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Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 57; Numer/Number 6/2006
ISSN 0423–104X

Przewidywanie możliwości nawrotu nadczynności tarczycy w przebiegu choroby Gravesa-Basedowa u dorosłych we wczesnym okresie leczenia farmakologicznego

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Streszczenie

Wstęp: Długoterminowa skuteczność farmakologicznego leczenia nadczynności tarczycy w przebiegu choroby Gravesa-Basedowa nadal pozostaje niezadowalająca i trudna do przewidzenia. Celem niniejszego badania była ocena przydatności oznaczeń przeciwciał blokujących wiązanie tyreotropiny (TBII) z receptorem w przewidywaniu możliwości nawrotu nadczynności tarczycy już we wczesnej fazie leczenia farmakologicznego.

Materiał i metody: Badaniem objęto 37 chorych z pierwszym incydentem nadczynności tarczycy w przebiegu choroby Gravesa-Basedowa w wieku 20–60 lat. Wszystkich chorych leczono tiamazolem przez okres 12 miesięcy. Przed, a następnie po 1, 3, 6, 9 i 12 miesiącach terapii dokonywano oceny klinicznej, ultrasonograficznego badania tarczycy i oznaczenia TBII (test II generacji) oraz tyreotropiny, wolnej trijodotyroniny i wolnej tyroksyny w surowicy.

Wyniki: Okres obserwacji po odstawieniu leku wynosił średnio 27,24 ± 5,81 miesięcy. U dwunastu z 37 chorych nastąpił nawrót nadczynności tarczycy po średnio 8,17 ± ± 6,91 miesiąca od zakończenia leczenia. Znacząca różnica w poziomach TBII w grupie chorych pozostających w remisji i chorych, u których doszło do nawrotu choroby widoczna była od pierwszego miesiąca terapii przez cały jej okres trwania. U chorych z TBII > 14 IU/l po 3 miesiącach oraz u chorych z TBII > 8 IU/l po 6 miesiącach leczenia znacznie częściej dochodziło do nawrotu nadczynności tarczycy w porównaniu z chorymi z niższymi poziomami TBII (czułość 50% i specyficzność odpowiednio 92% i 96%).

Wnioski: Oznaczanie TBII we wczesnej fazie leczenia farmakologicznego może okazać się pomocne w planowaniu dalszego leczenia nadczynności tarczycy i w odpowiednio wczesnym kwalifikowaniu chorych do bardziej radykalnych form terapii nadczynności tarczycy w przebiegu choroby Gravesa-Basedowa (terapia radiojodem, strumektomia).

(Endokrynol Pol 2006; 6 (57): 596–604)

Słowa kluczowe: *choroba Gravesa-Basedowa, nadczynność tarczycy, autoprzeciwciała, receptor TSH, TBII.*

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Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 57; Numer/Number 6/2006
ISSN 0423–104X

Predicting a relapse of Graves' hyperthyroidism in adults during the early phase of treatment with anti-thyroid drugs

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Abstract

Introduction: The long-term effectiveness of anti-thyroid drugs (ATD) in the treatment of Graves' hyperthyroidism (GH) is still unsatisfactory and difficult to predict.

The aim of this study was to evaluate the usefulness of a determination of serum level of thyrotropin-binding inhibiting immunoglobulins (second generation TBII assay) in predicting the possibility of relapse in the early phase of pharmacological treatment.

Material and methods: We investigated 37 patients within the 20–60 age range with the first occurrence of GH. All patients were treated with thiamazole for 12 months. Clinical assessment, ultrasound estimation of thyroid volume and determination of serum thyrotropin, free thyroxine, free triiodothyronine, thyroid autoantibodies and TBII levels were carried out at the onset and after 1, 3, 6, 9 and 12 months of ATD treatment.

Results: The mean follow-up period after ATD withdrawal was 27.24 ± 5.81 months. Of 37 patients 12 (32%) had a relapse of hyperthyroidism (mean time 8.17 ± 6.91 months after drug withdrawal). The difference in TBII levels between the relapse and the remission group was found to be significant after the first month of therapy until the end of ATD treatment. We observed that patients with TBII above 14 IU/L after 3 months and above 8 IU/L after 6 months of therapy relapsed more frequently than patients with lower levels (sensitivity 50% and specificity 92 and 96%, respectively).

Conclusions: The study confirmed that TBII estimation in the early phase of ATD could be useful in the proper planning of GH therapy and early qualification to more radical treatment (radioiodine or surgery).

(Pol J Endocrinol 2006; 6 (57): 596–604)

Key words: *Graves' disease, hyperthyroidism, autoantibodies, TSH receptor, TBII*

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Introduction

Graves' hyperthyroidism (GH) is an autoimmune, organ-specific disorder caused by thyroid-stimulating antibodies that lead to increased thyroid hormone production [1–3]. In the majority of European countries, including Poland, anti-thyroid drugs (ATD) are the first choice therapy in newly diagnosed patients with Graves' hyperthyroidism (GH) [4]. The main problem of ATD therapy, however, is its unsatisfactory long-term effectiveness, resulting in a relapse of up to 60% in properly qualified and treated patients [5–9].

In the past the long-term effect of ATD treatment was anticipated by evaluating several clinical or laboratory parameters. These parameters were age, gender, serum level of thyroid stimulating autoantibodies (TSAb and thyrotropin-binding inhibitory immunoglobulins), TBII, TSH, free T3/free FT4 ratio, (the FT3/FT4 ratio), thyroid volume, thyroid echogenicity, thyroglobulin, anti-thyroperoxidase autoantibodies (aTPO) and anti-thyroglobulin antibodies (aTG) [10–25]. Although these parameters, either alone or as a group of tests, were found to have some prognostic value, none of them exhibited satisfactory sensitivity, specificity or reproducibility. Moreover, the prognostic value of all of them was evaluated before or after completion of long-term ATD treatment [14, 26, 27]. During recent years a new assay system with human recombined TSH receptor immobilised either on plastic tubs or ELIZA plate wells has been introduced to measure the level of TBII in serum [28–30]. This test used in GH patients was soon found to be more sensitive and specific than the first generation assay [31–34]. Moreover, data recently published [28, 35–38], including our own results [39], have all confirmed that the present TBII assay indirectly estimates the presence of TSAb.

The aim of this study was to evaluate the usefulness of the second generation TBII in predicting the

long-term outcome of the therapy in the early phase of pharmacological treatment. In addition, we have also investigated whether some of the clinical or hormonal parameters can enhance the predictive value of TBII measurements during the first months of ATD treatment.

Material and methods

Patients

We enrolled consecutively patients with newly diagnosed yet untreated Graves' hyperthyroidism, referred by general practitioners to the outpatient clinic of the Department of Endocrinology, Warsaw Medical University. The exclusion criteria for the study were: large goitre (volume > 75 ml), age below 20 years, ongoing pregnancy, breast-feeding or the coexistence of serious illness. Patients with severe Graves' ophthalmopathy (GO) of NOSPECS class IV and higher were also excluded, as they could require immunosuppressive therapy. The diagnosis of Graves' hyperthyroidism was confirmed according to commonly accepted clinical, hormonal and immunological criteria [40].

Study protocol

All patients were initially treated with 40 mg of thiamazole (Thyrozol, Merck, Darmstadt, Germany) for one month and then the dose was reduced to the lowest required to maintain euthyroid status (usually 5–10 mg/day). The treatment period was 12 months. Clinical assessment (expressed as a Crooks' index), ultrasound estimation of thyroid volume, laboratory tests (serum TSH, FT4 and FT3) and determination of thyroid autoantibodies (aTPO, aTG) and TBII levels in serum were carried out at the onset and after 1, 3, 6, 9 and 12 months of ATD treatment. The shortest follow-up period after ATD withdrawal was 18 months. Relapse of Graves' hyperthyroidism was defined as a Crooks' index grade above 5.0 and serum FT4 and FT3 levels above normal. The study was approved by the Ethical Committee of Warsaw Medical University and all patients gave their written informed consent.

Clinical parameters and biochemical measurements

Crooks' index was calculated as previously described [41]. Serum TSH, FT3 and FT4 concentrations were determined by microparticle enzyme immunoassays (AxSym System, Abbott, Chicago, USA). Normal ranges were 0.49–4.67 μIU/ml, 1.45–3.48 pg/ml and 0.71––1.85 ng/dl, respectively. Serum FT3 results in pg/ml could be converted to the International System Units by multiplying by 1.536 and serum FT4 results in ng/dl by multiplying by 12.872. FT3/FT4 ratio was calculated according to the formula (pg/ml: ng/dl) × 10 [42]. Human TSH receptor autoantibodies (TBII) were determined by second-generation luminescence receptor assay (B.R.A.H.M.S Diagnostica GmbH, Henningsdorf, Germany). TBII values above 1.5 IU/l were defined as positive. Antibodies against native human thyroglobulin (aTG) and antibodies against native human thyroid peroxidase (aTPO) were determined by luminescence immunoassays (B.R.A.H.M.S. Diagnostica GmbH, Henningsdorf, Germany) with positive values > 60 U/l in both assays.

Statistical analysis

The statistical analysis was performed using Statistica for Windows. Data were analysed by the non-parametric Mann-Whitney U-test, Wilcoxon matched pairs test and χ^2 test.

Results

Baseline characteristics

We enrolled 41 patients (36 women, 5 men), aged 20–60 years (with a mean age of 41.0). Of these 37 patients (32 women and 5 men), aged 20–60 years (mean age 41.0) completed the study, 4 patients having dropped out because they had moved out of the district. The clinical characteristics of the group studied before ATD treatment are shown in Table I.

Relapse rates (outcome)

The majority of patients responded to the ATD treatment within the first month in terms of clinical improvement (Crooks' index) and serum TSH, FT4 and FT3 results. However, 9 patients (23.68%) were still slightly

Table I
Characteristics of the group of patients as a whole before ATD therapy

Tabela I
Charakterystyka całej grupy pacjentów przed terapią tyreostatykiem

Parameter	No. of patients (% of whole group)/Median (range)
Graves' ophthalmopathy	9 (24.32%)
Smokers	14 (35.14%)
Family history of AITD	14 (35.14%)
Crooks' index	23 (8–31)
TBII [IU/l]	7.52 (0.00–75.00)
TSH [mIU/l]	0.00 (0.00–0.04)
FT4 [ng/dl]	4.07 (1.5–8.6)
FT3 [pg/ml]	13.52 (4.55–31.42)
FT3/FT4	32.10 (2.94–83.80)
Thyroid volume (ml)	17.41 (7.00–74.03)

hyperthyroid (Crooks' index > 5.0, with typically low serum TSH and both serum FT3 and FT4 elevated). After 3 months of ATD all those investigated became clinically euthyroid, with serum FT4 and FT3 within the normal range. TSH levels in the sera of 5 patients, however, were suppressed and remained so until month 12th of therapy. In contrast to the clinical improvement seen from month 3rd of treatment in all patients, the normalisation of serum TBII level (immunological remission) was achieved only in 20 patients (54.05%). The mean follow-up period after ATD withdrawal was 27.24 ± 5.81 months. A relapse of hyperthyroidism occurred in 12 patients (32%), 9 female, 3 male, out of 37. The mean time of relapse after drug withdrawal in the group of patients as a whole was 8.17 ± 6.91 months. Within the first 6 months 6 patients (16%) had relapsed, while the remaining 6 patients relapsed within 13 months of the follow-up period.

Prediction of the relapse

a. TBII levels. Although before treatment TBII levels were higher in the relapse group compared to the remission group, the difference was not significant (19.7 ± 24.5 vs. 8.85 ± 7.64, p = 0.30) (Fig. 1). However, the difference in TBII levels became significant after the first month of therapy and remained significant ($p < 0.01$) until the end of ATD treatment (Fig. 1). It is of interest that in the relapse group the TBII level increased slightly during first month of treatment and was higher after 3 months of therapy than at the initial diagnosis. All patients in the relapse group had positive TBII levels during the 12 months of treatment. In contrast to this, in the remission group positive TBII values were observed in 25 patients (100%) after 1 month of treatment. Serum TBII levels decreased gradually in most patients from the remission group and we observed normalisation of TBII in 2 patients after 3 months of ATD, in 8 patients after 6 months, in 16 patients after 9 months and in 17 patients after 12 months of ATD in this group of patients.

Moreover, the median TBII level from the onset of GH in patients who relapsed very early after drug withdrawal was 16.29 IU/L (mean 22.56 ± 19.59) and was significantly higher than that observed in patients who relapsed later in the follow-up period (median 3.21 IU/l, mean 16.80 ± 28.94).

The median TBII levels observed in the relapse group before and during 12 months of the ATD were used to evaluate the predictive value of TBII for the relapse of hyperthyroidism (Tab. II). As shown, sensitivity in the prediction of the relapse reached 50 % at the beginning of ATD and was stable, but specificity, which was 80% at the beginning, had already reached over 90 % after the third month of the therapy. Figure 2 shows individual TBII levels during ATD therapy in patients who relapsed.

b. aTPO and aTG. We observed elevated aTPO levels in 31 patients (83.78%): 21 from the remission group

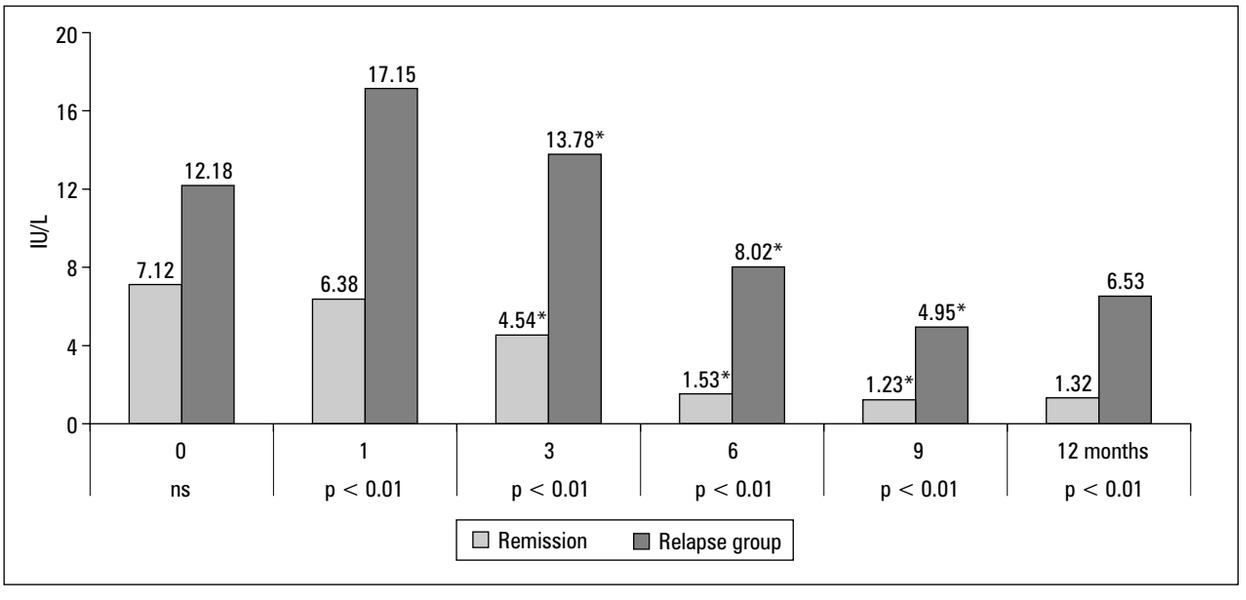

Figure 1. *TBII medians in the remission and the relapse groups before and during 12 months of ATD therapy; *denotes a significant decrease in comparison with prior value*

Rycina 1. *Mediany TBII w grupie chorych pozostających w remisji i w grupie chorych z nawrotem nadczynności tarczycy przed i w trakcie 12 miesięcy terapii tyreostatykiem; *oznacza statystycznie znaczące zmniejszenie w porównaniu z wartością obserwowaną w poprzednim punkcie czasowym terapii*

Table II
Prediction of hyperthyroidism relapse on the basis of TBII values. medians in the relapse group (n=12) during consecutive months of antithyroid therapy

Tabela II
Rokowanie nawrotu nadczynności tarczycy na podstawie wartości TBII (mediany) w grupie chorych z nawrotem nadczynności tarczycy w czasie kolejnych miesięcy terapii tyreostatykiem

Months of ATD therapy	TBII * [IU/l]	No. of all patients with given TBII value/ no. of patients who relapsed with given TBII value	Sensitivity (%)	Specificity (%)	Positive predictive value (PPV)	Negative predictive value (NPV)
Before	≥ 12	11/6	50	80	55	77
1	≥ 17	9/6	50	88	67	79
3	**≥ 14**	8/6	**50**	**92**	**75**	**79**
6	**≥ 8**	7/6	**50**	**96**	**86**	**80**
9	≥ 5	7/6	50	96	86	80
12	≥ 6	7/6	50	96	86	80

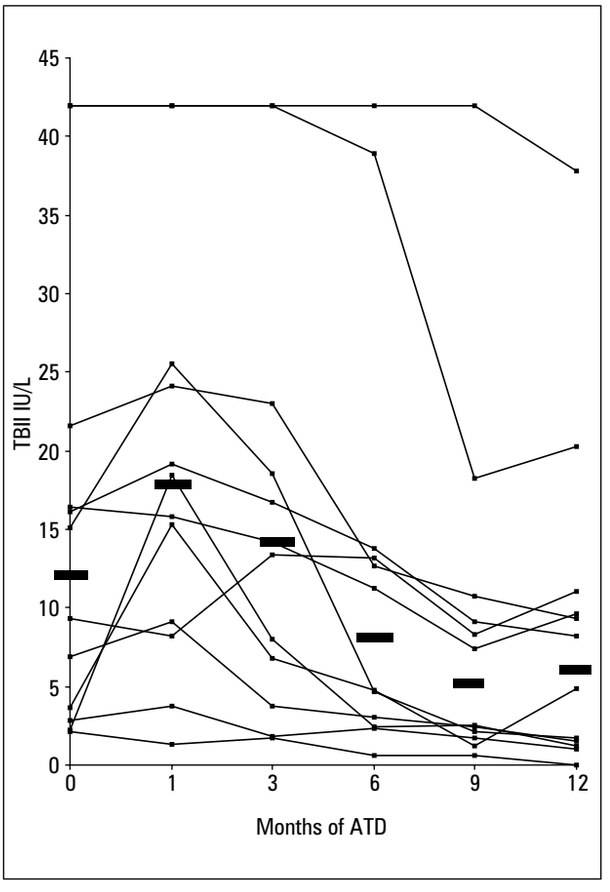

Figure 2. *Dynamics of TBII value in each patient from the relapse group during 12 months of ATD treatment. Black bars denote median TBII value at a particular point of ATD therapy. Normal upper TBII level 1.5 IU/L*

Rycina 2. *Dynamika wartości TBII w ciągu 12 miesięcy terapii u chorych z grupy nawrotu nadczynności tarczycy. Czarne prostokąty oznaczają mediany TBII w poszczególnych miesiącach terapii tyreostatykiem. Wartość negatywna TBII < 1,5 IU/l*

(84.00%) and 10 from the relapse group (83.30%). Elevated aTG was identified in 20 patients (54.05%): in 23 patients (52.00%) from the remission group and in 7 (58.33%) from the relapse group. After 12 months of therapy the percentage of positive aTPO and aTG levels decreased but the analysis performed did not provide any significant data for predicting the results of therapy in the early phase of ATD treatment.

c. TSH, FT4, FT3. There was no statistical difference between the groups in TSH, FT4, and FT3 values. However, after 12 months TSH remained suppressed in 4 patients in the relapse group compared to one patient from the remission group. When the values of the FT3/FT4 ratio were analysed a significant decrease in the FT3/FT4 ratio in the remission group was already observed after the first month of ATD therapy, while a similar decrease in the relapse group was seen much later, not until the month 9 of the therapy, for example (Fig. 3).
d. Thyroid volume. Although thyroid volume tended to be greater in the relapse group compared to the remission group, the differences before the therapy were not statistically significant (Fig. 4). Goitre (defined as a thyroid volume above 20 ml in women and 25 ml in men) was observed at the beginning in 58.33% of patients in the relapse group and in 28.00% in the remission group. The incidence of goitre decreased in both groups of patients at the end of treatment and reached 41.67% in the relapse group and 8.00% in the remission group.
e. Graves' ophthalmopathy (GO). Analysis performed for finding clinical predictors of the long-term effect of treatment showed that the presence of GO was significantly more frequent in the group of

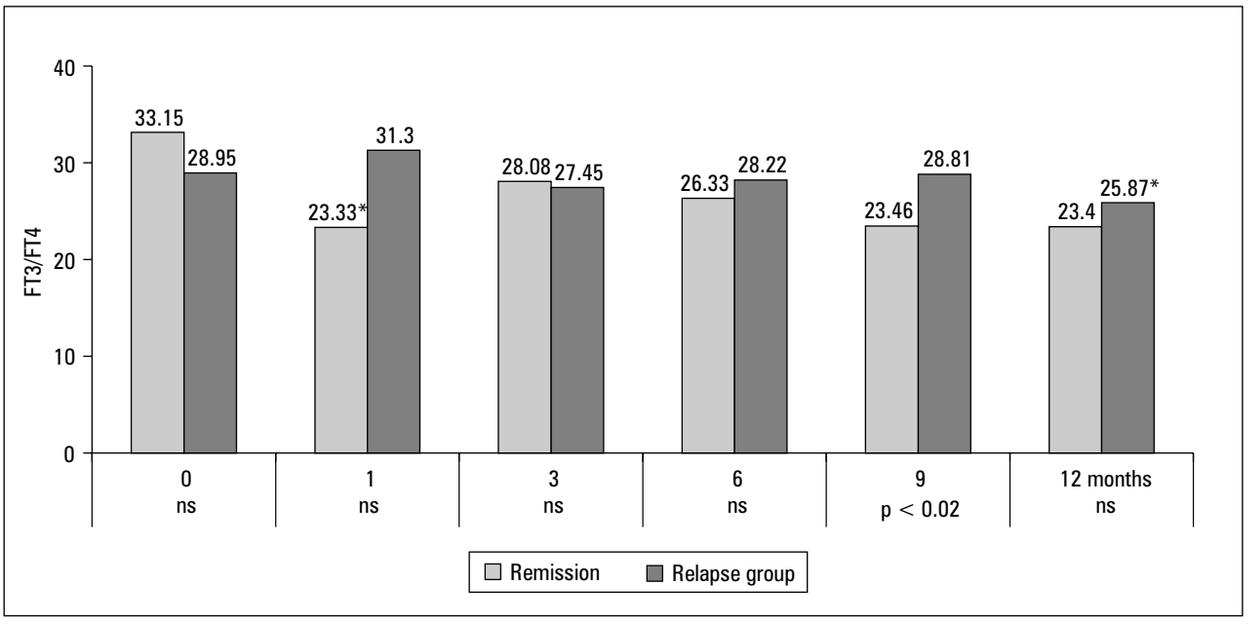

Figure 3. *Different dynamics of FT3/FT4 ratio values (medians) in the remission and relapse groups before and during ATD therapy; *denotes a significant decrease in comparison with prior value*

Rycina 3. *Dynamika wartości median wskaźnika FT3/FT4 w grupie chorych pozostających w remisji i w grupie chorych z nawrotem nadczynności tarczycy przed i w trakcie 12 miesięcy terapii tyreostatykiem; *oznacza statystycznie znaczące zmniejszenie w porównaniu z wartością obserwowaną w poprzednim punkcie czasowym terapii*

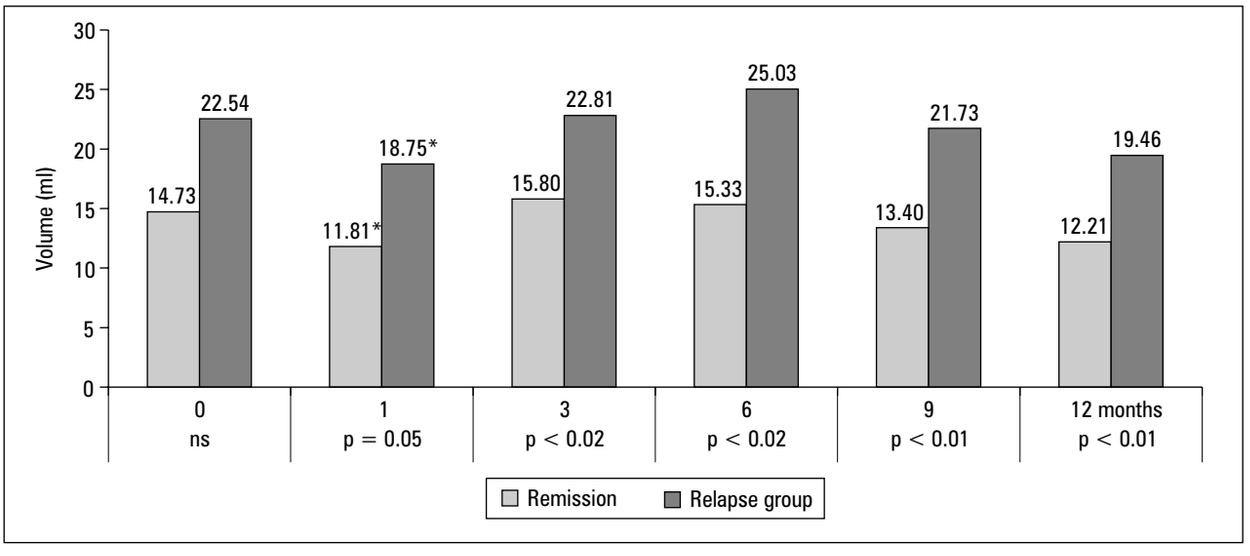

Figure 4. *Thyroid volume (medians) in the remission and relapse groups of patients during 12 months of ATD therapy; *denotes a significant decrease in comparison with prior value*

Rycina 4. *Objętość tarczycy (mediana) w grupie chorych pozostających w remisji i w grupie chorych z nawrotem nadczynności tarczycy przed i w trakcie 12 miesięcy terapii tyreostatykiem; *oznacza statystycznie znaczące obniżenie w porównaniu z wartością obserwowaną w poprzednim punkcie czasowym terapii*

patients with relapse of hyperthyroidism (50% vs 12%, $p < 0.01$).

The relapse and remission group did not differ in age, gender, tobacco smoking or family history of Graves' disease. The addition of the clinical and hormonal parameters investigated did not significantly enhance the possibility of prediction established by TBII level.

Discussion

The ability to predict the outcome of ATD therapy in patients with Graves' disease has proved to be a difficult task. Nevertheless, several clinical symptoms and laboratory findings have been analysed in the past to identify patients who are likely to achieve long-term remission.

The prospective good responder to ATD treatment is female rather than male [43, 44], older than 30 years [10, 45] and has a thyroid volume either of normal size or only moderately enlarged [10]. The serum TBII level in such a patient should be only mildly increased [10––13, 15, 16] and the serum thyroxine (T4) to triiodothyronine (T3) ratio should be below 20 [11, 18, 19]. In addition, the patient should not have a history of Graves' disease among his or her closest relatives [46], should be a non-smoker [47] and should have no signs of infiltrative ophthalmopathy [48] or thyroid dermopathy [49]. Nevertheless, even a patient matching these criteria would have no absolute confidence that long-term remission would be achieved. Most studies predicting the outcome of ATD treatment were performed after termination of ATD therapy [14, 25–27, 50, 51]. The results of these studies indicated that serum TSH and the level of TBII estimated in a group of patients with GH are both useful as markers of relapse or remission [27, 44], although in the individual patient either the concentration of TSH or the level of TBII may fail as an absolute predictor.

Lack of stable remission after long-term treatment decreases the quality of life and imposes an economic burden for both the patient and the public health system. In the present study, therefore, we were tempted to find out whether TBII measurements could be used to predict the relapse of hyperthyroidism at the early stage of treatment. Indeed, our results have confirmed that prediction before treatment is premature. On the other hand, we have shown that serum levels of TBII can predict the risk of relapse with 50% sensitivity and 96% specificity after 6 months of ATD treatment. Our group of patients was relatively homogenous; we included only these with the first onset of Graves' hyperthyroidism and excluded very young patients, those with very large goitre or the nodular variant of Graves' disease.

As has been shown, we were unable to demonstrate the presence of a correlation between the relapse of hyperthyroidism, age, gender, smoking and a family history of autoimmune thyroid disease, as was previously revealed [10, 43, 46, 48, 52, 53]. Similarly, a value above 55 of the FT3/FT4 ratio, suggested as a common phenomenon in GH [42], appeared only in a few patients in our group (8%). It is important, however, to underline the significant decrease in the FT3/FT4 ratio in our remission group after the first month of therapy.

On the other hand, we confirmed previous findings [48] that the coexistence of GO is much more frequent among patients who relapse after drug withdrawal. In 5 of our patients (13.51%) serum TSH remained almost totally suppressed (< 0.1 μIU/ml) until the end of the therapy, regardless of serum FT3 and FT4 normalisation. This might be explained by the interaction of TBII with the TSH receptor on thyrotrophs in the anterior pituitary [54], as all the patients had a positive result in TBII estimation (range 1.57–37.80 IU/L) This range of TBII can also confirm the heterogeneity of these autoantibodies [55–57].

It is of interest that the relapse in our patient with suppressed TSH was seen soon after ATD withdrawal. Such findings are compatible with previous [5, 58] and very recent [27] observations, that TSH concentration measured at the end of pharmacological treatment of hyperthyroidism is a very reliable predictor of relapse. Our data also suggest that a smooth increase in TBII levels in a very early phase of pharmacological therapy could be a predictor of relapse. This observation seems to be in accordance with the results presented by Takasu et al., who, on the other hand, identified a smooth decrease in TBII levels in the early phase of medical therapy as reliable predictor of stable remission of GH [59]. In addition, our results show that a considerable decrease in TBII, aTPO and aTG levels was observed only during the first 9 months of treatment and no further decrease was observed during the last 3 months of therapy. This is in agreement with the results of Edan et al. [60]. In 2 patients we observed a relapse despite negative TBII levels. The mechanism of relapse in such a situation remains unclear, but Mukuta et al. [61] reported a similar finding.

In summary, we suggest that measurement of TBII by the second generation assay helps in making a preliminary prediction of long-term outcome of ATD treatment in a relatively early phase of therapy. Although TBII is no absolute indicator of relapse in individual cases, we believe that unfavourable results with respect to assessment for these autoantibodies should be presented to the patient as leading to the conclusion that the chances of stable remission after 12 months of therapy are low and that a more radical type of therapy (radioiodine or surgery) should be considered. In another words, we believe that the high level of specificity of TBII determination allows patients to be identified who have little or no likelihood of achieving and maintaining long term remission of Graves' disease after ATD therapy. Our results also suggest that a combination of TBII values and thyroid volume, FT3/FT4 ratio levels or aTG concentrations does not assist prediction of a relapse of hyperthyroidism at the early stage of ATD treatment.

In conclusion: determination of TBII level *alone* at a relatively early stage of ATD treatment allows the chances of stable remission of hyperthyroidism to be evaluated in 50% of Graves' patients and is therefore helpful in the appropriate planning of disease management.

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