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Immunologic and Hormonal Effects of Prophylthiouracil Treatment Using Maintenance Dose in Graves' Disease Patients

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ABSTRAK

***Tujuan**: untuk menilai remisi imunologi setelah kondisi eutiroid tercapai paska pengobatan PTU dosis rumatan pada pasien penyakit Graves. **Metode:** penelitian ini merupakan penelitian intervensi dengan rancangan pre-post pada 25 orang pasien penyakit Grave yang berobat ke poli khusus endokrinologi metabolik RSUP Dr. M. Djamil Padang dan mendapat PTU selama 12 bulan. Darah pasien diperiksa pada awal dan akhir pengobatan untuk menilai remisi imunologis yang dicerminkan oleh kadar IL-4 serum. **Hasil:** setelah terapi rumatan, ditemukan penurunan bermakna kadar T3 (2,29±0,57 nmol/L vs. 1,87±0,34 nmol/L, p<0,05), penurunan bermakna kadar T4 (118,15±25,99 nmol/L vs. 94,15±23,76 nmol/L, p<0,05), peningkatan bermakna kadar TSH serum (0,379±0,548 vs. 0,859 ± 0,990, p<0,05) dan penurunan bermakna kadar IL-4 (12,23±5,74 vs. 3,84±0,42, p<0,05) meskipun penurunan ini belum mencapai batas normal. **Kesimpulan:** pengobatan dengan propiltiourasil dosis rumatan dapat menurunkan parameter hormonal secara bermakna hingga mencapai kondisi eutiroid namun tidak dapat menurunkan parameter imunologis (IL4) sampai batas normal.*

***Kata kunci:** respons hormonal, imunologis, kadar IL4, penyakit Graves.*

ABSTRACT

***Aim:** to assess immunologic remission in patients with Graves' disease following euthyroid condition at the end of treatment with maintenance dose of PTU. **Methods:** this is an intervention study using one-group pre-post design. Subjects were 25 Graves' disease patients visiting Metabolic Endocrinology Clinic at Dr. M.Djamil hospital Padang and met the inclusion criteria. Patients were given PTU treatment for 12 months. Blood samples were taken at the beginning and at the end of treatment to determine immunological remission reflected by differences in IL-4serum levels. **Results:** after maintenance therapy, we found significant decrease of T3 levels (2.29±0.57 nmol/L vs. 1.87±0.34 nmol/L, p<0.05), significant decrease of T4 levels (118.15±25.99 nmol/L vs. 94.15±23.76 nmol/L, p<0.05), significant increase of TSH levels (0.379±0.548 vs. 0.859±0.990, p<0.05) and significant decreased levels of IL-4 (12.23±5.74 vs. 3.84±0.42, p<0.05). The IL-4 level, however, did not decrease to the normal levels. **Conclusion:** PTU administration in maintenance dose can significantly reduce thyroid hormonal parameter levels down to euthyroid condition, but cannot reduce immunological parameter (IL4) to normal limit.*

***Key words:** hormonal, immunologic, interleukin-4, Graves' disease.*

INTRODUCTION

Graves' disease is the most common disease causing hyperthyroidism, accounting for 60-80% of all cases.[1] It is an autoimmune disease that has multifactorial origins including interaction of endogenous fragile factors with genetic and environmental factors. IgG antibodies bind to and activate thyrotropin receptor (thyroid stimulating antibody TSAB) causes follicular hypertrophy and hyperplasia resulting in enlargement of the gland and enhances hormon production.[2,3] It is suspected that autoimmune disorder plays a role because of low clonal T suppressor cells (Ts) that are genetically responsible for the production of TSAB.

Interleukin-4 stimulates isotype-secreting Cells Immunoglobulin G3 (IgG3-SCS), which are associated with the severity of Graves' disease. In addition, TRAb levels can also alter IgG1 that can stimulate the production of TRAb.[9-11]

There are two methods in the treatment of Graves' disease using anti-thyroid drugs. One is based on titration, treatment starts with a large dose (initial phase) and then based on clinical/ laboratory result, the dose was lowered to reach the lowest dose which still results in a state of euthyroid (maintenance phase). Treatment length may vary but usually lasts over 12-18 months The other is referred to as block-substitution, where treatment starts with a large dose continuously and in case of hypothyroidism, the coupled substitution therapy is done with thyroxine hormone to get back into euthyroid.[12] Abraham et al.[13] found titration method as effective as block-substitution method. Treatment that has minimum side effects should be the first choice in starting the treatment.

It has been know that treatment of Graves 'disease with anti-thyroid drugs either in the initial phase or maintenance phase will usually yield euthyroid conditions, but the effect on immunological conditions need further studied. Several studies have been conducted to find the effect of anti-thyroid against immunological parameter such as IL-4. Komiya et al.[14] reported that serum levels of IL-4 was not detected after 18 months of treatment with metimazol. Marina[15] in her study of 25 patients with Graves' disease reported significant decrease in serum levels of IL-4 after initial treatment with PTU, although it did not reach normal levels. She showed that euthyroid condition that has occurred after the initial treatment with PTU was not followed by immunological remission (normal levels of IL-4).

This study aims at revealing the effect of PTU against IL-4 levels after maintenance phase of hyperthyroid treatment. The importance of this study is that it will identify immunological remission of Graves' disease.

METHODS

This is an intervention study using one-group pre-post design. The research was conducted in the clinic and ward of internal medicine department Dr.M. Djamil hospital Padang. Measurements of T3, T4, TSH were performed at the Imunoserologi Laboratory of Dr. M. Djamil Hospital Padang and IL-4 was examined in Imunoserologi Health Center laboratory of West Sumatra Province. Subjects were patients with Graves' disease who had received initial treatment with PTU and met inclusion criteria: had received initial treatment before maintenance therapy of PTU, aged ≥ 15 y.o., and agreed to participate in the research. Exclusion criteria were: any accompanying allergic diseases, pregnant, liver disease/liver dysfunction, heart failure, and taking hormonal contraception. Sample size for this study was determined by formula of one group intervention pre and post design. Alfa was determined 0.05, β was 0.2, and the mean difference was expected to be 0.5 mmol/L. Based on the formula, 25 persons were recruited as subject.

Subjects who met inclusion criteria were checked for baseline parameters consisting of T3, T4, TSH, and IL-4 levels. All subjects received prophylthiouracil (PTU) produced by PT. Indofarma with a dose of 3x50 mg for 9 months (maintenance therapy) until total initial dosage and maintenance therapy for 12 months. They were clinically evaluated every month to assess drug compliance and adverse effects. After 3 months (month 6 of PTU treatment), serum levels of IL-4 were examined. After 9 months (month 12 of PTU treatment), the levels of T3, T4, TSH and serum IL-4 were re-examined. Finally, we analyze the data to answer whether euthyroid

condition after maintenance therapy with PTU will be followed by immunological remission through examination of serum levels of IL-4.

Levels of T3, T4 and TSH were measured using a reagent kit from Roche. Measurements used ECL method immuchemiluminescence tool from Roche Cobas e 411. Serum levels of IL-4 were measured using reagent kit of human IL-4 products from Bender Med System. Measurements used Elisa method.

Data were analyzed to compare the condition before and after the intervention. Shapiro Wilk normality test was used to view whether the data were normally distributed. If data were normally distributed, then analysis was followed by paired t test, but if the distribution was not normal, data transformation was done in advance. If data transformation resulted in a normal distribution, paired t test was used, but if the transformation did not produce normal distribution, then the Wilcoxon test was used.

RESULTS

PTU treatment at maintenance dose significantly lowered IL4 levels, but the reduction did not reach normal levels. (**Figure 1**)

Meanwhile, this treatment was associated with significant lower T3 levels, from 2.19±0.57 mmol/L to 1.87±0.34 mmol/L (**Figure 2**). The same effect was found for T4 levels where there was a significant decrease in T4 levels from 118.15 ± 25.99 mmol/L to 94.15 ± 23.76 mmol/L (**Figure 3**).

In conjunction with the decrease of T3 and T4, treatment with a maintenance dose of PTU produced a significant increase in TSH levels. TSH levels before PTU maintenance therapy ranged from 0.01 to 2.14 IU/ml with a mean of 0.379±0.548 IU/ml. TSH levels after PTU maintenance therapy ranged from 0.05 to 3.90 IU/ml with a mean of 0.859±0.990 but only 17 (68%) subjects reached normal levels. The remaining 8 (32%) subjects did not reach normal levels (**Figure 4**).

DISCUSSION

We had conducted an intervention study using one-group pre-post design. Assessment of

Table 1. Subjects characteristics

Characteristics	n (%)
Age	
- <30	9 (36)
- 30-40	5 (20)
- >40	11 (44)
Sex	
- male	7 (28)
- female	18 (72)
Smoking	
- yes	5 (20)
- No	20 (80)
Family History	
- yes	3 (12)
- No	22 (88)
Struma Grade	
- Grade I	3 (12)
- Grade II	15 (60)
- Grade III	7 (28)
Onset	
- <6 months	14 (56)
- 6-12 months	6 (24)
- >12 months	5 (20)

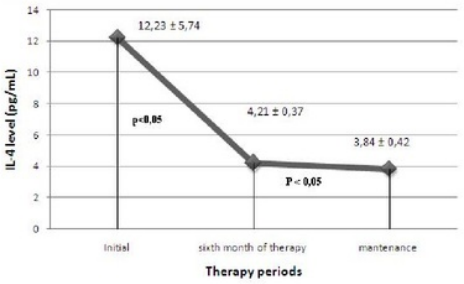

Figure 1. Levels of IL-4 at initial, 6 month of therapy, and after maintenance therapy

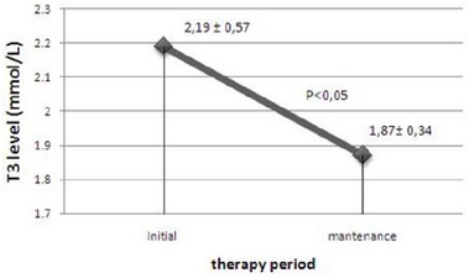

Figure 2. T3 serum levels at initial and after maintenance therapy

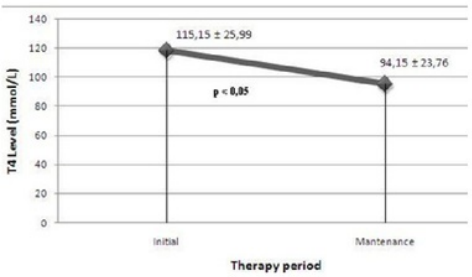

Figure 3. T4 serum levels at initial and after maintenance therapy

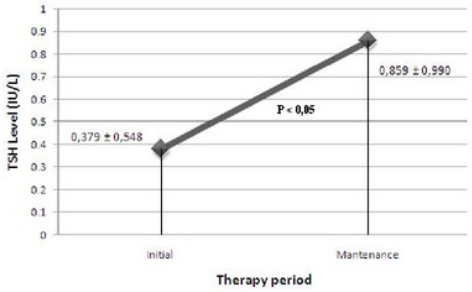

Figure 4. TSH serum levels at initial and after maintenance therapy

the effects of PTU dose in maintenance therapy was reflected on levels of IL4, T3, T4 and TSH before and after PTU therapy.

There were 25 subjects with Graves' disease included in this study, with range of age of 16-64 y.o. Subject's age range in this study was similar to Komiya et al.[14] who showed that out of 107 patients with Graves' disease there were patients who were 17-67 y.o. Graves' disease is most common found in patients aged <40 years, although 15% may occur in patients aged> 60 years.

In this study, female subjects (72%) were more frequent than males (28%). This is similar with the research by Humaidi MA.[16] that out of 28 patients with Graves' disease, 78.57% were female and 21.43% were male. Hartono[17] also showed that out of 30 Graves' patients, 90% were female and 10% were male. Graves' disease occurs ten times more frequent in women than in men. The influence of female hormone estrogen causes the risk of Graves' thyrotoxicosis in women being larger than males.[18]

This study also found that 20% of the subjects had history of smoking. Smoking is a risk factor for Graves' disease by RR 2.62. Smoking spurs hypoxia and nicotine in cigarettes could spur an increase in HLA-DR expression that can both stimulate and worsen inflammatory reaction.[19] It is stated that smoking is one of the independent risk factors for recurrence after medical therapy.[20]

Serum levels of IL-4 before PTU maintenance therapy ranged from 2.4 to 27.8 pg/ml with a mean of 12.23±5.74 pg/ml. In all subjects the levels of serum IL-4 before maintenance therapy with PTU did not reach normal levels, although at the same time the levels of T3 and T4 has reached normal levels. This might indicate that initial treatment before PTU maintenance therapy did not yield immunological remission following euthyroid condition.

Serum levels of IL-4 after PTU maintenance therapy ranged from 3.16 to 5.3 pg/ml with a mean of 3.84±0.42 pg/ml. After therapy with maintenance dose of PTU, mean levels of IL-4 significantly decreased ($p<0.05$). No subjects reached normal levels although at the same time levels of T3 and T4 has reached normal levels. The same condition indicates that PTU maintenance therapy did not yield immunological remission following euthyroid condition.

Komiya et al.[14] found that serum levels of IL-4 was not detected after 18 months of treatment with metimazol. Li[21] in his study of 42 Graves' patients got serum levels of IL-4 significantly higher than the 40 control patients before treatment. After 12 weeks of treatment with anti-thyroid drugs, serum levels of IL-4 downed near normal. Wei[22] in his study obtained serum levels of IL-4 significantly increased in 33 patients with Graves ophtalmopathy before treatment compared to 35 control patients. After 1 month of treatment, he found decreasing levels of IL-4 serum of patients with Graves ophtalmopathy. Our study found that the IL-4 levels decreased drastically during the first six months of treatment. However, no study has been able to explain the process and the condition comprehensively.

T3 levels before PTU maintenance therapy ranged from 1.38 to 3.1 nmol/L with a mean of 2.19±0.57 nmol/L. All subjects were within normal limit. T3 levels after PTU maintenance therapy ranged from 1.31 to 2.63 nmol/L with a

mean of 1.87±0.34 nmol/L. This result showed significant decrease ($p<0.05$) but remained within the normal limit. Nordling MA et al.[23] obtained mean of T3 levels after medical therapy as 1.8 nmol/L. Another study found that relapse frequently occurs in patients with Graves' initial high T3 levels.[24]

T4 levels before maintenance therapy of PTU ranged from 75 to 178 nmol/L with a mean of 118.15±25.99 nmol/L. All subjects were within normal limit. T4 levels after PTU maintenance therapy ranged from 66.02 to 164.47 nmol/L with a mean of 94.15±23.76 nmol/L. All subjects showed significant decrease ($p<0.05$) but remained within normal limit.

Komiya et al.[14] obtained T4 levels after therapy with 18 months of metimazol as 109±22 nmol/L in the group with increased IgE, and 106±21 nmol/L in the group with normal IgE. Relapse frequently occurs in patients with Graves' initial high T4 levels.

This study also found elevated levels of TSH due to antithyroid therapy, but only 17 out of 25 subjects reached normal levels and the other 8 subjects did not. The levels of TSH often remains high, and it may take many months or even years to recover because of prolonged pituitary suppression by thyroid hormone (lazy pituitary).

Komiya et al.[14] obtained a mean TSH levels after therapy as 2.18±1.61 mU/L in the group with increased IgE and 2.35±2.33 mU/L in the group with normal IgE. Yamada et al.[9] found mean TSH levels after 2-year therapy with metimazol as 1.06±0.91 μIU/ml.

The mechanism of remission from autoimmune disorders in patients with Graves is considered as a direct result of immunosuppressive tionamid drugs. Many clinical studies have demonstrated that remission during therapy with anti-thyroid drugs is not dependent on the dose and type (methymazol and PTU) but dependent on immunological regulatory that led patients to become euthyroid. In addition, the presence of individual response to the autoimmune process also affects the response of treatment.[24,25]

CONCLUSION

PTU maintenance dose can reduce IL-4 levels significantly but not to the normal levels. PTU therapy for 12 months gives a good response to the hormonal status of Grave's patients, yet it cannot suppress immunological activity to the normal stage.

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