block-replace regimen. Some evidence suggests that 12–18 months of drug therapy is more effective than a shorter duration (2).

Some previous studies have shown that high levels of FT<sub>4</sub> and TR-Ab at the onset of hyperthyroidism were potential predictors of relapse after therapy withdrawal (28, 29). Other parameters related to relapse, such as gender, age, and goiter size, are still controversial (23, 30, 31). In the present study, baseline characteristics, such as age, gender, serum FT<sub>4</sub> concentration, serum TR-Ab concentration, TR-Ab positive rate, and thyroid size, were not significantly different between the two groups, suggesting that the difference of relapse rate between the two groups

in our study might not be due to these parameters at the onset of hyperthyroidism. Furthermore, in the three treatment periods, the dosages of MMI were similar between the two groups, which might exclude the interference of the MMI regimen on the relapse of GD in the MMI+IID group.

Unlike some previous studies (16, 17), the levels of serum FT<sub>4</sub> did not significantly decrease in the MMI+IID group after IID treatment compared with the MMI group in our study. The reason for this result might be because the patients had been treated with MMI for 6 months and most of them achieved euthyroidism. Although FT<sub>4</sub> levels were not significantly different between the two groups after 18 months of treatment, the levels of TSH were markedly increased in the MMI+IID group compared with the MMI group. This finding might be due to the slightly lower FT<sub>4</sub> level in the MMI+IID group compared with the MMI group, although this result was not significant. Meanwhile, the serum TR-Ab level, the TR-Ab positive rate, and goiter size also decreased significantly in the MMI+IID group compared with the MMI group. Several previous studies have shown that TSH, TR-Ab, and goiter size at the end of antithyroid treatment were significantly linked to the relapse of hyperthyroidism and have been considered to be predictors of relapse of GD (4, 32).

The adverse effects of glucocorticoid treatment appear more likely after long-term treatment than after short-term treatment, even with high glucocorticoid doses. The adverse effects of glucocorticoids could be minimized by alternate-day therapy with less suppression of the hypothalamic-pituitary-adrenal axis. Although treatment with dexamethasone lasted for 3 months in our study, the interval of the treatment was relatively long, especially in the last month.

Considering the possibility of side effects caused by glucocorticoid therapy, we treated the patients with GD by interval IID combined with MMI. No obvious systemic adverse reactions were found in our study. Although some patients complained of mild pain and swelling in the site of injection, all of the patients could tolerate this therapy, and no patients dropped out due to the side effects of IID.

One limitation of our study is that the pathobiological and cytological changes of the thyroid were not observed after dexamethasone treatment. IID therapy is an innovative approach to the treatment of GD. The study of pathobiology and cytology may be helpful to elucidate the mechanism of dexamethasone in the reduction in the relapse of GD. Another limitation is that the study was not designed as a double-blind placebo-controlled study, and the effects of the injection procedure and psychological factors on the results of IID therapy might not be excluded. However, we believe that the large number of patients enrolled in this

study allowed a reasonable estimate of clinical benefit. The third limitation is that a prospective systematic way to evaluate the side effects should be done, although there were no patients who discontinued from the study due to side effects of IID; thus, the side effects might have been underestimated in our study.

In conclusion, a large amount of effort has been directed toward reducing the relapse of GD after medical therapy withdrawal. However, the optimal medical therapy for GD remains a subject of debate. Our finding provides an innovative approach to the treatment of GD. The IID might be helpful to the reduction in the relapse of GD.

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Address all correspondence and requests for reprints to: Xiaoming Mao, M.D., Professor, Department of Endocrinology, Affiliated Nanjing First Hospital, Nanjing Medical University, 68 ChangLe Street, Nanjing 210006, China. E-mail: maoxm@163.com.

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