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Predictive factors for recurrence in patients with Graves' Disease following treatment with methimazole

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ABSTRACT

Graves' disease (GD) contributes for 60–80% of all hyperthyroidism. Methimazole is the first line drug and most commonly used as antithyroid drug (ATD). However, the relapse rate following ATD therapy is 40–50%. The aimed of this study was to evaluate long-term ATD treatments and to identify prognostic factors that contribute to GD recurrence. A total of 46 GD patients who referred to the Endocrinology Clinic, Dr. Sardjito General Hospital, Yogyakarta between January 2016 and December 2018 with thyrotropin receptor antibody (TRAb) tested and treated with methimazole were included in this study. Size of goiter was measured based on WHO grading system and eye syndrome based on NOSPEC score system. Patients were classified into recurrence and remission groups based on TRAb evaluation at 12 month following treatment. Result of thyroid hormone level (FT4) and subject characteristic as predictive factors observed at 3-, 6- and 12-month post-treatment were compared and analyzed. Among 46 patient involved in this study, 23 patients demonstrated remission of hyperthyroidism based on TRAb evaluation at 12-month. The size of thyroid at onset of disease in 30 (65%) patients was grade 2 or above ($p<0.05$). Free FT4 levels at the end of observation (12 month) was 1.9±0.6 ng/dL in recurrent and 1.4±0.5 ng/dL in remission group ($p<0.05$). TRAb levels at early of study was higher in the recurrent group ($p<0.05$). Logistic regression analysis demonstrated that thyroid size, FT4 level, and TRAb at diagnosis were associated with recurrencies. In conclusion, GD patients with large thyroids size, high TRAb levels, and high FT4 level at the onset of disease tended to fail to respond to ATD and were associated with recurrence incidence.

ABSTRAK

Penyakit Graves (*Graves Disease*/GD) berkontribusi terhadap 60-80% semua kejadian hipertiroid. Methimazole adalah obat pilihan pertama dan paling sering digunakan sebagai obat antitiroid. Namun, tingkat kekambuhan setelah terapi masih tinggi yaitu 40-50%. Tujuan penelitian ini adalah untuk mengkaji keberhasilan terapi antitiroid jangka panjang dan mengidentifikasi faktor prognostik yang berkontribusi pada kekambuhan GD. Sebanyak 46 pasien GD yang dirujuk ke Klinik Endokrinologi - Rumah Sakit Umum Pusat Dr. Sardjito antara Januari 2016 dan Desember 2018 dan telah memiliki data pemeriksaan antibodi reseptor tirotropin (TSH receptor antibody/TRAb) dan mendapatkan terapi dengan methimazole dilibatkan dalam penelitian ini. Ukuran struma diukur berdasarkan sistem penilaian WHO dan sindrom mata berdasarkan sistem skor NOSPEC. Pasien diklasifikasikan ke dalam kelompok rekuren dan remisi berdasarkan evaluasi TRAb pada 12 bulan setelah perawatan. Hasil pemeriksaan dari kadar hormon tiroid (FT4) dan karakteristik subjek sebagai faktor prediksi diamati pada 3-, 6- dan 12-bulan pasca-pengobatan dan dibandingkan serta dianalisis. Dari 46 pasien yang terlibat penelitian, 23 pasien menunjukkan remisi hipertiroidisme berdasarkan evaluasi TRAb setelah 12 bulan terapi. Ukuran kelenjar tiroid pada awal timbulnya penyakit sebanyak 30(65%) pasien memiliki nilai skor kelas 2 atau lebih ($p<0,05$). Kadar FT4 pada akhir pengamatan (12 bulan) adalah 1,9±0,6 ng/dL pada kelompok rekuren dan 1,4±0,5 ng/dL pada kelompok remisi ($p<0,05$). Kadar TRAb pada awal studi lebih tinggi pada kelompok rekuren ($p<0,05$). Analisis regresi logistik menunjukkan bahwa ukuran tiroid, kadar FT4, dan TRAb pada saat diagnosis dikaitkan dengan kejadian rekurensi. Dapat disimpulkan, pasien GD dengan ukuran kelenjar tiroid besar, kadar TRAb tinggi, dan tingkat FT4 yang tinggi pada awal diagnosis penyakit cenderung gagal merespons terapi ATD dan dikaitkan dengan kejadian rekurensi.

Keywords:
Graves' disease;
recurrence;
antithyroid drugs;
predictive factors;
methimazole;

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INTRODUCTION

Graves' disease (GD) is among the most prevalent organ specific autoimmune diseases. It is the most common cause of hyperthyroidism worldwide, about 6080% of all thyrotoxicosis cases.[1] Graves is an autoimmune disease caused by the presence of antibodies called as TRAb (TSH receptor antibody) that are active against TSH receptors, thus stimulating the glands to synthesize and secrete thyroid hormones excessively. The causes of this disease can be familial and associated with other autoimmune diseases.[2] TRAb examination has 99% sensitivity and specificity for Graves' disease. This examination also helps diagnose PG in patients with struma nodular that appear simultaneously.[3]

The main mechanism of intratiroidal anti-thyroid drugs for inhibition of thyroid hormone synthesis competes with residues of thyroglobulin tyrosine for iodium from thyroid peroxidase (TPO)-catalyzed, thus causing a decrease amount of mono- and diiodotyrosine. In addition, another mechanism is to cause a relationship disorder between TPO-catalyzed and iodotyrosine to synthesis thyroid hormones, namely triiodothyronine (T3) and tetraiodothyronine (T4).[4] The antithyroid drug as methimazole (MMI, called thiamazole in US) predominantly appears to affect B cells and possibly accessory cell function. The ability of thionamide therapy to directly affect the immunological outcomes of GD has been supported by previous *in vitro* and *in vivo* experimental evidence.[5]

A previous study has revealed that MMI dose, pretreatment serum T3 levels, and goiter size were the major determinants of GD patients' therapeutic response to MMI.[3] By analyzing the factors affecting GD relapse, the efficacy of ATD as a treatment for GD, and the probability of recurrence of GD hyperthyroidism following the withdrawal of ATD therapy, therapeutic strategies for the treatment of GD may be improved.[2]

The present study was conducted to observe the relapse rate of patients with GD receiving longterm (12 months) treatment with ATD and to evaluate the predictive factors that affect the recurrence of hyperthyroidism in GD.

MATERIALS AND METHODS

Patients

The present study investigated patients with newlydiagnosed GD who were referred to the Endocrinology Clinic, at Dr. Sardjito General Hospital, Yogysakarta, Indonesia. A total of 46 patients with GD who were referred to the Endocrinology Clinic between January 2016 and December 2018. Patients who underwent the TRAb tests and treated with methimazole were included in this study.

Protocol of study

Following treatment and observation, patients were classified into remission and recurrent groups based on TRAb evaluation at 12 months following treatment. Various prognostic factors were analyzed and compared, including patient age, gender, size of thyroid prior to and following treatment, thyroid hormone levels, and states of

thyrotropin suppression were observed at 3-, 6- and 12-month post-treatment.

Diagnosis of GD based on symptoms of thyrotoxicosis and elevated free thyroxine (FT) 4 levels with low TSH and TRAb. The goiter was classified into three grades according to the World Health Organization (WHO) classification of goiter and eye syndrome as ophthalmopathy based on NOSPEC score system.[6,7]

All patients were administered methimazole daily at a starting dose of 1030 mg with followup visits at 2-4 weeks, followed by once every month and a titration regimen for 12 months. Clinical presentation and hormone level (FT4, TSH) were used to determine the titration dose. The TRAb levels and thyroid volume were measured at 12month intervals. If euthyroidism was achieved, which was defined as the elimination of the majority of hyperthyroidism symptoms and restored serum levels of TSH and FT4, pharmacological therapy was gradually adjusted and a continued dose of MMI was administered in order to maintain euthyroidism.

Remission was defined as the state when euthyroidism, demonstrated by normal ranges of FT4 and TSH levels, was achieved following the withdrawal of antithyroid drugs for 3 months and TRAb levels was converted to normal range. Relapse was defined as the state when clinical symptom and hyperthyroidism was detected at any time following treatment with ATD. Recurrence subject was defined when hyperthyroidism based on clinical symptom and laboratory result still occurred following the termination of ATD treatment.

A patient record was completed for each patient, including age, gender, duration of treatment, dose of ATDs administered, estimated volume of thyroid, relapse of disease status during and after treatment, duration of followup of serum TSH, FT3, and FT4 levels, and TRAb levels at the initiation and termination of treatment (12 months).

Statistical analysis

Data were presented as mean ± standard deviation (SD) or frequency and analyzed using t test or chi square. Logistic regression analysis was used to evaluate the factors affected clinical outcomes. A p value < 0.05 was considered significant.

RESULTS

Eleven patients were male and 35 patients were female. The mean age was 42±11 y.o. and the follow-up was 21±4.8 months. Following long-term treatment, 23 subjects demonstrated remission of hyperthyroidism based on TRAb evaluation at 12-month. The average age at diagnosis was 42.6±8.3 y.o. in the remission group, compared with 36.4±8.8 y.o. in recurrence group ($p<0.05$). The thyroid size of grade ≥ 2, often in recurrence group 16 (53.4%) compared with 14 (46.6%) in remission group ($p<0.05$). TRAb levels at prior study were significantly higher in the recurrence group compared with the remission group ($p<0.05$).

TABLE 1. Characteristics of patients with Graves' disease prior to treatment based on remission and recurrence group

Characteristic	Remission group (n=23)	Recurrence group (n=23)	p
Age (years)	42.6±8.3	36.4±8.8	<0.05*
Gender [n (%)]			
• Men	5 (45.4)	6(54.6)	<0.05**
• Women	18 (51.4)	17(48.5)	<0.05**
FT4 (ng/dL)			
• Prior study	4.3±2.2	4.7±1.9	<0.05*
• 3 month	2.1±0.9	2.5±1.1	>0.05*
• 6 month	1.6±0.4	1.7±0.9	>0.05*
• 12 month	1.4±0.5	1.9±0.6	<0.05*
TSHs (µIU/mL)	1.9±1.1	Uncountable	
Eye syndrome [n (%)]			
• Yes	10 (55.5)	8(44.5)	>0.05**
• No	13 (46.4)	15 (53.6)	
Size of goiter [n (%)]			
• Grade I	9 (56.2)	7 (43.8)	<0.05**
• Grade II and above	14 (46.6)	16 (53.4)	
TRAb (U/l)			
• 0 month	19.2±11.3	32.6±12.2	0.001*
• 12 month	1.1±0.5	19.4±5.3	
Mean daily doses of MMI treatment (mg/day)			
• 0 month	25.3±12.3	28.6±1.7	>0.05*
• 3 month	18.2±7.5	24.5±11.3	<0.05*
• 6 month	12.7±4.8	22.1±8.6	<0.05*
• 12 month	2.1±0.3	11.4±5.3	<0.05*

Eye syndrome was defined by a NOSPECS score ≥2; FT: free thyroxine; sTSH: sensitive thyroid stimulating hormone; TRAb: thyrotrophin receptor antibody; *) analyzed with t test; **) analyzed with chi square.

Logistic regression analysis demonstrated that the following factors significantly affected clinical outcomes between remission and recurrence i.e. thyroid size [OR=8.725; 95%CI= 4.10330.519; p=0.001]; TRAb level (OR=1.712; 95% CI=1.0422.116; p=0.001); and the FT4 level (OR=1.629; 95% CI=1.1042.654; p=0.023).

TABLE 2. Logistic regression analysis that affected disease outcomes

Variable	OR	95% CI	p
Age	1.02	0.726-1.255	0.135
Gender	0.89	0.913-1.478	0.085
Dose of treatment	1.14	0.682-1.792	0.213
Thyroid size	8.72	4.10330.519	0.001
TRAb level	1.71	1.0422.116	0.001
FT4 level	1.62	1.1042.654	0.023

DISCUSSION

The use of antithyroid drug (ATD) as methimazole treatment remains the primary method of management for GD induced hyperthyroidism in various countries. However, the relapse rate is high following the termination of ATD treatment.[5] ATD prognosis factors have previously been studied however, unified classification criteria for the prognosis of treated hyperthyroidism for remission, cure, drug withdrawal, and recurrence is yet to be established worldwide.[8]

Graves disease is an organ specific autoimmune disease of the thyroid caused by TRAb directing against the TSH receptor in the thyroid follicular cells. Treatment outcomes of ATD administration may be predicted trough TRAb levels at the time of drug withdrawal. In the present study, a number of patients with GD achieved a longterm remission following ATD therapy, which may be a result of the direct immunosuppressive action of ATDs.[9]

Based on guidelines from the American Thyroid Association (ATA)[10] and the European Thyroid Associationmanifestations, and potential therapies. Appropriate treatment requires an accurate diagnosis and is influenced by coexisting medical conditions and patient preference. This document describes evidence-based clinical guidelines for the management of thyrotoxicosis that would be useful to generalist and subspecialty physicians and others providing care for patients with this condition. Methods: The American Thyroid Association (ATA (ETA),[11] the standard duration of antithyroid therapy in GD ranges from 12-18 months. The rate to relapse and incidence of hyperthyroidism after the duration of therapy ranges from 30 to 70%. The relapse rate was high in those with positive TRAb at the time of drug withdrawal although the level of thyroid hormones were normal.[12]

The duration of therapy that is necessary for patients with GD remains unclear.[13] Previous studies have demonstrated that treatment durations of >18 months were not able to improve remission rates.[14] Furthermore, Quadbeck *et al.*[15] demonstrated that TSH suppression at the time of drug withdrawal was a predicting factor for the recurrence of GD. In the present study, the number of patients with normal TSHs level was still low in the recurrence group, as compared with the remission group at 3, 6 and 12 months following ATD treatments when euthyroidism was achieved.

CONCLUSION

In conclusion, patients with large thyroids size, high level of FT4 and TRAb following treatment with ATD experience recurrence. Therefore, the results of the present study suggested that GD patients with the above characteristics should be provided alternative treatment.

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