Practical Treatment with Minimum Maintenance Dose of Anti-Thyroid Drugs for Prediction of Remission in Graves’ Disease

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Abstract. Although many researchers have reported clinical and laboratory parameters for prediction of remission in Graves’ disease during or after anti-thyroid drug therapy, there is no reliable one to assure the complete remission. We prospectively examined a practical therapy with minimum maintenance dose of anti-thyroid drugs for prediction of remission in Graves’ disease. Fifty-seven patients with Graves’ disease were treated with anti-thyroid drugs at the initial dose of 30 mg/day of methimazole (MMI) or 300 mg/day of propylthiouracil (PTU). Then, doses were gradually decreased, and finally discontinued when the patients were able to maintain euthyroid (normal FT4 and TSH) for at least 6 months with the minimum maintenance dose (MMI 5 mg every other day or PTU 50 mg every other day). After discontinuation of drugs, FT4, FT3, TSH and TSH-binding inhibitory immunoglobulin (TBI) were measured every one to two months for the first 6 months and every 3-4 months for the next 18 months to confirm continuous remission. After 2 years of drug cessation, 46 (81%) of 57 patients were in remission and the other 11 patients had relapsed into thyrotoxicosis. At the time of drug discontinuation, the serum concentration of FT4, FT3 and TSH, titers of anti-thyroglobulin antibodies and anti-thyroid microsomal antibodies, goiter size were not different between the remission and relapse groups. At the time of drug cessation, the activities of TBI and thyroid-stimulating antibodies (TSAb) overlapped between the two groups, although they were significantly lower in the remission group than in the relapse group (p<0.01). Forty percent (4/10) of TBI positive patients and 71% (23/32) of TSAb positive patients continued to be in remission. On the other hand, thyrotoxicosis relapsed in 5 (11%) of 47 TBI negative and 2 (8%) of 25 TSAb negative patients. These data indicate that minimum maintenance therapy to keep euthyroid (normal FT4 and TSH) for 6 months is a practical measure for 81% prediction of remission in Graves’ disease. The measurement of TBI or TSAb gave little additional information for predicting remission.

Key words: Graves’ disease, Anti-thyroid drug, Treatment, Remission, Anti-TSH receptor antibody

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ANTITHYROID drugs (ATD), such as methimazole (MMI) and propylthiouracil (PTU), have long been used for the drug therapy of Graves’ disease. A major clinical problem of ATD therapy is that there is no reliable way to predict the remission [1, 2]. Many clinical and laboratory parameters, such as TRH test [3, 4], T3 suppression test [5-7], goiter size [8, 9], technetium-99m thyroid uptake [10], serum thyroglobulin [11], T3/T4 ratio [12] or FT3/FT4 ratio [13], have been examined for prediction of remission. However, the actual remission rate in the patients evaluated with one of the above markers was between 60 and 80%. Antithyroid autoantibodies, especially TBI and TSAb, which are the main pathogenic factor causing Graves’ thyrotoxicosis, have also been reported as predictive parameters [8, 9, 14]. Using these parameters many studies reported that remission was predicted in about 80% of the patients. On the contrary, some other studies reported TBI or TSAb was not a good marker for predicting remission [15, 16], although it was useful for predicting the relapse of thyrotoxicosis. Combining the parameters mentioned above, the remission rate improved to 80 to 90%. Some parameters for cellular
immunity have been reported to be more useful for prediction of remission [9], but not suitable for clinical use. The measurement of many parameters at the same time is not practical, especially for cost-effectiveness. Several studies reported that the remission rate was improved by long-term ATD treatment compared with short-term treatment [17, 18], although there are controversial reports [19, 20]. In cases with intractable disease, the long-term administration of ATD for 8–21 years has been recommended [21].

In this study we prospectively examined for the practical measure of prediction of remission with minimum maintenance therapy using ATD.

Materials and Methods

Patients

We studied 57 patients (mean age, 48.1 years old; 13 men and 44 women) with Graves’ disease who attended our thyroid clinic. The ATD therapy was started with MMI 30 mg/day or PTU 300 mg/day and then ATD dose was decreased to 20 mg/day or 200 mg/day, respectively when serum FT4 and FT3 values decreased into normal range. ATD dose was further decreased gradually (15 mg→10 mg→5 mg) when serum FT4 and TSH were kept in normal for 3 to 6 months or when TSH value was increased over normal range. Last patients were kept in euthyroid on the minimum maintenance dose (MMI 5 mg every other day or PTU 50 mg every other day). Finally, we discontinued ATD medication when their serum FT4 and TSH had been kept at normal for six months. This observation period of six months with minimum maintenance dose was decided based on our previous study that up to 80% of patients relapsed into Graves’ thyrotoxicosis within 6 months after cessation of ATD (9). During minimum maintenance therapy, serum FT4, FT3, TSH and TBII were measured every month for at least 6 months. After discontinuation of ATD, FT4, FT3, TSH and TBII were measured every 1–2 months for the first 6 months and every 3–4 months for the next 18 months to confirm continuous remission. When patients had increased thyroid hormones and/or suppressed TSH during minimum maintenance therapy, the ATD dose was increased and we repeated the protocol of minimum maintenance therapy. During the two year observation period, they were considered to have a relapse of thyrotoxicosis when they had increased thyroid hormones and suppressed TSH. We regarded the patients as being in remission when they kept euthyroid (normal FT4, FT3 and TSH) for at least 2 years. Informed consent was obtained from all patients.

Measurements

The serum levels of FT4 and FT3 were measured using commercial radioimmunoassay kits (FT4: Eiken Chemical Co. Ltd., Tokyo, Japan. FT3: Ortho-Clinical Diagnostics, Amersham, UK) as previously described [22]. The serum TSH was measured by SPAC-S TSH kit (Daichi Radioisotope Laboratory Ltd., Tokyo, Japan) (February 1991–June 1993), Berilux TSH (Hoechst Japan, Tokyo, Japan) (July 1993–June 1995), Ab bead TSH kit EIKEN (Eiken Immunoochemical Laboratory, Tokyo, Japan) (July 1995–April 1999) and ECLusys TSH (Boehringer Mannheim, Roche Diagnostics K.K., Penzberg, Germany) (May 1999–now). The lower detection limit in each kit was 0.05, 0.04, 0.05 and 0.02 μU/ml, respectively. The normal reference range in each kit was 0.6–5.4, 0.6–3.7, 0.5–3.7 and 0.4–3.8 μU/ml, respectively. Anti-thyroglobulin antibody (TGA) and anti-thyroid microsomal antibody (MCPA) were measured by particle aggregation assay. TBII was measured using a commercial kit (TRAb; Baxter Travenol Co., Japan) and the cut-off value was 12% [22]. TSAb activity was measured by the activity to induce cAMP release from the rat thyroid cell line FRTL-5 as previously described. The normal cut-off value was below 140% [22].

Statistical analysis

For the comparison of various parameters between the groups of remission and relapse, the Mann-Whitney U test was used. A p value below 0.05 was considered significant.

Results

Of 57 patients with Graves’ disease, 46 (80.7%) patients maintained euthyroid for at least 2 years
after drug cessation and were considered to be in remission. The remaining 11 (19.3%) patients relapsed into thyrotoxicosis within 2 years. Nine of them relapsed within 8 months after withdrawal of ATD. The relapse rate after discontinuation of drugs was not related to the activities of TSAb at the time of drug cessation (data not shown). Clinical and laboratory data at the time of ATD discontinuation was shown in Table 1. Values of FT4, FT3, TSH and titers of TGPA or MCPA, and goiter size were not different between the two groups. The duration of ATD treatment was not different in the two groups.

There were obvious overlaps of TBI and/or TSAb activities at the time of drug cessation between the remission and relapse groups (Fig. 1), although there were significant differences between the two. The remission rate was 89% (42/47) for TBI negative patients and 92% (23/25) for TSAb negative ones. However, 40% (4/10) of TBI positive patients and 71% (23/32) of TSAb positive patients maintained remission after ATD cessation (Fig. 1). All patients with TBI more than 30% and/or TSAb more than 2000% relapsed into thyrotoxicosis.

**Discussion**

At the present time the most useful parameters for predicting remission of Graves’ disease are believed to be TBI and/or TSAb in combination with or without several other markers. The predictive value is reported to be 80 to 90% [8, 9, 14, 15]. In this study, the remission rate for TBI and/or TSAb negative patients was similar to that in the previous reports. However, without these markers, the remission rate of the patients in this study, wherein ATD treatment was simply discontinued after 6 month therapy with minimum maintenance dose, was 81%, which was not so different from those mentioned above.

According to our protocol, ATD was discontinued even when TBI and/or TSAb antibodies were positive, and acutely TBI was positive in 16% (10/57) and TSAb was positive in 56% (32/57) of the patients at the time of ATD cessation. The high activity of TSAb at the end of treatment has been reported to be useful for prediction of relapse [6–9] rather than remission. In our result, higher TSAb activity of more than 2000% was indicative of relapse. However, positive TSAb was not useful for prediction of relapse, since 71% of TSAb positive patients kept in remission. This means that about 70% of patients would have to futilely continue ATDs, if disappearance of TSAb was defined as a marker of ATD discontinuation. Thus, TBI and/or TSAb measurement cannot be recommended for prediction of remission, because it gives only a slightly more reliable guarantee than our simple practical approach.

In order to obtain the satisfactory condition of normal FT4 and TSH for at least 6 months under a minimum maintenance dose, it took considerable time in this study. However, the shortest duration

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**Table 1.** Clinical and laboratory data at the time of cessation of anti-thyroid drugs in patients with Graves’ disease

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 57)</th>
<th>Remission (n = 46)</th>
<th>Relapse (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.1 ± 10.2</td>
<td>48.8 ± 10.2</td>
<td>44.9 ± 10.1</td>
</tr>
<tr>
<td>Male/Female</td>
<td>13/44</td>
<td>12/34</td>
<td>1/10</td>
</tr>
<tr>
<td>FT4 (ng/dl)</td>
<td>1.17 ± 0.17</td>
<td>1.17 ± 0.16</td>
<td>1.15 ± 0.19</td>
</tr>
<tr>
<td>FT3 (pg/ml)</td>
<td>3.78 ± 0.52</td>
<td>3.76 ± 0.55</td>
<td>3.89 ± 0.47</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>1.94 ± 1.11</td>
<td>2.06 ± 1.14</td>
<td>1.46 ± 0.84</td>
</tr>
<tr>
<td>TBI (%)</td>
<td>9.1 ± 10.9</td>
<td>6.3 ± 5.1</td>
<td>20.9 ± 18.8*</td>
</tr>
<tr>
<td>TSAb (%)</td>
<td>549 ± 1185</td>
<td>186 ± 157</td>
<td>2066 ± 2150*</td>
</tr>
<tr>
<td>TGPA (2×100)</td>
<td>3.27 ± 2.12</td>
<td>3.30 ± 2.20</td>
<td>3.00 ± 1.41</td>
</tr>
<tr>
<td>MCPA (2×100)</td>
<td>5.63 ± 2.47</td>
<td>5.58 ± 2.51</td>
<td>5.88 ± 2.42</td>
</tr>
<tr>
<td>Goiter size (cm)</td>
<td>3.68 ± 0.56</td>
<td>3.69 ± 0.56</td>
<td>3.69 ± 0.63</td>
</tr>
<tr>
<td>Duration of treatment (months)</td>
<td>71.0 ± 37.7</td>
<td>73.5 ± 38.8</td>
<td>60.3 ± 32.2</td>
</tr>
</tbody>
</table>

Data indicate mean ± SD.

Significantly different from remission group at p<0.01 (*).
of drug administration was 12 months in this study. Therefore we could apply this protocol to every patient and easily controllable patients would accordingly have a shorter period of drug therapy. On the other hand, intractable cases would require longer duration of more than 8 years, as in the cases reported by Shizume [21].

We are now using a sensitive TSH assay from which the normal value of serum TSH is clearly measurable, hence we do not need the TRH test for evaluation of complete euthyroid condition.

In conclusion, a simple protocol for discontinuing ATD when patients have maintained euthyroid for 6 months with a minimum maintenance dose was an effective and inexpensive approach in Graves' disease. When using this protocol, measurement of TBII or TSAβ gave little additional information for prediction of remission in Graves' disease.

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References


