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The efficacy of immunosuppressive treatment of Graves' orbitopathy is not affected by previous anti-thyroid drugs or by radioiodine therapy of Graves' disease

Wcześniejsze leczenie choroby Gravesa lekami tyreostatycznymi lub radiojodem nie wpływa na skuteczność leczenia immunosupresyjnego orbitopatii tarczycowej

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Abstract

Introduction: We studied the efficacy of immunosuppressive treatment of GO in a group of patients who had been treated with anti-thyroid drugs (the ATD group) and in another group that had undergone radioiodine therapy (the 131-I group).
Material and methods: A total of 214 patients with exacerbation of GO were studied; the ATD group consisting of 168 patients, and the 131-I group consisting of 46 patients. All patients were treated with methylprednisolone IV pulses (total dose 8.0 g) followed by orbital irradiation (20 Gy in 10 fractions). CAS and IO indices, TSH, fT4, and TRAb levels were evaluated prior to, and 1, 6, and 12 months after treatment.
Results: One month after treatment the CAS index decreased significantly in both groups, against values before treatment, $p < 0.05$. In the ATD group the median level of TRAb-0 before treatment was 5.6 IU/L (min = 0.1; max = 114.0), and 12 months later (TRAb-12) it was 1.4 IU/L (min = 0.1; max = 75.3) ($p < 0.05$). In the 131-I group the median level of TRAb-0 was 14.3 IU/L (min = 0.6; max = 90.0) *vs.* TRAb-12 of 3.65 IU/L (min = 0.1; max = 41.0) ($p < 0.05$). In the ATD group the median value of IO-0 before treatment was 5.0 (min = 1.0; max = 12.0) *vs.* IO-12 of 2.0 (min = 0.0; max = 8.0) ($p < 0.05$). In the 131-I group the median value of IO-0 was 5.0 (min = 2.0; max = 9.0) *vs.* IO-12 of 2.0 (min = 0.0; max = 6.0) ($p < 0.05$).
Conclusions: The severity of GO in the ATD and 131-I groups did not differ significantly over the course of observation despite differences noted in their TRAb levels. The efficacy of GO treatment did not differ between these groups. **(Endokrynol Pol 2016; 67 (6): 554–561)**

Key words: *Graves' orbitopathy, radioiodine therapy, intravenous steroids, orbital irradiation*

Streszczenie

Wstęp: Porównano skuteczność leczenia immunosupresyjnego orbitopatii tarczycowej (GO) u pacjentów leczonych wcześniej doustnymi lekami tyreostatycznymi (grupa ATD) oraz u pacjentów po leczeniu radiojodem (grupa 131-I).
Materiał i metody: Przebadano 214 pacjentów z zaostrzeniem GO. Grupa ATD składała się ze 168 pacjentów leczonych lekami tyreostatycznymi. Grupa 131-I składała się z 46 pacjentów leczonych radiojodem. Wszyscy pacjenci byli leczeni pulsami dożylnymi methylprednisolonu (łączna dawka 8,0 g), a następnie poddawani radioterapii oczodołów (20 Gy w 10 frakcjach). Indeksy CAS i IO, stężenia TSH, fT4 oraz TRAb oceniano przed leczeniem, a następnie 1, 6 i 12 miesięcy po leczeniu.
Wyniki: W obu grupach miesiąc po leczeniu indeks CAS istotnie zmniejszył się w porównaniu z wartościami wyjściowymi, $p < 0,05$. W grupie ATD mediana stężenia TRAb-0 wynosiła 5,6 U/l (min = 0,1; max = 114,0) przed leczeniem i 1,4 U/l (min = 0,1; max = 75,3) ($p < 0,05$) 12 miesięcy po leczeniu (TRAb-12). W grupie 131-I mediany stężenia TRAb-0 i TRAb-12 wynosiły odpowiednio 14,3 IU/L (min = 0,6; max = 90,0) i 3,65 IU/l (min = 0,1; max = 41,0) ($p < 0,05$). Mediana wartości indeksu IO przed leczeniem (IO-0) w grupie ATD wynosiła 5,0 (min = 1,0; max = 12,0), a po leczeniu (IO-12) 2,0 (min = 0,0; max = 8,0) ($p < 0,05$). W grupie 131-I mediany wartości IO-0 i IO-12 wynosiły odpowiednio 5,0 (min = 2,0; max = 9,0) i 2,0 (min = 0,0; max = 6,0) ($p < 0,05$).
Wnioski: Stopień zaawansowania GO u pacjentów w grupie ATD i 131-I nie różnił się znamiennie statystycznie przez cały okres obserwacji. Mimo że stężenia TRAb w grupie 131-I zawsze przekraczały górny zakres wartości prawidłowych i były wyższe niż w grupie ATD, skuteczność leczenia GO w obu grupach była taka sama. **(Endokrynol Pol 2016; 67 (6): 554–561)**

Słowa kluczowe: *orbitopatia tarczycowa; leczenie radiojodem; glikokortykosteroidy dożylne; radioterapia oczodołów*

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Introduction

Graves' orbitopathy (GO) is a rare disease associated with autoimmune disorder — Graves' disease (GD), with a prevalence of about 25% in GD patients [1–3]. According to Tanda et al. [4], some 20% of patients suffering from Graves' disease have inactive or mild GO, 6% have active and moderate-to-severe GO, and only 0.3% develop dysthyroid optic neuropathy (DON). The remaining 73.7% of Graves' patients are free of ocular symptoms. The prevalence of GO tends to decline over the years, perhaps due to the decrease in smoking habits or to earlier diagnosis [4–7]. As only limited groups of GO patients are available for randomised clinical trials (RCTs), precise GO pathogenesis and targeted treatment remain uncertain [2, 8]. It is believed that higher TRAb titres are present in patients with more severe GO [9, 10]. Radioiodine treatment is associated with an increased risk of ophthalmopathy and more severe course than that after antithyroid medication [11, 12]. After radioiodine, persistent elevated TRAb levels were observed for over five years [13, 14].

The aim of our study was to evaluate the efficacy of immunosuppressive treatment of GO in patients who had earlier been treated with anti-thyroid drugs (the ATD group) or who had undergone radioiodine therapy (the 131-I group).

Material and methods

Over the years 2000–2008 more than four hundred patients were admitted to our Endocrinology Department of the University Hospital, presenting with exacerbation of the eye syndrome in the course of Graves' disease. The patients who voluntarily participated in this prospective observational study signed their written consent and underwent follow-up for a period of 12 months after completion of their GO treatment. The drop-out rate was 46% (i.e. of 400 enlisted patients 214 completed this study). The study was approved by the Bioethics Committee of the Jagiellonian University. Before admission to our Department, patients had been treated elsewhere for hyperthyroidism, either with anti-thyroid drugs (ATD group) or with radioiodine (131 I-group). The ATD group consisted of 168 patients, 119 females and 49 males, of mean age 52.2 ± 11.2 years. The 131-I group consisted of 46 patients, 37 females and 9 males, of mean age 52.1 ± 13.3 years. All patients were evaluated by the same ophthalmologist. Severity and activity of GO were graded using the Clinical Activity Score (CAS) [15] ranging between 0 and 7 and the NOSPECS (No signs or symptoms; Only signs; Soft tissue involvement; Proptosis; Extraocular muscle involvement; Corneal involvement; Sight loss) classification [16], as expressed by the Orbitopathy Index (IO), ranging between 0 and 15. Orbital CT evaluations were performed for all patients. Patients were rendered euthyroid prior to application of methylprednisolone pulses. CAS and IO indices, TSH, FT4, and anti-TSH receptor antibody (TRAb) levels were evaluated prior to, and 1, 6, and 12 months after treatment. Patients were treated with intravenous methylprednisolone pulses (1 g for two consecutive days each week to a total dose of 8.0 g) followed by orbital irradiation a month later (20 Gy total dose in 10 daily fractions). No major side effects of glucocorticoid therapy were observed.

The ATD group

The mean TSH and fT4 concentration before GO treatment was 2.34 ± 8.81 μU/mL and 18.34 ± 12.24 pmol/mL, respectively. Methimazole was used in 133 patients and L-thyroxin in 131 patients. Thyroidectomy was performed in 26 (15.8%) patients. Enlargement of the extraocular muscles was observed in the CT-scans of 85.1% of patients. The mean time of GO duration was 12.5 ± 20.3 months. The mean time of hyperthyroidism treatment was 31.5 ± 52.4 months. After IV pulses 41.1% of patients had to continue their therapy with oral glucocorticosteroids while awaiting their radiotherapy, during radiotherapy, and up to two months post therapy.

The 131-I group

Radioiodine treatment was offered to patients with IO < 3 and CAS < 3. In this group, TSH blood concentration prior to 131-I treatment was 0.24 ± 0.58 μU/mL. The mean radioiodine activity administered was 496 ± 141 MBq. On admission to our Clinic due to GO, 35 of 46 patients (76%) were hypothyroid (mean TSH concentration 23.9 ± 24.5 μU/mL). To maintain euthyroidism, patients were treated with L-thyroxin. Prior to their radioiodine treatment thyroidectomy was performed in 17.4% of patients. Eight patients received I-131 treatment twice and one patient three times. In 87% of patients, enlargement of extraocular muscles was observed in orbital CT. The mean time of GO duration was 11.9 ± 17.8 months. The mean time of hyperthyroidism treatment was 72.3 ± 67.8 months. After IV methylprednisolone pulses, 28.3% of patients had to continue their therapy with oral glucocorticosteroids until radiotherapy, during radiotherapy, and up to two months post therapy.

Laboratory tests

TSH concentrations were measured using radioimmunoassay (RIA) by Byk-Mallincrodt and immunoradiometric assay (IRMA) by Brahms GmbH, (normal range 0.4–4.0 μU/mL). fT4 concentrations were measured

using electrochemiluminescence immunoassay (ECLIA) by Roche Diagnostics (normal range 12–22.0 pmol/L). TRAb concentrations were measured using radioimmunoreceptor assay (RRA, TRAK human) by Brahms GmbH (normal value < 2.0 IU/L).

Statistical analysis

We evaluated the efficacy of GO treatment. The ATD and 131-I groups were compared in terms of GO activity and severity, and with respect to TRAb levels during the follow-up period. Descriptive and inferential statistical data analysis was performed. Arithmetic means, standard deviations (± SD), and medians (min, max) were calculated. The Shapiro-Wilk test was used to test the normal distribution of data. For data with normal distribution, Student's *t*-test was applied. For data with non-normal distribution, U-Mann-Whitney and Wilcoxon signed-rank tests were applied. Since for non-Gaussian distributions the t-test may be valid if the number of samples exceeds 50 due to the property of robustness, the t-test was also applied in our analysis. The assumed level of significance was $\alpha < 0.05$. SoftStat Statistica, version 9.0 software was used.

Results

The ATD group

In this group, the median value of the CAS-0 index prior to treatment and CAS-1 one month after treatment was 4 points (min = 0, max = 7) and 1 point (min = 0, max = 7), respectively ($p < 0.05$) (Fig. 1, Table I).

The median IO-0 values in the ATD group prior to treatment and after 12 months (IO-12) of observation were 5 points (min = 1, max = 12) and 2 points (min = 0, max = 8), respectively ($p < 0.05$) (Table I). As based on t-test for paired samples and Wilcoxon signed-rank test, the IO values after 1, 6, and 12 months of observation were significantly lower than those before treatment ($p < 0.05$).

In the ATD group, no differences between median IO-0 values for female and male patients were observed: 5 points (min = 2, max = 12) and 5 points (min = 1, max = 12), respectively. However, after 12 months, these differences were significant: median IO-12 values were 2 points (min = 0, max = 7) and 3 points (min = 0, max = 8), respectively. Indeed, this difference remained significant during the follow-up period.

Before treatment, over 90% of patients experienced soft tissue swelling and extraocular muscle dysfunction. Within this subgroup, 30% developed severe (grade 3) symptoms. Proptosis was diagnosed in 53% of patients, of whom 6% experienced marked proptosis. Corneal pathology was observed in 21.4% of patients including severe damage in 1.2% of patients. Dysthyroid optic neuropathy (DON) was observed in 8.3% of patients, including severe DON, detected in 3.0% of patients. Aggravation of GO was observed in three patients one month after and in four patients six months after completion of treatment.

After 12-month follow-up upper lid retraction, soft tissue swelling, or extraocular muscle dysfunction (mainly grades 1 or 2) were present in 52.3%, 40.5%, and 60.7% of patients, respectively. In 46.7% of patients IO of 2 or 3 was stated, hence they still experienced symptoms of mild Graves' orbitopathy.

In the ATD group, TSH and fT4 concentrations did not differ significantly throughout the 12-month follow-up. The median value of TRAb-0 level was 5.6 IU/L (min = 0.1; max = 114.0) *vs.* 1.4 IU/L (min = 0.1; max = 75.3) for TRAb-12 ($p < 0.05$). TRAb concentrations at 1, 6, and 12 months after treatment were lower than the baseline level (Table I), (Wilcoxon signed-rank test, $p < 0.05$). Since the distribution of TRAb values was right-skewed, we took logarithms of these values and analysed their distribution using the Shapiro-Wilk test, followed by the t-test ($p < 0.05$) (Fig. 2).

The 131-I group

In this group, the median values of CAS-0 index prior to treatment and CAS-1 one month after treatment were 4 (min = 2, max = 7) and 2 (min = 0, max = 6), respectively ($p < 0.05$) (Fig. 1, Table I).

The median values of IO-0 in this group prior to treatment and after 12 months (IO-12) of observation were 5 (min = 2, max = 12) and 2 (min = 0, max = 6), respectively ($p < 0.05$) (Table I). Based on the t-test for paired samples and the Wilcoxon signed-rank test, IO values after 1, 6, and 12 months of observation were significantly lower than those before treatment ($p < 0.05$).

About 90% of patients in this group presented with upper eyelid retraction, soft tissue swelling and extraocular muscle dysfunction before treatment. Among them, 21.7% and 24.0% had severe soft tissue swelling and extraocular muscle dysfunction (grade 3), respectively. Proptosis was present in 54.3% of patients, but none of them developed severe proptosis. Corneal damage was observed in 19.6% of patients. No symptoms of DON were found in this group. Aggravation of GO was observed in three patients one month after and in one patient six months after completion of the treatment.

After 12-month follow-up, upper lid retraction, soft tissue swelling and extraocular muscle dysfunction remained with various degrees of severity (mainly grade 1 and 2) in 56.5%, 43.5%, and 67.4% of patients, respectively. 20.5% of patients had an IO of 4, hence they still experienced symptoms of moderately severe orbitopathy.

Table I. *Comparison of TRAb levels and of IO and CAS scores in the ATD and 131-I groups*
Tabela I. *Porównanie stężenia TRAb, indeksów IO i CAS w grupie ATD i 131-I*

Parameter	ATD median (min-max)	131-I median (min-max)	Difference p-value
TRAb 0 [IU/L]	5.6 (0.1–114.0)	14.3 (0.6–90.0)	0.0013
TRAb 1 [IU/L]	2.2 (0.01–51.9)	7.7 (0.1–80.0)	0.0001
TRAb 6 [IU/L]	1.6 (0.1–78.8)	4.65 (0.1–96.0)	0.0009
TRAb 12 [IU/L]	1.4 (0.1–75.3)	3.65 (0.1–41.0)	0.0129
IO 0	5.0 (1.0–12.0)	5.0 (2.0–9.0)	0.7155
IO 1	3.0 (0.0–10.0)	4.0 (1.0–8.0)	0.1610
IO 6	3.0 (0.0–9.0)	3.0 (0.0–7.0)	0.8657
IO 12	2.0 (0.0–8.0)	2.0 (0.0–6.0)	0.9461
CAS 0	4.0 (0.0–7.0)	4.0 (2.0–7.0)	0.1588
CAS 1	1.0 (0.0–7.0)	2.0 (0.0–6.0)	0.0151

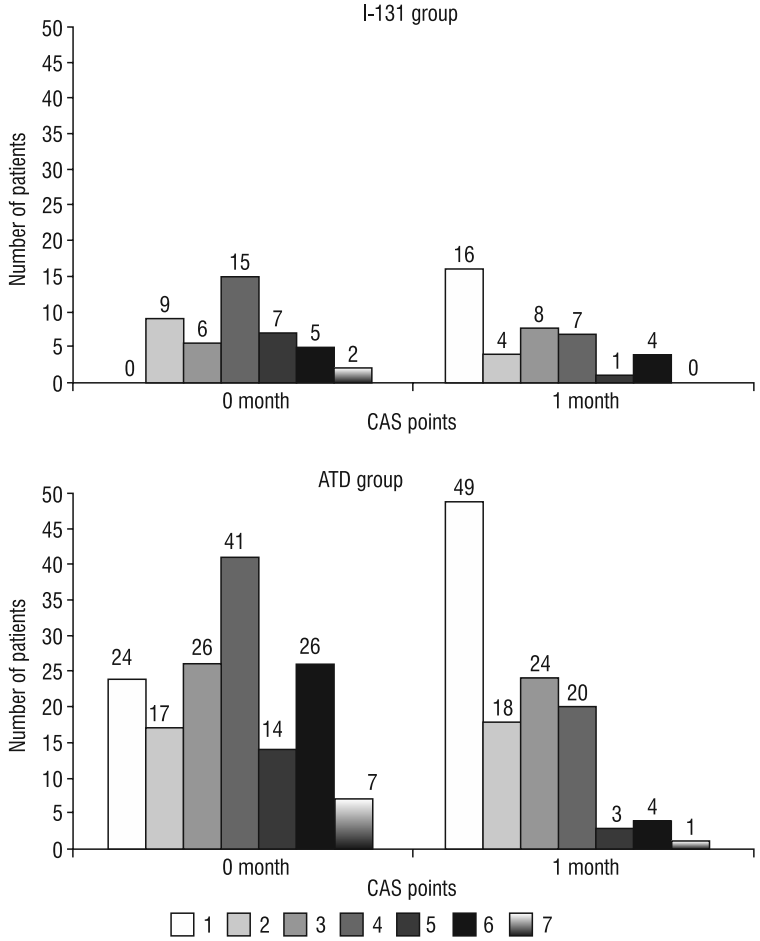

Figure 1. *Distribution of Clinical Activity Score (CAS) prior to and 1 month after GO treatment in the ATD and 131-I groups*
Rycina 1. *Rozkład indeksu CAS przed leczeniem i 1 miesiąc po leczeniu GO w grupie ATD i w grupie 131-I*

In the 131-I group, TSH and fT4 concentrations remained within normal range and did not differ significantly throughout the 12-month follow-up. The median TRAb-0 value prior to treatment was 14.3 IU/L (min = 0.6; max = 90.0) *vs.* TRAb-12 of 3.65 IU/L (min = 0.1; max = =41.0) ($p < 0.05$) (Table I). TRAb concentrations after 1, 6, and 12 months of treatment were significantly lower than the baseline level, as shown by t-test for paired

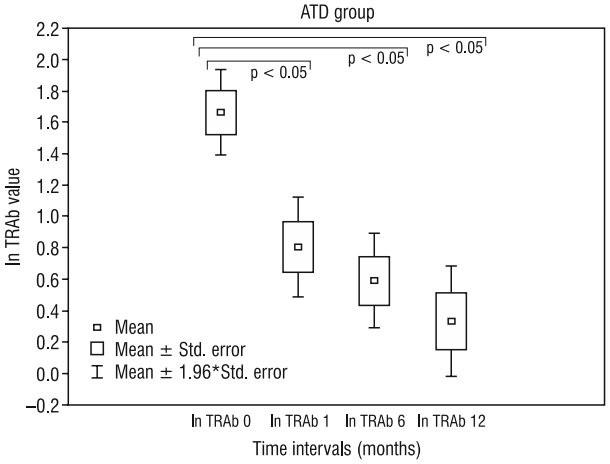

Figure 2. *TRAb concentration prior to, and 1, 6, and 12 months after treatment in the ADT group (t-test for paired samples, natural logarithms of variables)*

Rycina 2. *Stężenie TRAb przed leczeniem oraz po 1, 6, i 12 miesiącach w grupie ATD (test t dla prób zależnych dla zmiennych zlogarytmowanych)*

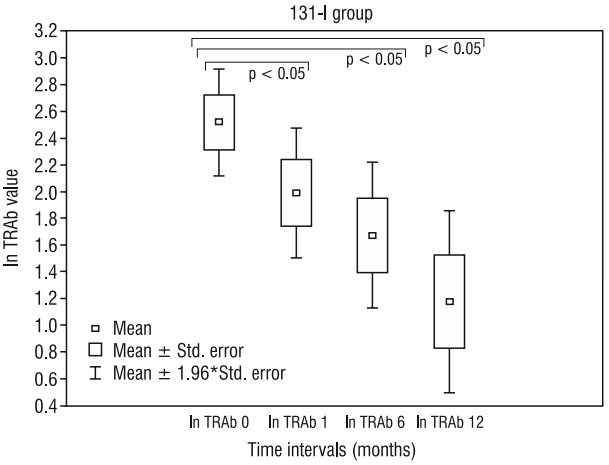

Figure 3. *TRAb concentration prior to, and 1, 6, and 12 months after treatment in the 131-I group (t-test for paired samples, natural logarithms of variables)*

Rycina 3. *Stężenie TRAb przed leczeniem oraz po 1, 6, i 12 miesiącach w grupie 131-I (test t dla prób zależnych dla zmiennych zlogarytmowanych)*

samples applied to natural logarithms of variables (Fig. 3) and Wilcoxon signed rank test ($p < 0.05$).

Comparison between ATD and 131-I groups (Table I)

The activity and severity of GO in patients of the ATD and 131-I groups did not differ, despite differences in TRAb levels (Table I). We note that the percentage of patients after thyroidectomy in both groups did not differ significantly.

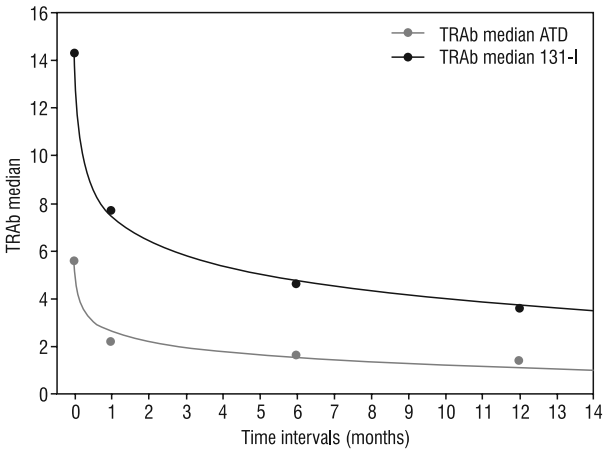

Figure 4. *Time-dependence of TRAb concentration over 12 months in the ATD group, $y = 2.6354–1.4099*\log_{10}(x)$, and in the 131-I group, $y = 7.4554–3.4544*\log_{10}(x)$*

Rycina 4. *Porównanie zmian stężenia TRAb w grupie ATD opisane równaniem $y = 2.6354–1.4099*\log_{10}(x)$ i w grupie 131-I opisane równaniem $y = 7.4554–3.4544*\log_{10}(x)$ w czasie 12-miesięcznej obserwacji*

After treatment, CAS-1 decreased significantly in both groups, with respect to CAS-0 ($p < 0.05$). The CAS-1 score was significantly higher in the 131-I group ($p < 0.05$).

Independently of the method of analysis chosen (mean or median), TRAb levels in the 131-I group were always above normal level and significantly higher than those in the ATD group throughout the follow-up period ($p < 0.05$) (Table I, Fig. 4).

In the ATD group the course of median TRAb level (y) *vs.* time, in months (x), could be approximated by the equation $y = 2.6354–1.4099*\log_{10}(x)$, while in the 131-I group the respective approximation was $y = 7.4554–3.4544*\log_{10}(x)$, as shown in Figure 4.

There was no significant difference in the course of IO between the ATD and 131-I groups (Table I). In the ATD group the course of the median IO (y) *vs.* time, in months (x), could be approximated by the expression $y = 4.0812*\exp(–0.0595*x)$. In the 131-I group the course of the median IO could be approximated by $y = 4.6481*\exp(–0.0713*x)$. The IO *vs.* time dependences over 12 months in both groups are shown in Figure 5.

Before treatment there was no significant difference between both groups with respect to age, sex, GO duration, IO, CAS-0 and fT4 levels. In the 131-I group, hyperthyroidism was significantly extended in time ($p < 0.05$), and pre-treatment levels of TSH were significantly higher than in the ATD group (6.7 ± 16.3 *vs.* 2.34 ± 8.81 U/L, $p < 0.05$).

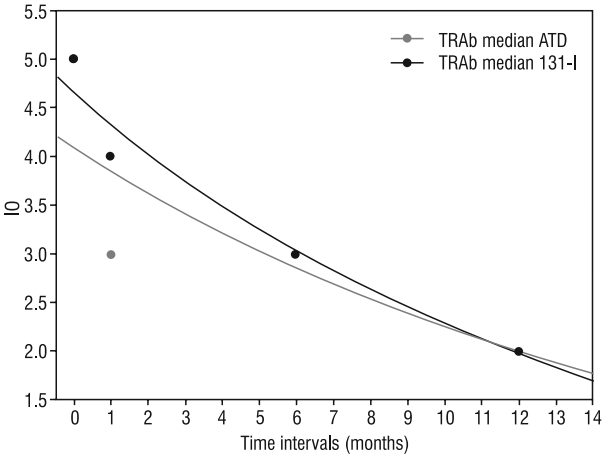

Figure 5. *Time-dependence of the IO over 12 months in the ATD group, y = 4.0812*exp (–0.0595*x), and in the 131-I group, y = 4.6481*exp (–0.0713*x)*

Rycina 5. *Porównanie zmian indeksów IO w grupie ATD opisane równaniem y = 4.0812*exp(–0.0595*x) i w grupie 131-I opisane równaniem y = 4.6481*exp(–0.0713*x) w czasie 12-miesięcznej obserwacji*

Discussion

It is well known that radioiodine treatment may prolong thyrotropin receptor (TSH-R) autoimmunity in patients with Graves' disease, leading to *de novo* orbitopathy occurrence or to exacerbation of symptoms of concurrent GO. The likely pathogenesis of this phenomenon is the sudden release of thyroid antigens by 131-I-damaged thyroid cells, causing an increase in the production of autoantibodies, including TRAb [11, 13]. It is estimated that GO aggravation after 131-I treatment affects up to 20% of patients [11] and is more predominant in patients who had earlier manifested eye symptoms [2, 8] or in those with prolonged hypothyroidism following radioiodine treatment [17]. Male patients are more prone to GO exacerbation [18]. We also found significantly higher mean and median IO values in men in our ATD group over the follow-up period, suggesting a more severe and resistant course of GO in male patients. However, this trend was not observed in our 131-I group, presumably due to the small number of men (19.6%) in this group.

In a multi-centre study by Prummel et al. conducted in 2003 [19], proptosis was observed in 63% of newly referred patients with GO, while keratopathy was detected in 16% and optic nerve involvement in 21% of their patients. In our study, the percentage of the above-mentioned pathologies was comparable, except for DON, diagnosed in only 8.3% patients of our ATD group. The median values of IO prior to treatment and after 12 months of observation were 5 and 2, respectively, in both groups, thus the two groups did not differ with respect to severity, neither on admission to our Department nor at the end of the follow-up period, which is in agreement with a retrospective study conducted by Sisti et al. [20]. However, it is believed that patients after radioiodine treatment tend to develop more severe GO [11].

Thyroidectomy may have an impact on the course of GO. Weber et al. [21] observed either improvement or subsidence of eye symptoms after surgery. In contrast, our patients - despite their previous thyroidectomy — were still hyperthyroid and, for that reason, had been treated with methimazole or 131-I before admission to our Department to treat their GO exacerbation. Therefore, we assumed that prior thyroidectomy in these patients would not affect the efficacy of our GO treatment. We note that since the percentages of operated patients in the ATD and the 131-I groups did not differ, both groups are comparable with respect to the subject of our study.

Our treatment protocol, established in the year 2000, was based on our clinical experience and on published work available at the time, as summarised in the review of Zang et al. [22]. Like Macchia et al. in 2001 [23], we administered 1 g of methylprednisolone for two consecutive days each week, but we did not exceed the cumulative dose of 8.0 g.

In 2008 in the *Thyroid* journal, following reported cases of acute liver failure associated with high cumulative doses of methylprednisolone, EUGOGO recommended not to exceed a cumulative dose of methylprednisolone of 8.0 g [24]. By that time, we had completed our patient recruitment.

For orbital irradiation we applied a cumulative dose of 20 Gy, which was in line with the studies conducted by Marcocci et al. in 2001 [25] and by Ng et al. in 2005 [26].

We used a combination of methylprednisolone pulses followed by orbital irradiation, with good clinical outcome, low rate of recurrence, and no major clinical side effects. This treatment had already been proposed in 1983 by Bartalena et al. [27], who reported a better outcome of the combined therapy. Several studies confirmed the efficacy of orbital irradiation as based on the meta-analysis by Viani et al. [28], although Otsuka et al. [29] found no significant differences in terms of the therapeutic effect between groups treated with steroid pulses with or without orbital irradiation. There are no large RCTs comparing the advantage of this combined treatment over IV glucocorticosteroids alone [28, 30, 31]. As reported in a randomised study, lower orbital doses of 12 Gy were sufficient in reducing soft tissue changes, and higher doses were required in patients with ocular motility impairment [32]. It is generally accepted that orbital irradiation should be considered in patients with

diplopia and impaired motility [24, 26, 30, 32]. This has been confirmed by our clinical observation.

We found our treatment to be effective, since the rate of recurrence was low. Both groups responded well, and decreases in CAS and IO indices were significant. However, the CAS-1 score was significantly higher in the 131-I group, which might suggest that in patients with GO after radioiodine treatment glucocorticoid therapy is less effective. Following a recent multicentre randomised control trial [33], lower doses of IV glucocorticoids have been suggested. The efficacy and safety of different IV glucocorticosteroid therapy protocols are still under debate. Presently, there are no generally accepted recommendations or guidelines for treatment of GO [20, 34–36].

Elevation of TRAb blood concentration is an important GO risk factor [9]. TRAb levels increase after radioiodine treatment and remain elevated over considerably longer periods than in patients undergoing ATD therapy or surgery [10, 13, 14]. In our study, TRAb levels in the I-131 group were systematically above normal level and were always higher than those in the ATD group. In particular, we note that in our ATD group, TRAb levels returned to normal within one month after treatment.

We also note that despite the differences in TRAb levels, the efficacy of the applied immunosuppressive treatment was comparable in both studied groups. It is believed that higher TRAb titres are associated with more severe Graves' orbitopathy [9, 10]. However, this was not confirmed by our study. On the contrary, we found no statistically significant difference between the distribution of IO (which is relevant to the severity of GO) in the ATD and 131-I groups over respective time intervals.

Conclusions

Treatment of Graves' Orbitopathy in its moderate to severe form remains difficult.

GO severity in the ATD and in the 131-I group of patients did not differ significantly over the course of their observation.

Although TRAb levels in the 131-I group were always above normal level and higher than those in the ATD group; the efficacy of GO treatment in both groups did not differ significantly.

References

1. Wiersinga WM, Kahaly GJ. Graves' Orbitopathy: A Multidisciplinary Approach — Questions and Answers. Karger, Basel 2007; 34–36.
2. Bartalena L, Macchia PE, Marcocci C et al. Effects of treatment modalities for Graves' hyperthyroidism on Graves' orbitopathy: a 2015 Italian Society of Endocrinology Consensus Statement. J Endocrinol Invest 2015; 38: 481–487.
3. Bartalena L, Fatourechi V. Extrathyroidal manifestations of Graves' disease: a 2014 update. J Endocrinol Invest 2014; 37: 691–700.
4. Tanda ML, Piantanida E, Liparulo L et al. Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. J Clin Endocrinol Metab 2013; 98:1443–1449.
5. Perros P , Žarković M , Azzolini C et al. PREGO (presentation of Graves' orbitopathy) study: changes in referral patterns to European Group On Graves' Orbitopathy (EUGOGO) centres over the period from 2000 to 2012. Br J Ophthalmol 2015; 99: 1531–1535.
6. Sawicka-Gutaj N, Gutaj P, Sowiński J et al. Influence of cigarette smoking on thyroid gland- an update. Endokrynologia Polska 2014; 65: 54–62.
7. Wiersinga WM Smoking and thyroid. Clin Endocrinol (Oxf). 2013; 79: 145–51.
8. Bartalena L. Graves' orbitopathy: imperfect treatments for a rare disease. Eur Thyroid J 2013; 2: 259–269.
9. Eckstein AK, Plicht M, Lax H et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. J Clin Endocrinol Metab 2006; 91: 3464–3470.
10. Jang SY, Shin DY, Lee EJ et al. Correlation between TSH receptor antibody assays and clinical manifestations of Graves' orbitopathy. Yonsei Med J 2013; 54: 1033–1039.
11. Acharya SH, Avenell A, Philip S et al. Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: a systematic review. Clin Endocrinol (Oxf) 2008; 69: 943–950.
12. Król A, Koehler A, Nowak M et al. Radioactive iodine (RAI) treatment of hyperthyroidism is safe in patients with Graves' orbitopathy — a prospective study. Endokrynologia Polska 2014; 65: 40–45.
13. Laurberg P, Wallin G, Tallstedt L et al. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. Eur J Endocrinol 2008; 158: 69–75.
14. Andrade VA, Gross JL, Maia AL. Serum thyrotropin-receptor autoantibodies levels after I therapy in Graves' patients: effect of pretreatment with methimazole evaluated by a prospective, randomized study. Eur J Endocrinol 2004; 151: 467–474.
15. Mourits MP, Prummel MF, Wiersinga WM et al. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf) 1997; 47: 9–14.
16. Werner SC. Classification of the eye changes of Graves' disease. Am J Ophthalmol 1969; 68: 646–648.
17. Stan MN, Durski JM, Brito JP et al. Cohort study on radioactive iodine-induced hypothyroidism: implications for Graves' ophthalmopathy and optimal timing for thyroid hormone assessment. Thyroid 2013; 23: 620–625.
18. Perros P, Crombie AL, Matthews JN et al. Age and gender influence the severity of thyroid-associated ophthalmopathy: a study of 101 patients attending a combined thyroid-eye clinic. Clin Endocrinol (Oxf) 1993; 38: 367–372.
19. Prummel MF, Bakker A, Wiersinga WM et al. Multi-center study on the characteristics and treatment strategies of patients with Graves' orbitopathy: the first European Group on Graves' Orbitopathy experience. Eur J Endocrinol 2003; 148: 491–495.
20. Sisti E, Menconi F, Leo M et al. Long-term outcome of Graves' orbitopathy following high-dose intravenous glucocorticoids and orbital radiotherapy. J Endocrinol Invest 2015; 38: 661–668.
21. Weber KJ, Solorzano CC, Lee JK et al. Thyroidectomy remains an effective treatment option for Graves' disease. Am J Surg 2006; 191: 400–405.
22. Zang S, Ponto KA, Kahaly GJ. Clinical review: Intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. J Clin Endocrinol Metab 2011; 96: 320–332.
23. Macchia PE, Bagattini M, Lupoli G et al. High-dose intravenous corticosteroid therapy for Graves' ophthalmopathy. J Endocrinol Invest 2001; 24: 152–158.
24. Bartalena L, Baldeschi L, Dickinson AJ et al. Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. Thyroid 2008; 18: 333–346.
25. Marcocci C, Bartalena L, Tanda ML et al. Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: results of a prospective, single-blind, randomized study. J Clin Endocrinol Metab 2001; 86: 3562–3567.
26. Ng CM, Yuen HK, Choi KL et al. Combined orbital irradiation and systemic steroids compared with systemic steroids alone in the management of moderate-to-severe Graves' ophthalmopathy: a preliminary study. Hong Kong Med J. 2005; 11: 322–330.
27. Bartalena L, Marcocci C, Chiovato L et al. Orbital cobalt irradiation combined with systemic corticosteroids for Graves' ophthalmopathy: comparison with systemic corticosteroids alone. J Clin Endocrinol Metab 1983; 56: 1139–1144.

28. Viani GA, Boin AC, De Fendi LI et al. Radiation therapy for Graves' ophthalmopathy: a systematic review and meta-analysis of randomized controlled trials. Arq Bras Oftalmol 2012; 75: 324–332.
29. Ohtsuka K, Sato A, Kawaguchi S et al. Effect of steroid pulse therapy with and without orbital radiotherapy on Graves' ophthalmopathy. Am J Ophthalmol 2003; 135: 285–290.
30. Vilar-González S, Lamas-Oliveira C, Fagúndez-Vargas MA et al. Thyroid orbitopathy, an overview with special attention to the role of radiotherapy. Endocrinol Nutr 2015; 62: 188–199.
31. Ruchała M, Hernik A, Zybek A. Orbital radiotherapy in the management of Graves' orbitopathy — current state of knowledge. Endokrynologia Polska 2014; 65: 388–396.
32. Johnson KT, Wittig A, Loesch C et al. A retrospective study on the efficacy of total absorbed orbital doses of 12, 16 and 20 Gy combined with systemic steroid treatment in patients with Graves' orbitopathy. Graefes Arch Clin Exp Ophthalmol 2010; 248: 103–109.
33. Bartalena L, Krassas GE, Wiersinga W et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. J Clin Endocrinol Metab 2012; 97: 4454–4463.
34. Kahaly GJ, Pitz S, Hommel G et al. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab 2000; 90: 5234–5240.
35. van Geest RJ, Sasim IV, Koppeschaar HP et al. Methylprednisolone pulse therapy for patients with moderately severe Graves' orbitopathy: a prospective, randomized, placebo-controlled study. Eur J Endocrinol 2008; 158: 229–237.
36. Zhu W, Ye L, Shen L et al. A prospective, randomized trial of intravenous glucocorticoids therapy with different protocols for patients with graves' ophthalmopathy. J Clin Endocrinol Metab 2014; 99: 1999–2007.