Long-term Methimazole Therapy in Juvenile Graves’ Disease: A Randomized Trial

Fereidoun Azizi, MD,* Miralireza Takyar, MD, PhD,* Elham Madreseh, MSc,* Atieh Amouzegar, MD*

BACKGROUND AND OBJECTIVES: Recent studies show that long-term (LT) antithyroid drugs reduce relapse of hyperthyroidism in patients with Graves’ disease. Our objective was to evaluate the effectiveness and safety of LT methimazole treatment and to compare remission rates in Graves’ disease patients after LT and short-term (ST) therapy.

METHODS: In this randomized, parallel group trial, 66 consecutive patients with untreated juvenile Graves’ hyperthyroidism were enrolled. After a median 22 months of methimazole treatment, 56 patients were randomly assigned to either continue low-dose methimazole treatment (n = 24, LT group) or to discontinue treatment (n = 24, ST group). Twenty-four patients in LT group completed 96 to 120 months of methimazole treatment. Patients in both groups were managed for 48 months after discontinuation of treatment.

RESULTS: Except for 3 cases of cutaneous reactions, no other adverse events were observed throughout 120 months of methimazole therapy. Serum free thyroxine, triiodothyronine, thyrotropin, and thyrotropin receptor antibody remained normal, and the required daily dosage of methimazole was gradually decreased from 5.17 ± 1.05 mg at 22 months to 3.5 ± 1.3 mg between 96 and 120 months of treatment (P < .001). Hyperthyroidism was cured in 92% and 88% of LT patients and in 46% and 33% of ST patients, 1 and 4 years after methimazole withdrawal, respectively.

CONCLUSIONS: LT methimazole treatment of 96 to 120 months is safe and effective for treatment of juvenile Graves’ disease. The four-year cure rate of hyperthyroidism with LT methimazole treatment is almost 3 times more than that of ST methimazole treatment.

WHAT’S KNOWN ON THIS SUBJECT: Long-term antithyroid drug treatment reduces the relapse rate of hyperthyroidism in patients with Graves’ disease.

WHAT THIS STUDY ADDS: Long-term methimazole treatment of juvenile Graves’ hyperthyroidism is a safe and effective treatment option.


*Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; and *Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
Hyperthyroidism is not a common disease among children and adolescents, and in a majority of cases it is caused by diffuse toxic goiter, which accounts for only 1% to 5% of all patients with Graves’ disease. There is no definitive cure for this disease; that is, sustained euthyroidism cannot be achieved for all patients by any of the 3 therapeutic options available: antithyroid drugs (ATDs), surgery, and radiiodine treatment. Moreover, potential complications are associated with all 3 treatment modalities.

ATDs, frequently chosen as the initial treatment of diffuse toxic goiter for children and adolescents in most countries, are associated with side effects and a high relapse rate (>70% after 2 years of treatment) in children. Therefore, many children and adolescents eventually receive ablative therapy. Radioiodine therapy induces remission in a significant proportion of patients; however, a great majority remains dependent on thyroid hormones for their whole lives, resulting in concerns about the oncogenic and genetic damage in young patients after this therapy. Subtotal thyroidectomy can also achieve high rates of remission, although complications such as hypoparathyroidism and laryngeal nerve damage may occur.

In a few studies, it has recently been reported that long-term (LT) treatment with ATDs is effective and safe in children and adolescents. In a more recent meta-analysis, it was shown that this mode of treatment has low rates of complications and is associated with higher remission rates compared with short-term (ST) therapy.

In this study, we report a randomized clinical trial to analyze the effects of long-term methimazole treatment in young patients with Graves’ disease. We also aim to compare the rate and variables associated with remission of hyperthyroidism in adolescents undergoing LT and ST methimazole therapy.

METHODS

This randomized, parallel group trial was conducted between May 2000 and March 2017 in Tehran, an area of severe iodine deficiency. The protocol was approved by the ethics committee of the Research Institute for Endocrine Sciences, and informed consent was obtained from all patients or their parents.

Untreated children and adolescents with diffuse toxic goiter were included in this prospective study. All patients were treated with methimazole for durations ranging between 18 and 24 months. They were then randomly assigned in a 1:1 ratio to continue methimazole (LT group) or to discontinue methimazole treatment (ST group).

Patients

Those with the first episode of hyperthyroidism and without previous treatment with ATDs, radiiodine, or surgery were considered eligible. Inclusion criteria were as follows: age ≤18 years, thyrotropin <0.4 mU/L, free thyroxine (FT4) >23 pmol/L and/or triiodothyronine (T3) >200 ng/dL, and no history or evidence of comorbidity. The only key exclusion criterion included mental dysfunction. Sixty-six children and adolescents with diffuse toxic goiter met the criteria and were enrolled in the study.

Procedures

All patients had diffuse goiter without nodularity on palpation and diffuse uptake of radioisotope in thyroid scintigraphy. Baseline clinical characteristics, including age, sex, presence or absence of orbitopathy, goiter grade, and serum levels of FT4, T3, and thyrotropin, were documented. Goiter was graded according to World Health Organization criteria, and orbitopathy was classified as “absent” or “present,” according to Werner’s classification. Venous blood samples were drawn before treatment and at each visit thereafter for measurement of serum, FT4, T3, and thyrotropin. Determination of thyrotropin receptor antibody (TRAb) was performed at baseline, at the end of methimazole treatment, at the time of recurrence of hyperthyroidism, and 4 years after discontinuation of methimazole.

All patients received 0.25 to 0.5 mg/kg per day of methimazole in 2 divided doses in the first month. Using the titration method, methimazole was tapered to maintain serum FT4 concentrations between 10 and 22 pmol/L and serum thyrotropin <5.06 mU/L. All patients were treated for 18 to 24 months (median: 22 months; mean: 20.7 ± 2.7) before random assignment. Patients and their parents were instructed to stop methimazole and to visit the physician if the child developed a sore throat, fever, or diffuse rash, which would need a complete blood count test and assessment of percentage of neutrophils. Three patients had side effects, 4 had relapse of hyperthyroidism, 1 became hypothyroid, and 2 left follow-up; these 10 patients (15%) were excluded from the study. The remaining 56 patients were assigned by simple random assignment (by using the table of random digits) into 2 groups. All patients received 18 to 24 months of methimazole treatment before random assignment. The ST group received no additional treatment and was followed for 48 months. On the basis of a previous study, which has been included in our review article, it was calculated that each additional year of ATDs in adolescents could increase remission rate by 14%; therefore, an additional
6 years were added to the current 2-year treatment scheduled, to obtain maximum effects. The LT group received methimazole treatment of a mean 109 ± 6 months (range: 96–120 months), after which the drug was discontinued, and they were managed for an additional 48 months.

Patients in the LT group were scheduled to receive methimazole treatment for at least 96 months but not over 120 months. In this group, 2 patients relapsed, 1 became hypothyroid, and 1 left follow-up. Four patients (of the ST group) also were lost to follow-up, leaving 24 patients in each group who completed their assigned course of methimazole treatment. After random assignment, all patients, whether in the ST or the LT group, were managed up for 48 months after discontinuation of methimazole. Patients were scheduled to be seen at 6, 9, 12, 18, and 24 months before random assignment and every 6 months thereafter until 48 months after methimazole discontinuation (Fig 1).

**Laboratory Measurements**

Serum fT4 and T3 were measured by radioimmunoassay, and serum thyrotropin was measured by immunoradiometric assay, both by using kits from Izotop (Budapest, Hungary). We measured TRAbs by immunoenzymometric assay kits from BioVendor Laboratory Medicine, Inc (Brno, Czech Republic) and DiaMetra (Milan, Italy). Interassay and intra-assay coefficients of variation for all tests were 8% and 10%, respectively. TRAb was defined as negative for values that were <1, gray zone for values between 1 and 1.5, and positive for values >1.5 IU/mL.

**Definitions**

Hyperthyroidism was considered as thyrotropin <0.4 mU/L in combination with fT4 >23 pmol/L and/or T3 >200 ng/dL, whereas subclinical hyperthyroidism was defined as thyrotropin <0.4 mU/L with serum fT4 and T3 within normal ranges. Overt hypothyroidism was considered as thyrotropin above the upper limit of normal, that is, >5.06 mU/L for a Tehranian population, in combination with fT4 <9 pmol/L. Subclinical hypothyroidism was defined as thyrotropin >5.06 mU/L, with normal serum fT4 and T3 concentrations.21

**Study Outcomes**

The primary outcome in both groups was a relapse in hyperthyroidism after the discontinuation of methimazole. The secondary key outcomes were the occurrence of both clinical and subclinical hypo-and hyperthyroidism during LT methimazole treatment.

**Safety**

Safety was assessed on the basis of adverse events that occurred during treatment. Expected adverse events included agranulocytosis, skin reactions, hepatic side effects, and arthralgia.

**Statistical Analysis**

We based the sample size for the trial on our primary aim in the study to detect a difference of 10% in relapse rate between the LT and ST ATD treatment groups, with a type 1 error (α error) of .05 (1 sided) and a power of at least 80. Baseline and outcome variables were compared with the use of Mann-Whitney, χ², and Fisher’s exact tests. Wilcoxon signed ranks test was used to compare means at 18 to 24 months of treatment and at the end of 96 to 120 months. Time-to-treatment failure (relapse of Graves’ hyperthyroidism after the end of ATD therapy) was documented using a Kaplan-Meier curve. Cox proportional hazards models were performed to assess the strength of the association between the length of remission and the clinical and laboratory variables. We evaluated the predictive values for relapse of Graves’ hyperthyroidism after ATD...
withdrawal using both univariate and multivariate analyses. A value of \( P < .05 \) was considered significant. Statistical analysis was performed using SPSS 9.05 software (SPSS Inc, Chicago, IL).

**RESULTS**

**Study Patients**

In Table 1, we show patients’ characteristics at baseline in 48 patients who completed all phases of study. Age, sex, goiter degree, percentage of patients with ophthalmopathy, and serum concentrations of \( fT4 \), \( T3 \), and thyrotropin were not statistically different at entry between the ST and LT groups. In addition, mean serum \( fT4 \), \( T3 \), thyrotropin, and TRAb concentrations and methimazole dosage required to maintain euthyroidism did not differ between the 2 groups after completion of a median of 22 months of methimazole therapy.

In Fig 2, we illustrate changes in \( fT4 \), \( T3 \), and thyrotropin concentrations and methimazole dosage during 96 to 120 months of LT methimazole treatment in 24 children and adolescents with hyperthyroidism. Of interest was the gradual decrease in daily dosage of methimazole after the original 18 to 24 months of treatment. Mean daily dose of methimazole was 5.17 ± 1.05 mg at 22 months and 3.5 ± 1.3 mg at the end of 96 to 120 months of methimazole treatment (\( P < .001 \)). Mann-Whitney and Fisher’s exact test, or \( X^2 \) test, were used for continuous and categorical variables, respectively (no significant differences were found). Serum thyrotropin concentration was <0.1 mU/L in all patients in both groups at baseline.

**Primary Outcomes**

After 48 months of methimazole withdrawal, the primary outcome, which was a relapse of hyperthyroidism, was detected in 16 patients (67%) in the ST group and in 3 patients (12.5%) in the LT group (\( P < .001 \)). In Fig 3, we show the Kaplan-Meier curve for relapse of hyperthyroidism. The number of patients in the ST group who had a relapse at each time point after methimazole discontinuation was as follows: 10 within the first 6 months, 3 from 6 to 12 months, 2 in the second year, and 1 in the third year. Relapse of hyperthyroidism in 3 patients in the LT group occurred at 6, 11, and 44 months after discontinuation of methimazole. Hyperthyroidism was cured in 92% and 88% of patients in the LT methimazole group and in 46% and 33% of patients in the ST methimazole group 1 and 4 years after methimazole withdrawal, respectively. Log-rank test showed that the relapse rate during the time after methimazole withdrawal was lower in patients receiving methimazole for long-term (\( P < .0001 \)).

**Factors Related to Relapse Rate**

In the univariate analyses, duration of methimazole therapy and serum FT3 level were the factors that affected the outcome of methimazole treatment. In multivariate analyses, serum FT3 level was no longer an important factor, and only duration of methimazole treatment was a factor that affected the outcome (Table 2).

**Safety and Adverse Events**

During the first 6 months of methimazole treatment, 3 adolescents experienced cutaneous reactions; 2 were treated with antihistamines, and 1 was shifted from methimazole to propylthiouracil. No serious complications, such as agranulocytosis, occurred. During LT treatment with low-dose methimazole, we observed no adverse events related to methimazole treatment.

**DISCUSSION**

In this study, we show that LT methimazole treatment of juvenile Graves’ hyperthyroidism is both effective and safe. It is also demonstrated that management of hyperthyroidism with methimazole

---

**TABLE 1 Clinical and Laboratory Characteristics of Patients With Graves’ Disease According to Treatment Regimen at the Baseline and After 18–24 Months of Methimazole Treatment (Time of Randomization)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Methimazole ST (n = 24)</th>
<th>Methimazole LT (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in y, mean ± SD</td>
<td>15.67 ± 2.65</td>
<td>15.25 ± 2.85</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>20 (83.3)</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>Baseline values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves’ orbitopathy, No. (%)</td>
<td>7 (29.2)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Goiter grade, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15 (62.5)</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>2</td>
<td>6 (25)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>3</td>
<td>3 (12.5)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>( fT4 ) in pmol/L, mean ± SD</td>
<td>40.9 ± 8.4</td>
<td>40.2 ± 6.4</td>
</tr>
<tr>
<td>( T3 ) in ng/dL, mean ± SD</td>
<td>434 ± 155</td>
<td>446 ± 90</td>
</tr>
<tr>
<td>Thyrotropin in IU/mL</td>
<td>All &lt;0.1</td>
<td>All &lt;0.1</td>
</tr>
<tr>
<td>TRAb in IU/L, mean ± SD</td>
<td>15.7 ± 2.7</td>
<td>16.1 ± 4.21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data after 18–24 mo of methimazole treatment, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>( fT4 ) in pmol/L</td>
</tr>
<tr>
<td>( T3 ) in ng/dL</td>
</tr>
<tr>
<td>Thyrotropin in IU/mL</td>
</tr>
<tr>
<td>TRAb in IU/L</td>
</tr>
<tr>
<td>Maintenance dose in mg</td>
</tr>
</tbody>
</table>
for long-term offers a higher chance of remission than ST methimazole treatment after discontinuation of medication; 92% and 88% of patients cured in our results within 1 and 4 years after methimazole withdrawal, respectively. The rate of adverse events after the initial 18 to 24 months of methimazole therapy was nil, indicating that LT therapy is an effective and safe management for juvenile Graves' hyperthyroidism.

Graves' disease is accompanied by repeated episodes of remission and relapse of thyroid hyperfunction for many years. Of the 3 modalities of treatment available for this disease, only ATDs could restore normal homeostasis of the hypothalamic pituitary thyroid axis. However, remission takes a long time to achieve, and it is not sustained in many patients, as a majority of them have recurrence after the customary 18 to 24 months of treatment.6,22,23 In recent studies, it has been suggested that LT treatment with antithyroid medications is effective and safe both in adults24,25 and in children and adolescents.15,16 In a recent systematic review and meta-analysis, researchers illustrated the superiority of LT over ST ATD treatment.17

ATDs are reported to have direct immunosuppressive action on both humoral and cellular immunity26; however, it was pointed out in some evidence that the main reason behind such immunosuppression could be the restoration of euthyroidism in patients with hyperthyroidism rather than direct effects on the immune response, which in turn plays a major role in the remission of Graves' disease.27 This led to the hypothesis that through direct immunosuppression and/or restoration of the euthyroid state, continuous LT ATD therapy is important in the maintenance of a normal immune system, prevention of autoimmune dysfunction and recurrence of hyperthyroidism,26,28 and overall beneficial effects in the management of Graves' hyperthyroidism. In the

FIGURE 2
Trend of serum fT4, T3, and thyrotropin and methimazole dosages during 96 to 120 months of LT methimazole treatment in 24 adolescents with hyperthyroidism.
result of this study, it was demonstrated that LT methimazole treatment results in a relatively complete cure of juvenile Graves’ hyperthyroidism. The findings of the present study support those of several retrospective studies and 1 prospective study in which it was demonstrated that duration of medical treatment may be a predictive marker of relapse in juvenile hyperthyroidism.

Family history, young age, large goiter, severity of biochemical hyperthyroidism, serum TRAb concentration at onset, and the end of treatment have all been considered as predictive factors for relapse of Graves’ disease in children and adolescents. Because of the small number of relapses after LT methimazole treatment, we could not evaluate these predictive factors. However, few factors were associated with relapse of hyperthyroidism in the ST methimazole group.

In several large cohort studies, increased mortality from vascular causes in radioiodine-treated hyperthyroid adults has been shown. In addition, ablative treatments cause hypothyroidism and require the subsequent administration of levothyroxine throughout the patient’s life; however, in 1 study, it was shown that levothyroxine treatment is not always successful, and 30% to 40% of these patients may have subclinical hypothyroidism. Considering the low frequency of side effects in patients on small doses of ATDs and the fact that the clinical impression is that euthyroid patients on ATDs have fewer complaints than those taking levothyroxine, we support the recommendation of LT methimazole treatment to all juvenile hyperthyroid patients. In addition, continuous methimazole administration causes fewer events of subclinical hypothyroidism and dyslipidemia, and patients on LT methimazole therapy have better neuropsychological test results compared with levothyroxine-treated patients with radioiodine-induced hypothyroidism.

The strengths of this study are that we report the longest follow-up for continuous methimazole therapy in juvenile Graves’ patients in an iodine-replete region, our study is prospective in design, and we compare the remission rate of LT versus ST methimazole treatment of 4 years after drug withdrawal. However, our study does have a few

### Table 2 Cox Regression Analysis of the Hyperthyroidism Relapse After Methimazole Withdrawal

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.119 (0.034–0.412)</td>
<td>0.01</td>
<td>0.104 (0.021–0.529)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sex</td>
<td>0.821 (0.298–3.162)</td>
<td>0.885</td>
<td>1.305 (0.345–4.932)</td>
<td>0.65</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.952 (0.810–1.12)</td>
<td>0.555</td>
<td>0.908 (0.749–1.10)</td>
<td>0.324</td>
</tr>
<tr>
<td>Goiter grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.982 (0.358–2.616)</td>
<td>0.970</td>
<td>1.271 (0.424–3.810)</td>
<td>0.668</td>
</tr>
<tr>
<td>3</td>
<td>0.617 (0.080–4.747)</td>
<td>0.643</td>
<td>0.422 (0.053–3.398)</td>
<td>0.418</td>
</tr>
<tr>
<td>fT4, pmol/L</td>
<td>0.852 (0.661–1.098)</td>
<td>0.215</td>
<td>0.907 (0.681–1.208)</td>
<td>0.505</td>
</tr>
<tr>
<td>T3, ng/dL</td>
<td>1.043 (1.012–1.074)</td>
<td>0.006</td>
<td>1.023 (0.989–1.059)</td>
<td>0.188</td>
</tr>
<tr>
<td>Thyrotropin, mU/L</td>
<td>0.802 (0.517–1.246)</td>
<td>0.327</td>
<td>0.885 (0.482–1.652)</td>
<td>0.717</td>
</tr>
<tr>
<td>Maintenance dose, mg</td>
<td>1.473 (0.893–2.429)</td>
<td>0.129</td>
<td>0.804 (0.369–1.750)</td>
<td>0.582</td>
</tr>
</tbody>
</table>

Thyrotropin, fT4, T3, and maintenance dose at time of medication withdrawal. ST treatment groups, female sex, and goiter grade 1 were considered as reference.

a Univariate analyses.

b Multivariate analyses.
limitations. First, the number of patients enrolled does not allow subscale comparison, in particular for predictive factors of relapse, after LT treatment. Second, the findings are from patients in a west Asian country and may not be generalizable to other populations. Third, the study was not double blinded; therefore, selection, attainment, and other forms of biases may have influenced the results.

CONCLUSIONS

LT methimazole treatment is a safe and effective treatment option for juvenile Graves’ hyperthyroidism, having higher recovery rates than the ST treatment.

ACKNOWLEDGMENTS

We thank Ms Niloofar Shiva for the critical editing of English grammar and syntax in the manuscript and Ms Tahereh Fakhimi for typing the manuscript.

ABBREVIATIONS

ATD: antithyroid drug
FT4: free thyroxine
LT: long-term
ST: short-term
TRAb: thyrotropin receptor antibody

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES


19. Perez C, Scrimshaw NS, Munoz JA. Technique of endemic goitre surveys.


Long-term Methimazole Therapy in Juvenile Graves' Disease: A Randomized Trial
Fereidoun Azizi, Mirlireza Takyar, Elham Madreseh and Atieh Amouzegar
Pediatrics 2019;143;
DOI: 10.1542/peds.2018-3034 originally published online April 30, 2019;
Long-term Methimazole Therapy in Juvenile Graves' Disease: A Randomized Trial
Fereidoun Azizi, Miralireza Takyar, Elham Madreseh and Atieh Amouzegar
Pediatrics 2019;143;
DOI: 10.1542/peds.2018-3034 originally published online April 30, 2019;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/143/5/e20183034