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Graves' ophthalmopathy in patients treated with radioiodine 131-I

Oftalmopatia u pacjentów leczonych radiojodem 131-I

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Abstract

Background: Radioiodine treatment of hyperthyroidism in Graves' disease patients may cause or aggravate the course of ophthalmopathy (GO). We evaluated the activity and severity of ophthalmopathy in patients who acquired GO following radioiodine therapy.
Material and methods: Between 2003 and 2005, 763 Graves' disease patients (50.9% of the total number of 1,500 patients referred to our Department) were treated with radioiodine 131-I. This treatment was only offered to patients with NOSPECS score < 3 and CAS < 3. Following their radioiodine treatment, in 39 patients (5.1% of all Graves' disease patients), mean age 53.9 ± 11.6 years, onset of GO was observed within 12 months of post-treatment follow-up.
Results: In 39 patients who developed GO after 131-I treatment, median values of hTRAb and NOSPECS score were 15.4 U/L (IQR = 22.9) and 5.0 points (max = 8.0; min = 2.0), respectively, at the time of their GO onset. Patients were qualified for methylprednisolone pulse therapy (8.0 g) and subsequent radiotherapy (20 Gy). Median concentration of hTRAb and NOSPECS score at one, six and 12 months post-GO therapy were: 10.0 U/L (IQR = 21.6) and 4.0 (max = 6.0; min = 1.0); 7.5 U/L (IQR = 1.1) and 3.0 (max = 10.0; min = 0.0); 2.8 U/L (IQR = 8.3) and 3.0 (max = 6.0; min = 0.0), respectively. A positive association between hTRAb and NOSPECS score was observed over the control period. IL-6 and IL-2 concentration prior to and one month after treatment remained elevated.
Conclusions: Since 5% of our Graves' disease patients developed severe GO following radioiodine treatment, an association between radioiodine therapy and severe ophthalmopathy cannot be excluded. IL-6 and IL-2 concentrations remained elevated after glucocorticoid therapy. **(Pol J Endocrinol 2011; 62 (3): 214–219)**

Key words: *Graves' ophthalmopathy, radioiodine treatment*

Streszczenie

Wstęp: Leczenie radiojodem nadczynności tarczycy u pacjentów z chorobą Gravesa może spowodować pojawienie się oftalmopatii (GO) *de novo* lub jej zaostrzenie. W pracy oceniono aktywność i stopień zaawansowania GO u pacjentów po leczeniu radiojodem.
Materiał i metody: W latach 2003–2005763 pacjentów z chorobą Gravesa (50,9% z 1500 pacjentów skierowanych do naszego ambulatorium) leczono radiojodem 131-I. Leczenie proponowano pacjentom z NOSPECS < 3 i CAS < 3 punkty. U 39 pacjentów (5,1% pacjentów z chorobą Gravesa), średnia wieku 53,9 ± 11,6 roku, obserwowano rozwój oftalmopatii w ciągu roku po leczeniu.
Wyniki: U 39 pacjentów z GO po leczeniu 131-I mediany stężenia hTRAb i NOSPECS wynosiły na początku choroby 15,4 U/L (IQR = 22,9) i 5 punktów (max = 8,0; min = 2,0) odpowiednio. Pacjentów zakwalifikowano do leczenia pulsami metylprednizolonu (8,0 g) i uzupełniającej radioterapii (20 Gy). Mediany stężenia hTRAb i NOSPECS po 1, 6 i 12 miesiącach wynosiły 10,0 U/L (IQR = 21,6) i 4,0 (max = 6,0; min = 1,0); 7,5 U/L (IQR = 12,1) i 3,0 (max = 10,0; min = 0,0); 2,8 U/L (IQR = 8,3) i 3,0 (max = 6,0; min = 0,0), odpowiednio. W czasie obserwacji stwierdzono dodatnią zależność pomiędzy stężeniem hTRAb i NOSPECS. Odnotowano podwyższone stężenia IL-6 i IL-2 przed leczeniem i 1 miesiąc po leczeniu glikokortykoidami.
Wnioski: Ponieważ 5% badanych pacjentów z chorobą Gravesa zachorowało na ciężką GO po leczeniu radiojodem, nie można wykluczyć związku pomiędzy leczeniem 131-I a następowym rozwojem oftalmopatii. Stężenia IL-6 i IL-2 pozostały podwyższone po leczeniu glikokortykoidami. **(Endokrynol Pol 2011; 62 (3): 214–219)**

Słowa kluczowe: *oftalmopatia Gravesa, leczenie radiojodem*

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Introduction

Graves' ophthalmopathy (GO) is clinically associated with autoimmune thyroid disease and the production of autoantibodies to thyroidal antigens. In particular, autoantibodies to thyroid stimulating hormone receptor (TSH-R) may be involved in the pathogenesis of GO, as TSH-R is expressed in retro-orbital fibroblasts and fat cells [1]. The course of GO appears to be affected by treatment of thyrotoxicosis and there is growing evidence that the application of radioiodine therapy may enhance the risk of GO occurrence, or its severity.

In Bartalena et al. randomised study [2] which confirmed the results of an earlier randomised trial by Tallstedt et al. [3], radioiodine treatment of hyperthyroidism was found to cause or aggravate the course of GO in 15% of patients studied, while only 3% of patients treated with methimazole developed GO. Although such consequences of radioiodine treatment are recognised, the mechanisms by which GO is promoted are not well understood. The rise of antibody titers observed following radioiodine application is probably due to the release of antigens from radiation-damaged thyrocytes. The rapid development of hypothyroidism after 131-I treatment implicates TSH-R activation as an important factor in the evolution of GO [4, 5].

In our retrospective analysis, we evaluated the activity and severity of ophthalmopathy in patients who acquired GO following their radioiodine therapy.

Material and methods

At our Department of Endocrinology between 2003 and 2005, 763 Graves' disease patients (50.9% of the total number of 1,500 patients referred) underwent radioiodine 131-I therapy. Following their radioiodine treatment, in 31 females and eight males (i.e. 5.1% of all Graves' patients), mean age 53.9 ± 11.6 years, onset of GO was observed within 12 months of post-treatment follow-up (mean time of onset: 23.4 ± 22.8 weeks).

All patients received methimazole prior to radioiodine for 3-12 months at out-patient facilities other than our Department. Methimazole was discontinued seven days before radioiodine therapy. Over the period of 6-8 weeks following 131-I administration, control of hyperthyroidism was achieved with a β-blocker (propranolol). 131-I therapy was only offered to patients with NOSPECS (**N**o signs or symptoms; **O**nly signs; **S**oft tissue involvement; **P**roptosis; **E**xtraocular muscle involvement; **C**orneal involvement; **S**ight loss) total eye score (TES) < 3 points and clinical activity score (CAS) < 3 points [6, 7]. Prior to their 131-I treatment, mean TSH concentration in this group was 0.24 ± 0.58 μU/ml and mean 24-hour 131-I uptake was 54.0 ± 14.6%. The mean activity of 131-I applied was 496 ± 141 MBq. Of patients in the group referred to our Department due to eye problems, 82% were hypothyroid. Their median level of maximum TSH after 131-I treatment was 6.2 μU/ml (IQR = 13.8). Patients were rendered euthyroid with appropriate doses of L-thyroxine at the time of their GO treatment. Throughout the 12 month follow-up, all these patients were maintained euthyroid. Patients were qualified for methylprednisolone pulse therapy (2.0 g per week for four consecutive weeks) and subsequent radiotherapy (20 Gy).

The severity and activity of GO were evaluated according to NOSPECS classification, presented as TES and CAS prior to and one, six, and 12 months after 131-I treatment.

For laboratory measurements, the following methods were used: TSH — ECLIA (Roche), hTRAb (thyrotropin receptor antibodies) — TRAK human RRA (Brahms), IL-2 (interleukin 2) — OPTEIA (Pharmingen), IL-6 (interleukin 6) — ELISA KIT II BD (Bioscenses). Basic statistics (mean ± SD, median, IQR), U-Mann-Whitney test, Wilcoxon test, Spearman's rank correlation test, Shapiro-Wilk test or Fisher's test were applied in our statistical analysis, all with the use of a StatSoft STATISTICA version 9.0 package.

Results

In patients who developed GO after 131-I treatment, median values of hTRAb and NOSPECS were 15.4 U/L (IQR = 22.9) and 5.0 points (max = 8.0; min = 2.0), respectively, at the time of their GO onset. Patients reported for control one, six and 12 months post-therapy. Median concentration of hTRAb and NOSPECS score at one, six and 12 months were: 10.0 U/L (IQR = 21.6) and 4.0 (max = 6.0; min = 1.0); 7.5 U/L (IQR = 12.1) and 3.0 (max = 10.0; min = 0.0); 2.8 U/L (IQR = 8.3) and 3.0 (max = 6.0; min = 0.0), respectively.

In about 56% of the total number of patients (22/39), CAS exceeded 4 points, while about 80% of these patients developed moderately severe or severe GO. The relation between TES and CAS was found to be significant, based on the Fisher's test ($p < 0.05$) (Table I). A positive correlation between CAS and NOSPECS (TES) prior to and one month after GO therapy was found (correlation coefficient r = 0.71 and r = 0.68, respectively, $p < 0.05$).

The results of GO therapy after one month post-I-131 treatment are illustrated by differences in CAS over this period. The difference between median values of CAS (4.0; max = 7.0; min = 2.0) prior to and one month after therapy (2.0; max = 5.0; min = 0.0), illustrated in Figure 1, was found to be statistically significant ($p < 0.05$, Wilcoxon paired data test).

Table I. Patient characteristics in different groups of disease activity (CAS) prior to glucocorticoid therapy (n = 39). The relation between TES and CAS is statistically significant (Fisher's test, p < 0.05)

Tabela I. Charakterystyka pacjentów w zależności od aktywności choroby (CAS) przed leczeniem glikokortykoidami (n = 39). Stwierdzono znamienną zależność między TES i CAS (test Fishera, p < 0.05)

TES	CAS < 4 pts n = 17 patients	CAS ≥ 4 pts n = 22 patients
Mild 1–4 pts	60 %	21%
Moderately severe 5–8 pts	40%	68%
Severe > 8 pts	0 %	11%

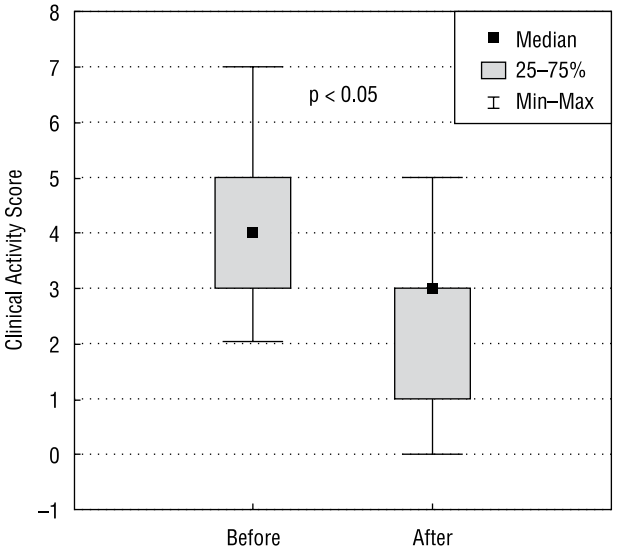

Figure 1. *Clinical Activity Score (CAS) prior to and one month after GO therapy*

Rycina 1. *Indeks aktywności choroby przed leczeniem i 1 miesiąc po leczeniu GO*

Differences in median hTRAb levels prior to treatment and after consecutive time intervals, shown in Figure 2, were found to be statistically significant ($p < 0.05$, Wilcoxon paired data test). No correlations were observed between hTRAb and CAS, TES or interleukin levels. A positive correlation between hTRAb levels prior to and one, six, and 12 months after treatment was found (correlation coefficient $r = 0.79$, $r = 0.76$, and $r = 0.57$, respectively, $p < 0.05$).

Differences in median TES values prior to treatment and after consecutive time intervals, shown in Figure 3, were found to be statistically significant ($p < 0.05$, Wilcoxon paired data test). A positive correlation between TES level prior to and one, six, and 12 months after treatment was found (correlation

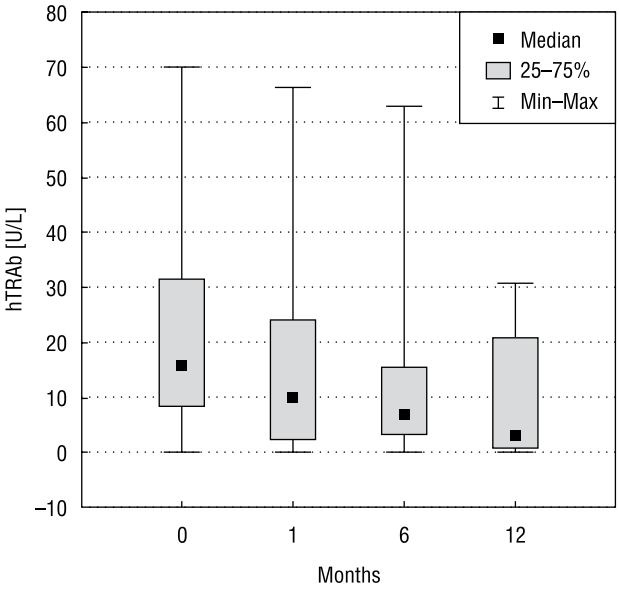

Figure 2. *hTRAb levels over 12 months after GO therapy. Differences between median hTRAb levels over consecutive time intervals are statistically significant (Wilcoxon test, p < 0.05)*

Rycina 2. *Stężenie hTRAb w okresie 12 miesięcy po leczeniu GO. Stwierdzono znamienne statystycznie różnice pomiędzy medianami stężeń hTRAb w kolejnych przedziałach czasowych (test Wilcoxona, p< 0.05)*

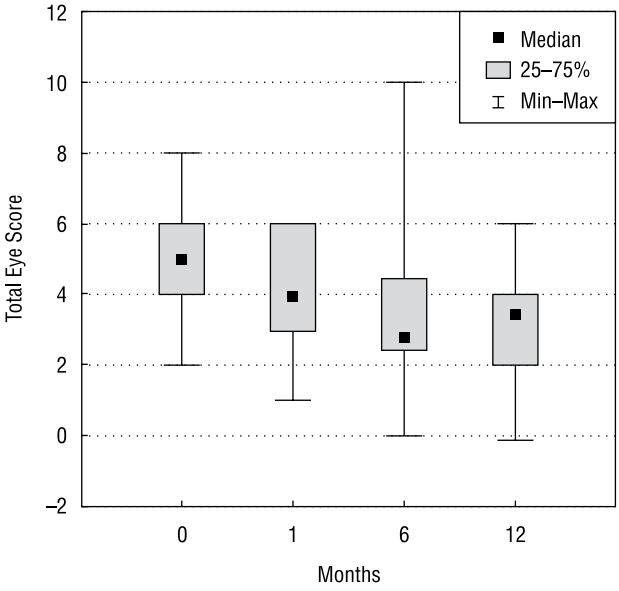

Figure 3. *Total Eye Score (TES) over 12 months after GO therapy. Differences between median TES values over consecutive time intervals are statistically significant (Wilcoxon test, p < 0.05)*

Rycina 3. *Indeks oftalmopatii (TES) w okresie 12 miesięcy po leczeniu GO. Stwierdzono znamienne statystycznie różnice pomiędzy medianami TES w kolejnych przedziałach czasowych (test Wilcoxona, p < 0.05)*

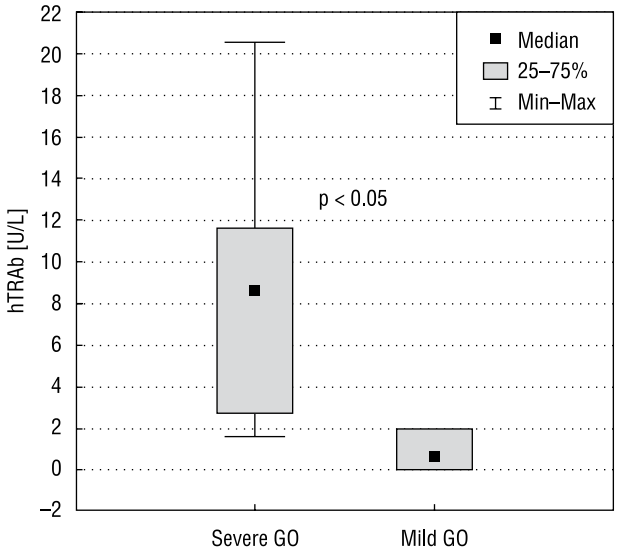

Figure 4. *hTRAb levels 12 months after GO therapy in patients with mild (CAS < 4) and severe (CAS ≥ 4) ophthalmopathy*

Rycina 4. *Stężenia hTRAb 12 miesięcy po leczeniu GO w grupie pacjentów z łagodną (CAS < 4) i ciężką (CAS ≥ 4) oftalmopatią*

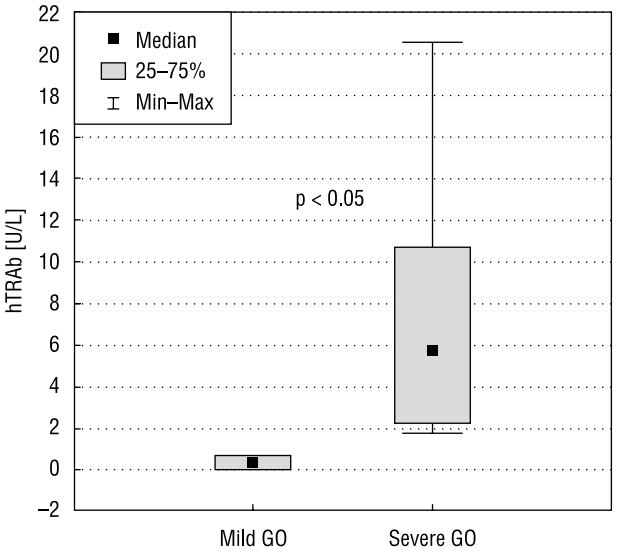

Figure 5. *hTRAb levels 12 months after GO therapy in patients with mild (TES < 5) and severe (TES ≥ 5) ophthalmopathy*

Rycina 5. *Stężenia hTRAb 12 miesięcy po leczeniu GO w grupie pacjentów z łagodną (TES < 5) i ciężką (TES ≥ 5) oftalmopatią*

coefficient r = 0.81, r = 0.57, and r = 0.69 respectively, $p < 0.05$).

Over the 12 month period, a decrease of hTRAb concentration and a decrease of TES were observed, although this association was not found to be statistically significant.

The prevalence of hTRAb at 12 months after steroid therapy was also studied. Some 93% of patients were hTRAb-positive before treatment. At 12 months following GO therapy, 55% of patients still remained hTRAb-positive while the TES of most patients had significantly improved, as illustrated in Figure 3.

On dividing patients into mild and severe GO based on values of CAS (CAS < 4 and CAS ≥ 4, respectively) we found that the difference between median levels of hTRAb was statistically significant 12 months after GO therapy (U-Mann-Whitney test, $p < 0.05$). The differences in median levels of hTRAb prior to, and one and six months after therapy were not significant. We also noted the difference in distributions of hTRAb values between these groups (Figure 4).

On dividing patients into mild and severe GO based on TES (TES < 5 and TES ≥ 5, respectively), we observed similar features. The difference between median levels of hTRAb prior to and 12 months after GO therapy was statistically significant (U-Mann-Whitney test, $p < 0.05$), there was also a difference in hTRAb distribution in each group (Figure 5).

Prior to treatment, the distribution of IL-2 and IL-6 values in our group of patients was quite skewed (with low minima of 2.6 pg/ml and 3.5 pg/ml, respectively and very high maxima of 365.8 pg/ml and 418.0 pg/ml, respectively). The median values were close to the upper normal range: IL-2 = 18.4 pg/ml (normal range 0–20.8 pg/ml) and IL-6 = 10.6 pg/ml (normal range 0.7–12.1 pg/ml). In 50% of the patients, IL-2 and IL-6 concentrations prior to and one month post-treatment remained elevated and did not correlate with hTRAb concentrations or with NOSPECS values. The decrease of IL-2 concentration correlated with the decrease of IL-6 concentration over the one month period (correlation coefficient r = 0.52, $p < 0.05$). The IL-2 concentration prior to GO treatment correlated with maximum TSH concentrations after I-131 treatment (correlation coefficient r = 0.50, $p < 0.05$).

In our group of GO patients, we observed a high percentage of severe (grade 3) upper lid retraction (24%), soft tissue oedema (21%) and muscle impairment (30%) following their radioiodine treatment. Six months later, we considered our therapy to be effective, as worsening of GO was observed in only one patient.

Discussion

In the 1990s, two randomised, controlled trials [2, 3] demonstrated that radioiodine therapy is associated with a small but definite risk of GO progression. Anti-thyroid drug treatment (ATD) and thyroidectomy are associated with a gradual decrease in hTRAb concentration, while hTRAb levels seem to increase over a one year period after I-131 administration [8, 9]. Laurberg et al. [8] measured hTRAb in serum before and five years after the

initiation of medical therapy, surgery or radioiodine in Graves' patients with hyperthyroidism [8]. Radioiodine therapy led to worsening of autoimmunity against the TSH receptor. The number of patients entering remission with disappearance of serum hTRAb during five years of follow-up was considerably lower than after other types of therapy [8].

It seems that peak incidence of GO occurs six months after 131-I administration, but GO may develop at any time (1-24 months) after radioiodine treatment, as shown by Acharaya et al. [10] in their analysis of randomised control trials. In our group of patients, onset of GO was observed most frequently within 12 months post-131-I therapy. However in some patients, the first symptoms of GO were not observed until after two years, which may be explained by the extended period of hTRAb elevation in patients treated with 131-I [8].

It has been suggested that in patients with active GO, anti-thyroid drugs should be the treatment of choice for hyperthyroidism and GO should be treated promptly [11]. However, Menconi et al. [12] showed in a randomised study that total thyroid ablation (near total thyroidectomy followed by radioiodine therapy) gave a better outcome of GO immunosuppressive treatment than near–total thyroidectomy alone. Therefore, it has been recently proposed that patients with active GO be treated early with ablative therapy for their hyperthyroidism, with concomitant GO therapy [13]. EUGOGO has no clear-cut opinion on treating hyperthyroidism in GO, i.e. by anti-thyroid medication or by more aggressive ablation [14].

A recent systematic review by Acharaya et al. [10] and the study by the Swedish Thyroid Study Group [15] published several years after the randomised controlled trials by Tallstedt and Bartalena [2, 3] confirm that I-131 therapy can cause exacerbation of GO. Other established risk factors of GO worsening after radioiodine are smoking [15, 16], severity of hyperthyroidism expressed by pre-treatment serum T3 level of ≥ 5 nmol/l [3] or untreated hypothyroidism following 131-I treatment [17]. Of all patients referred to our Department due to eye problems, 82% were hypothyroid, some of them with TSH levels as high as 91.7 μU/ml. Since normalisation of thyroid function is considered to be essential in reducing severity and improving the outcome of GO treatment [18, 19], our patients remained euthyroid over the one year follow-up period.

In the randomised controlled trials analysed by Acharaya et al. [10], no correlation was observed between hTRAb levels and the progression of ophthalmopathy. In our study, no correlations were observed between hTRAb and CAS, TES or interleukin levels. However, over the 12 month period of follow-up, a decrease of hTRAb concentration and a decrease of TES were observed, although this association was not statistically significant. According to the study by Eckstein et al. [20], a high hTRAb level represents an independent risk factor for developing more severe GO, and should be considered a risk factor for GO progression after radioiodine therapy.

Radioiodine is more likely to induce progression of pre-existing GO than cause de novo occurrence of this complication [2]. A small but significant proportion of patients (5%) experience severe GO [18]. Indeed, in our study, onset of GO was observed in 5.1% of patients with Graves' disease treated with radioiodine 131-I, and 80% of these patients were diagnosed with moderately severe or severe GO with a pre-treatment CAS value of ≥ 4 points. In several retrospective studies and randomised trials, the risk of GO development or progression after hyperthyroidism therapy with anti-thyroid drug treatment or surgery has been compared to radioiodine treatment [2, 3, 21, 22]. The risk of GO after 131-I treatment varied between 15% and 39%, compared to the risk of GO after ATD (anti-thyroid drugs) of 3- 21% and after surgery, where the risk was 16% [21]. Although the absolute risk is fairly small, it cannot be ignored [10].

Worsening of pre-existing thyroid-associated ophthalmopathy after radioiodine therapy can be prevented by the administration of glucocorticoids [2, 22, 23]. This treatment can also ameliorate pre-existing GO [2, 22, 23] and should be standard practice [10].

In patients without clinical signs of pre-existing GO, prednisolone prophylaxis may also be beneficial [9, 22], although its routine use following 131-I has yet to be justified [10].

To establish whether cytokine levels correlate with GO activity and severity, we measured IL-2 and IL-6 concentrations in our patients prior to and one month after treatment. In our study, the median concentrations of IL-2 and IL-6 in euthyroid patients with moderate to severe GO and CAS ≥ 4 points prior to treatment were around upper normal ranges.

Wakelkamp et al. [24] found IL-6 levels and sIL-2R to be significantly elevated in moderately severe GO euthyroid patients treated with anti-thyroid drugs, compared to healthy controls. In their study, the increase of pro-inflammatory interleukins was attributed to active eye disease rather than to thyroid autoimmune disease or related to the thyroid status. The cytokine levels did not correlate with GO activity (CAS) or severity (NOSPECS). This is in agreement with our study, where in some 50% of patients IL-2 and IL-6 concentrations prior to and one month post-treatment remained elevated and did not correlate with hTRAb levels or with NOSPECS values. Łącka et al. [25] found a significant serum IL-6 increase in euthyroid GO patients with CAS ≥ 4 points, compared to healthy controls. Two weeks after

glucocorticoid therapy, serum IL-6 had decreased in most of their patients. On the other hand, Myśliwiec et al. [26] found increased serum IL-6 levels in patients with GO compared to controls, and no change after glucocorticoid treatment.

As far as we know, sIL-2R rather than IL-2 serum concentrations were studied on active GO patients, as circulating levels of sIL-2R appear to correlate with the activity of several autoimmune diseases. The levels of IL-2, IL-6, sIL-2R, and sIL-6R have been found to be significantly higher in patients with active GO than in control patients [27–29]. The levels of sIL-2R and sIL-6R decreased after glucocorticoid treatment [27] and did not correlate with hTRAb levels [28, 29]. Similarly, in our study, IL-2 concentrations did not correlate with hTRAb levels. *In vitro* studies of orbital tissue have also demonstrated higher mRNA levels of proinflammatory IL-6 and IL-2 in active GO, compared to inactive GO orbital tissues [30].

It appears that while the role of cytokine is evident in the autoimmune process which occurs in the orbit as GO develops, there is as yet no consensus as to the best serum cytokine in terms of indicating the severity of GO or acting as a predictor of treatment efficacy or an indicator of the best treatment strategy.

Conclusions

Since 5% of our Graves' disease patients developed severe GO following radioiodine treatment, an association between radioiodine therapy and severe ophthalmopathy cannot be excluded. Preventive administration of glucocorticoids should be recommended in patients with Graves' disease, even with mild ophthalmopathy, when planning radioiodine therapy. IL-6 and IL-2 concentrations remained elevated after glucocorticoid therapy.

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