

# Factors affecting the course of Graves' orbitopathy and poor response to glucocorticoid treatment followed by orbital radiotherapy

Agnieszka Jagiełło-Korzeniowska<sup>1</sup>, Andrzej Sokołowski<sup>2</sup>,  
Alicja Hubalewska-Dydejczyk<sup>3</sup>, Bożena Romanowska-Dixon<sup>1</sup>,  
Agata Bałdys-Waligórska<sup>3,4</sup>

<sup>1</sup> Chair and Department of Ophthalmology and Ocular Oncology, Jagiellonian University Medical College, Cracow, Poland  
Head: Prof. Bożena Romanowska-Dixon, MD, PhD

<sup>2</sup> Department of Statistics, Cracow University of Economics, Cracow, Poland  
Head: Prof. Andrzej Sokołowski, PhD

<sup>3</sup> Chair and Department of Endocrinology, Jagiellonian University Medical College, Cracow, Poland  
Head: Prof. Alicja Hubalewska-Dydejczyk, MD, PhD

<sup>4</sup> Department of Endocrinology and Internal Medicine, Faculty of Health Science and Medicine, Andrzej Frycz Modrzewski  
Krakow University, Cracow, Poland  
Head: Prof. Filip Gołkowski, MD, PhD



## ABSTRACT

Graves' orbitopathy is a rare autoimmune disorder characterized by the inflammation of orbital tissues. The course of disease can be described in terms of its activity and severity.

**Aim:** The aim of our study was to determine the factors affecting the activity and severity of Graves' orbitopathy, as well as to identify the predictive factors of poor response to glucocorticoid treatment followed by orbital irradiation.

**Methods:** We performed a prospective observational study of 214 patients with Graves' orbitopathy who were divided into two groups depending on the treatment they had previously obtained for their Graves' disease. They received i.v. methylprednisolone pulses followed by orbital radiotherapy. They were examined and had their TSH, TRAb and FT<sub>4</sub> levels evaluated prior to treatment and after 1, 6 and 12 months.

**Results:** A pre-treatment TRAb concentration higher by one unit (U/L) implied a mean increase in the relative risk of active orbitopathy by 4.7% ( $p = 0.0362$ ). A TRAb concentration higher by one U/L 1 month after treatment implied a mean increase in the relative risk of moderate-to-severe and severe GO by 8.7% ( $p = 0.0167$ ) 6 months after treatment. As regards poor response to treatment, patients with moderate-to-severe and severe Graves' orbitopathy on admission carried a higher risk of being non-responders. Each point scored on the NOSPECS scale prior to treatment increased the relative risk of the patient being a non-responder by 30%.

**Conclusions:** Patients with higher TRAb levels have a higher risk of active Graves' orbitopathy and moderate-to-severe and severe Graves' orbitopathy. Monitoring TRAb serum concentration in those patients is of great importance. Patients with more severe Graves' orbitopathy carry a higher risk of being poor responders to immunosuppressive treatment. Therefore, careful monitoring of patients with Graves' orbitopathy and their early referral to specialized centers is essential.

**Key words:** Graves' orbitopathy, Graves' disease, TRAb, NOSPECS, glucocorticoid treatment, orbital radiotherapy

## HIGHLIGHTS

The course of Graves' Orbitopathy is affected by TRAb concentration. About 30% of patients receiving immunosuppressive treatment do not respond to the therapy. Patients with more severe Graves' Orbitopathy (NOSPECS >5) carry a higher risk of being a non-responder. Careful monitoring of GO patients and early referral to specialized centers is essential.

## INTRODUCTION

Graves' orbitopathy (GO) is an autoimmune disorder closely related to autoimmune thyroid disease. The autoimmune response is triggered by antibodies (TRAbs) against the thyroid-stimulating hormone receptor (TSH-R), which is expressed in orbital fibroblasts. This leads to an inflammatory infiltration of orbital tissues, increased production of glycosaminoglycans (GAGs) and adipogenesis. The insulin-like growth factor 1 receptor (IGF-1R) is also expressed by orbital fibroblasts and plays an essential role in GO pathogenesis [1–3]. The evolution of GO is self-limiting and may be described by the Rundle curve [4]. The first three phases of GO correspond to an active inflammation of orbital tissues. The first phase involves worsening signs and symptoms. During the second, plateau phase, no further exacerbation is observed. The third phase of gradual improvement is followed by the final, inactive phase with no further progression. As the active inflammation resolves, orbital tissue fibrosis ensues [5, 6].

Disease *activity* can be assessed by the Clinical Activity Score (CAS), which comprises the typical signs of inflammation: redness, pain, swelling and impaired function. The scored signs and symptoms include: eyelid swelling, eyelid erythema, conjunctival redness, chemosis, inflammation of the caruncle or plica, pain behind the globe and pain on gaze [7]. A CAS  $\geq 3$  indicates an active disease [8].

Within disease *severity* the functional and cosmetic changes related to the inflammation and fibrosis of the extraocular muscles and soft tissues are evaluated. The features considered in GO severity assessment are: palpebral aperture, soft-tissue involvement, exophthalmos, extraocular muscle dysfunction, corneal pathology and sight loss due to optic nerve compression. GO severity can be evaluated by means of the NOSPECS and EUGOGO classifications [9, 10].

Precise assessments of GO activity and severity are of great importance as they determine the choice of treatment. Surgical interventions, except for orbital decompression in dysthyroid optic neuropathy (DON), should not be undertaken while there is active inflammation of orbital tissues. On the other hand, all immunomodulatory therapies are of benefit during active GO [1, 11]. Patients with mild GO should be monitored, while patients with moderately severe and active GO should be treated with intravenous steroid pulses as a treatment of choice. Glucocorticoid treatment may be followed by orbital radiotherapy to enhance its efficacy [6, 12]. Both treatment modalities have an anti-inflammatory effect and have proved to be effective [13, 14].

Steroids induce anti-inflammatory proteins, inhibit key inflammatory mediators, decrease glycosaminoglycan production and suppress the function of immunocompetent cells [15]. They have a positive impact on visual acuity, orbital tissue oedema, inflammation of extraocular muscles and ocular motility [16]. Radiotherapy particularly im-

proves ocular motility in GO patients by diminishing eye muscle enlargement and soft-tissue swelling [17]. It acts on lymphocytes, which are radiosensitive and infiltrate the orbit [18]. Radiotherapy also inhibits nitric oxide production, which reduces inflammatory pain and oedema [1].

Although effective in terms of reducing inflammation, both glucocorticoids and radiotherapy are not targeted treatments for GO. This may be the reason why  $\frac{1}{3}$  of all patients do not respond to these treatment modalities [6, 19, 20].

The aim of our study was to determine the factors affecting the activity and severity of GO and to search for predictive factors which determine poor response to glucocorticoid treatment followed by orbital irradiation. Since radioiodine ( $^{131}\text{I}$ ) treatment for Graves' disease (GD) may result in *de novo* GO or may exacerbate the course of concurrent GO [21–23], we divided our patients into two groups, depending on the treatment they received for GD: the ATD group – treated with anti-thyroid drugs, and the  $^{131}\text{I}$  group – additionally treated with radioiodine.

## MATERIALS AND METHODS

We performed a prospective observational study of 214 patients treated between 2000 and 2008 for GO. The study was conducted in accordance with Helsinki Declaration. Patients gave their written informed consent to take part in the study and the study was approved by the Jagiellonian University Bioethics Committee. Patients were divided into two groups depending on the treatment they had previously received for their GD: a group, consisting of 168 patients, who had been treated with antithyroid drugs (the ATD group) and another, including 46 subjects, who had been treated with radioiodine (the  $^{131}\text{I}$  group). For a detailed description and comparison of the two groups see table 1 in our previous article [24].

Patients were examined by the same ophthalmologist and had their TSH, TRAb and FT<sub>4</sub> levels evaluated prior to treatment and after 1, 6 and 12 months. The activity and severity of GO were evaluated by means of CAS and NOSPECS classifications, respectively. GO severity was expressed by the Orbitopathy Index (IO). All patients were rendered euthyroid and received 1.0 g of methylprednisolone intravenously for 2 consecutive days each week, up to a total dose of 8.0 g. The treatment was followed by orbital irradiation with a total dose of 20 Gy in 10 daily fractions 1 month later.

We assumed that CAS  $\geq 3$  and IO  $\geq 3$  represented active GO and proceeded to search for factors affecting GO activity. Using logistic backward step-wise regression, we analysed whether radioiodine therapy, age, gender and pre-treatment TSH, FT<sub>4</sub> and TRAb (TSH-0, FT<sub>4</sub>-0, TRAb-0) levels had any influence on GO activity.

We determined the factors affecting GO severity. We assumed that IO > 5 represents moderate to severe and severe

GO [25]. Using logistic regression, we evaluated the risk of moderate-to-severe and severe GO (IO > 5) with respect to TRAb concentration.

Finally, we analysed the relationship between CAS and IO using the chi-squared test for independence. Before treatment, all patients were divided into three groups with respect to IO (IO 1–2, IO 3–8, IO 9–15) [26] and assigned to subgroups of CAS ≤ 3 or CAS > 3.

In our study, patients who required additional treatment with oral glucocorticoids after intravenous methylprednisolone pulses and subsequent orbital radiotherapy were classified as non-responders. To identify the predictive factors of poor response to combined immunosuppressive treatment in both groups we performed a discriminant analysis with a backwards variable selection, which included age, gender, duration of hyperthyroidism, duration of GO, pre-treatment TSH, FT<sub>4</sub> and TRAb (TSH-0, FT<sub>4</sub>-0, TRAb-0) levels, as well as GO activity and severity prior to treatment (CAS-0 and IO-0 respectively).

## RESULTS

We found that the only factors affecting GO activity in our patients were pre-treatment TRAb levels (TRAb-0) and age. As seen in table 1, TRAb-0 concentration higher by one unit (U/L) in both groups (ATD and <sup>131</sup>I) analysed together, implied a mean increase in the relative risk of active orbitopathy of 4.7% (p = 0.0362). In turn, each year of age increased the mean relative risk of active GO by 2.8% (p = 0.0603).

TABLE 1

Influence of age and TRAb-0 on GO activity.				
Variable	n	Relative risk	95% confidence interval	p
Age	171	1.028	0.999–1.059	0.0603
TRAb-0	171	1.047	1.003–1.092	0.0362

The correlation between TRAb concentration and GO severity expressed by the IO was investigated using Spearman's rank correlation coefficient. The values of TRAb concentration and their logarithms were analysed over all observation times. A positive correlation between TRAb and IO over time observation was found in both <sup>131</sup>I and ATD groups. In both these groups, TRAb-0 concentrations prior to treatment correlated positively with TRAb concentrations after 1, 6 and 12 months (p < 0.05). A similar correlation was observed with respect to the ophthalmopathy index IO. Higher IO-0 and TRAb-0 values resulted in high-

er ophthalmopathy index values and TRAb concentrations over the time of observation.

As shown in table 2, in the <sup>131</sup>I group, TRAb concentration 1 month after treatment (TRAb-1) correlated with the parallel IO-1 and was a good predictor of the IO value after 6 months (IO-6). TRAb-1 concentration higher by one U/L implied a mean increase in relative risk of moderate-to-severe and severe GO (IO-1 > 5) by 5.6% (p = 0.0498), and of IO-6 > 5 by 8.7% (p = 0.0167).

TABLE 2

Risk of moderate to severe and severe GO (IO > 5) with respect to TRAb concentration prior to and 1 month after GO treatment – logistic regression. The coefficients with an asterisk are statistically significant; p < 0.05.					
Independent variable	Dependent variable	n	Relative risk	95% confidence interval	p
TRAb-0	IO-0 > 5	40	1.009	0.980–1.039	0.5230
	IO-1 > 5	38	1.019	0.988–1.051	0.2294
	IO-6 > 5	36	1.049	1.005–1.094	0.0284*
	IO-12 > 5	35	0.971	0.847–1.114	0.6676
TRAb-1	IO-1 > 5	32	1.056	1.000–1.115	0.0498*
	IO-6 > 5	32	1.087	1.016–1.162	0.0167*
	IO-12 > 5	29	0.987	0.865–1.126	0.8405

\*Coefficients with an asterisk are statistically significant; p < 0.05.

As shown in table 3, we also found that IO depends on CAS. All patients with very severe GO (IO 9–15) on admission had a CAS- 0 > 3 and all patients with mild GO (IO 1–2) on admission had a CAS-0 ≤ 3.

TABLE 3

Relationship between the CAS and IO index.		
IO-0	CAS-0 ≤ 3 (n), (%)	CAS 0 > 3 (n), (%)
<b>p = 0.0000</b>		
<b>IO 1–2</b>	10 10.99%	0 0.00%
<b>IO 3–8</b>	81 89.01%	106 90.60%
<b>IO 9–15</b>	0 0.00%	11 9.40%
<b>Total</b>	91 100%	117 100%

As regards poor response to treatment, 28% (13/46) of patients in the  $^{131}\text{I}$  group were classified as non-responders. A discriminant analysis with backwards variable selection revealed that only TSH-0 ( $p = 0.0498$ ) and IO-0 ( $p = 0.0574$ ) remained as variables likely to predict patients' poor response to treatment in this group. Since the efficiency of correct classification was only 73%, TSH-0 and IO-0 were not the decisive factors. In the ATD group, 41% (69/167) of patients were classified as non-responders. The only variable likely to predict a patient's poor response to treatment in this group was IO-0 ( $p < 0.05$ ). Since the efficiency of correct classification was only 60%, IO-0 was probably not a decisive factor. As shown in table 4, the final model of logistic regression revealed that each IO-0 point scored prior to treatment increased the relative risk of the patient being a poor responder by 30% (RR = 1.30; 95% CI 1.10–1.54;  $n = 163$ );  $p < 0.05$ .

FIGURE 1

Theoretical log-normal distributions of IO-0 in subgroups of patients who required (poor response,  $n = 82$ ) or did not require ( $n = 131$ ) oral glucocorticoid treatment after methylprednisolone pulses (total:  $n = 213$  patients).

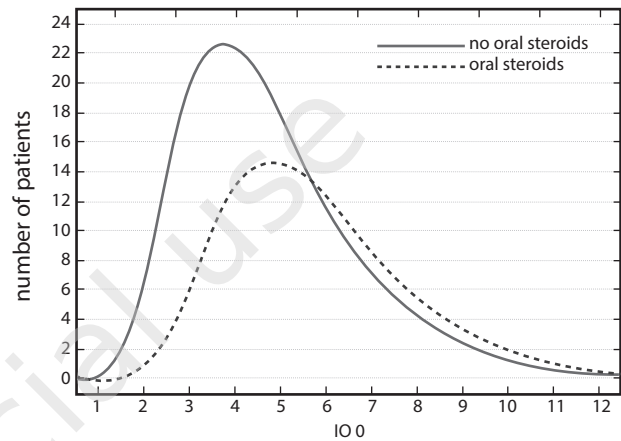


TABLE 4

Variables likely to predict a patient's poor response to treatment in the ATD group. Model of logistic regression. Coefficients with an asterisk are statistically significant;  $p < 0.05$ .

N = 109	Gender	Age	Duration of GO	TSH-0	FT4-0	TRAb-0	CAS-0	IO-0
RR	1.08	0.98	1.00	1.01	1.01	1.01	0.70	1.87
95% CI	0.41–2.88	0.94–1.02	0.98–1.02	0.93–1.10	0.97–1.05	0.99–1.03	0.46–1.07	1.25–2.79
p	0.8745	0.2470	0.8208	0.7300	0.5508	0.4423	0.0980	0.0020*

\*Coefficients with an asterisk are statistically significant;  $p < 0.05$ .

We analysed the empirical distribution and theoretical log-normal distributions of IO-0 of non-responders ( $n = 82$ ) and responders ( $n = 131$ ) in both groups obtaining a cut-off value of  $\text{IO-0} > 5$ , which means that patients whose IO-0 exceeded 5 carried a higher risk of being a non-responder. As shown in figure 1, the proposed cut-off value takes into account that poor responders comprised approximately 40% of all patients (sensitivity 47%, specificity 71%, positive predictive value 51%, negative predictive value 68%).

## DISCUSSION

The objective of our study was to identify factors likely to influence GO activity, severity and poor response to combined immunosuppressive treatment (intravenous methylprednisolone pulses and subsequent orbital radiotherapy). Previous studies have already found that TRAb concentration has an impact on the course of Graves' orbitopathy. Higher TRAb serum levels increase the risk of active GO and moderate-to-severe or severe GO [25]. We performed TRAb measurements using a second-generation thyrotropin-binding inhibitor immunoglobulin (TBII) assay (TRAK human by BRAHMS GmbH, Germany); however,

TRAb can also be evaluated by means of different functional TSH-receptor stimulating immunoglobulin (TSI) bioassays [27].

In our study, a TRAb level higher by one unit (U/L) before treatment implied a mean increase in relative risk of active GO by 4.7%. Gerding et al. measured TSH binding inhibiting immunoglobins (TBII) and TSH-receptor stimulating immunoglobins (TSI) in 63 patients with GO. They compared 2 measurement modalities and found that TBII and TSI serum levels were strongly related to each other, as well as strongly correlated with the CAS value. Gerding et al. also found a correlation between proptosis and both TBII and TSI [28]. Similar results were obtained by Jang et al [27].

We found a positive correlation between TRAb and the severity of GO (IO) over the entire observation period. In the study by Eckstein et al., TBII concentrations were higher in subjects with severe GO than in subjects with mild GO during the entire observation time [25]. Just like in our study, the authors used a second-generation thyrotropin-binding inhibitor immunoglobulin (TBII) assay (TRAK human by BRAHMS GmbH, Germany) and established the TBII cut-off values for the prediction of severe GO. Prediction of se-

vere GO was possible after 4 months of observation, which is in line with our results. Our study showed that in the radioiodine-treated group, TRAb concentration 1 month after treatment was a good predictor of GO severity after 6 months. TRAb concentration higher by one U/L implied a mean increase in relative risk of moderate-to-severe and severe GO 6 months after treatment by 8.7% (tab. 2). These results again confirm the role TRAb play in the pathogenesis of Graves' orbitopathy. TRAb level before treatment is a better predictor for GO activity. High TRAb concentrations at the onset of Graves' orbitopathy may occur in patients with a mild and with a severe course of GO; however, in patients with a severe course of the disease, TRAb levels remain elevated for a considerably longer period of time. It should be noted, though, that in long-lasting GO, in an inactive fibrotic stage, TRAb levels no longer correlate with GO severity [28].

Given that a higher TRAb level is a risk factor of active and severe GO, careful monitoring of TRAb serum concentration in GO patients is essential.

The limitation of this study is the use of high-dose intravenous methylprednisolone pulses of 1 g for 2 consecutive days each week. This treatment protocol is no longer recommended. The reason for this choice of treatment in our study was that the data were collected between 2000 and 2008, when high-dose i.v. glucocorticoids were still commonly used [16, 29]. Since lower doses have the same or only slightly lower efficacy and a much lower rate of adverse events, the current regimen recommended by the European Group on Graves' Orbitopathy (EUGOGO) starts with 0.5 g of methylprednisolone once weekly for 6 weeks, followed by 0.25 g once weekly for 6 weeks, up to a cumulative dose of 4.5 g. The high-dose regimen is still used, but it is now reserved for more severe cases with diplopia. This regimen begins with 0.75 g once weekly for 6 weeks, followed by 0.5 g once weekly for 6 weeks, up to a cumulative dose of 7.5 g [6]. The cumulative dose is almost the same as in the old protocols (8 g), but it is more staggered and single doses are not administered on consecutive days, which increases treatment safety. The only exception is DON, which should be treated as follows: 0.5–1.0 g of methylprednisolone for 3 consecutive days for 2 weeks [6, 30].

Cumulative doses exceeding 8 g can cause acute liver damage and should be avoided [31, 32]. In our study, we did not exceed the cumulative dose of 8.0 g of methylprednisolone. Since the efficacy of higher doses of steroids is the same, even outperforming the new regimen in eye motility improvement, we believe that application of the old treatment modality does not influence the subject of our study [33].

Another disadvantage of this study is our failure to investigate our patients' smoking habits, as this could have affected our results. Smoking has been proven to be a risk factor for the occurrence of GO and for its progression following

<sup>131</sup>I treatment. It increases the risk of severe GO and reduces response to treatment. The effect of smoking depends on the daily number of cigarettes smoked [34].

As regards poor response to treatment, in our study 28% of patients after radioiodine therapy administered for GD and 41% of patients on antithyroid drugs were classified as non-responders. This is in line with other studies, which confirm that about one third of patients do not respond to steroid immunosuppressive treatment [6, 19, 20]. There might be several reasons for this relatively low response rate.

The first one might be a wrong interpretation of patients' response to therapy. For patients in the first phase of the Rundle curve, during which the signs and symptoms are naturally worsening, lack of evident improvement after immunosuppressive treatment may in fact reflect the inhibition or delay of GO progression. This implies that the treatment is in fact effective [1, 35]. Another explanation for the low response rate might be incorrect qualification of patients for immunosuppressive treatment. Patients with an inactive fibrotic disease with very advanced GO and severe symptoms are unlikely to respond to treatment [28]. Occasionally, these patients end up being treated with glucocorticoids even though they would better benefit from surgical approach [16]. This is why a very meticulous evaluation of disease activity using the Clinical Activity Score is so important. There are some patients, however, who score low in the CAS classification, yet their disease is visibly progressing. They present with a "white eye phenotype" with minimal signs or symptoms of inflammation, but with progressing proptosis, diplopia or restriction of eye movements. Some of these patients do not respond to steroids [36].

We aimed at identifying predictive factors of poor response to the applied treatment for GO. In the <sup>131</sup>I group, the pre-treatment TSH level (TSH-0) and the severity of GO before treatment (IO-0) were the only variables likely to predict a patient's poor response to treatment. In the ATD group, the only factor influencing patients' response to treatment was IO-0. Each IO-0 point scored prior to treatment increased the relative risk of the patient being a poor responder by 30%. We obtained a cut-off value of IO-0 > 5 for being a non-responder, which means that patients whose IO-0 exceeded 5 carried a higher risk of being a non-responder.

Proptosis is one of the main symptoms of GO and plays an important role in assessing the severity of GO. Patients with more severe GO tend to have more pronounced proptosis. However, the beneficial effect of steroids and orbital radiotherapy on proptosis is limited [13, 17, 37, 38], which may be the reason why patients with more advanced GO were less likely to improve after treatment [39, 19]. In our study, 54% of patients in the <sup>131</sup>I group and 53% of patients

in the ATD group had proptosis – a result which is similar to those reported in other studies [40, 41].

Other risk factors which increase the probability of a poor response to glucocorticoid treatment mentioned in the literature are smoking and a low-density lipoprotein cholesterol (LDLc) serum level exceeding 190 mg/dL [42, 43]. Early response to treatment is also a predictive factor of later response. In the study by Bartalena et al., patients who deteriorated at 6 weeks did not improve at 12 or 24 weeks. Of patients whose condition remained unchanged at 6 weeks, only 28% did later improve [35].

Both intravenous steroid pulses and orbital radiotherapy are based on non-specific immunosuppression, which may also explain the high rate of poor response to treatment. IV glucocorticoids affect dendritic and T-cells, inhibit the function and reduce the number of immune cells in orbital tissues. IV glucocorticoids also decrease the synthesis of prostaglandins and pro-inflammatory proteins [15]. Radiotherapy affects radiosensitive lymphocytes and fibroblasts in the orbit, thus reducing inflammation [13, 38].

Fortunately, a more targeted treatment already exists and will hopefully decrease the number of non-responders. The TSH-R and IGF-1-R play a crucial role in active inflammation, adipogenesis and increased production of glycosaminoglycans, leading to the expansion of ocular muscles and to the build-up of orbital fat [2, 3]. They form a signalling complex present in orbital fibroblasts that was not targeted by any previously available GO treatment until January 2020, when the US Food and Drug Administration (FDA) approved teprotumumab for the management of Graves' orbitopathy. Teprotumumab is a human IGF-1R inhibitory monoclonal antibody reacting with the IGF-1-R/TSH-R complex and attenuating the signalling initiated by IGF-1, TSH and thyroid-stimulating immunoglobulins [37]. Teprotumumab was tested in 2 randomised double-blind placebo-controlled multicentre trials [44], where 84 pa-

tients were treated with teprotumumab and 84 received placebo. They were followed up for 24 weeks. Patients in the teprotumumab group had a significant improvement in CAS and diplopia as compared to the placebo group. Moreover, 77% of patients in the active treatment group achieved a reduction in proptosis of at least 2 mm as compared to 13% in the placebo group [44].

Although these results are very promising, we still lack randomized studies comparing the efficacy of teprotumumab and i.v. glucocorticoids. The long-term efficacy and safety of teprotumumab remains unknown. Another clear obstacle is the cost of the new drug, which leaves steroids as a perhaps imperfect but current gold standard of treatment. Given that GO severity is a risk factor of poor response to immunosuppressive treatment, careful monitoring of GO patients and early referral to specialized centers is essential.

## CONCLUSIONS

Patients with higher TRAb levels have a higher risk of active GO.

Higher TRAb concentrations increase the risk of moderate-to-severe and severe GO.

Monitoring of TRAb serum concentration in patients with GO is essential.

Older patients have a higher risk of active GO.

Patients with a more active disease tend to have more severe GO.

Patients with more severe GO carry a higher risk of being poor responders to immunosuppressive treatment.

Careful monitoring of GO patients and early referral to specialized centers is essential.

A high percentage of GO patients do not respond to intravenous steroid pulses and orbital radiotherapy.

Fortunately, new more targeted treatments are already becoming available.

## CORRESPONDENCE

**Agata Bałdys-Waligórska, MD, PhD**

Andrzej Frycz Modrzewski Krakow University, Faculty of Health Science and Medicine, Department of Endocrinology and Internal Medicine  
30-705 Kraków, ul. Gustawa Herlinga-Grudzińskiego 1  
e-mail: awalig@cm-uj.krakow.pl

## ORCID

Agnieszka Jagiełło-Korzeniowska – ID – <http://orcid.org/0000-0003-0195-2778>  
Andrzej Sokołowski – ID – <http://orcid.org/0000-0002-2787-6665>  
Alicja Hubalewska-Dydejczyk – ID – <http://orcid.org/0000-0001-5208-4689>  
Bożena Romanowska-Dixon – ID – <http://orcid.org/0000-0001-6940-5485>  
Agata Bałdys-Waligórska – ID – <http://orcid.org/0000-0002-5539-6642>

## References

1. Wilmar WM, Kahaly GJ. Graves' Orbitopathy A Multidisciplinary Approach-Questions and Answers. 3<sup>rd</sup>, revised and expanded edition. Basel 2017.
2. Tsui S, Naik V, Hoa N et al. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in Graves' disease. *J Immunol.* 2008; 181(6): 4397-405.

3. Krieger CC, Place RF, Bevilacqua C et al. TSH/IGF-1 receptor cross talk in Graves' ophthalmopathy pathogenesis. *J Clin Endocrinol Metab.* 2016; 101(6): 2340-7.
4. Rundle FF, Wilson CW. Development and course of exophthalmos and ophthalmoplegia in Graves' disease with special reference to the effect of thyroidectomy. *Clin Sci* 1945; 5: 177-94.
5. Bartalena L, Piantanida E, Gallo D et al. Epidemiology, Natural History, Risk Factors, and Prevention of Graves' Orbitopathy. *Front Endocrinol (Lausanne)*. 2020; 11: 615993. <http://doi.org/10.3389/fendo.2020.615993>.
6. Bartalena L, Kahaly GJ, Baldeschi L et al.; EUGOGO †. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol.* 2021; 185(4): G43-G67. <http://doi.org/10.1530/EJE-21-0479>.
7. 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(1): 9-14. <http://doi.org/10.1046/j.1365-2265.1997.2331047>.
8. Bartalena L, Baldeschi L, Boboridis K et al.; European Group on Graves' Orbitopathy (EUGOGO). The 2016 European Thyroid Association/ European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J.* 2016; 5(1): 9-26. <http://doi.org/10.1159/000443828>.
9. Werner SC. Modification of the classification of the eye changes of Graves' disease. *Am J Ophthalmol.* 1977; 83: 725-7. [http://doi.org/10.1016/0002-9394\(77\)90140-4](http://doi.org/10.1016/0002-9394(77)90140-4).
10. Barrio-Barrio J, Sabater AL, Bonet-Farriol E et al. Graves' Ophthalmopathy: VISA versus EUGOGO Classification, Assessment, and Management. *J Ophthalmol.* 2015; 2015: 249125. <http://doi.org/10.1155/2015/249125>.
11. Bartalena L. Graves' orbitopathy: imperfect treatments for a rare disease. *Eur Thyroid J.* 2013; 2(4): 259-69. <http://doi.org/10.1159/000356042>.
12. Kim JW, Han SH, Son BJ et al. Efficacy of combined orbital radiation and systemic steroids in the management of Graves' orbitopathy. *Graefes Arch Clin Exp Ophthalmol.* 2016; 254(5): 991-8. <http://doi.org/10.1007/s00417-016-3280-7>.
13. Prummel MF, Terwee CB, Gerding MN et al. A randomized controlled trial of orbital radiotherapy versus sham irradiation in patients with mild Graves' ophthalmopathy. *J Clin Endocrinol Metab.* 2004; 89(1): 15-20. <http://doi.org/10.1210/jc.2003-030809>.
14. 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(2): 229-37. <http://doi.org/10.1530/EJE-07-0558>.
15. Längericht J, Krämer I, Kahaly GJ. Glucocorticoids in Graves' orbitopathy: mechanisms of action and clinical application. *Ther Adv Endocrinol Metab.* 2020; 11: 2042018820958335. <http://doi.org/10.1177/2042018820958335>. eCollection 2020.
16. Zang S, Ponto KA, Kahaly GJ. Clinical review: Intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. *J Clin Endocrinol Metab.* 2011; 96(2): 320-32. <http://doi.org/10.1210/jc.2010-1962>.
17. Mourits MP, van Kempen-Harteveld ML, García MB et al. Radiotherapy for Graves' orbitopathy: randomised placebo-controlled study. *Lancet.* 2000; 355(9214): 1505-9. [http://doi.org/10.1016/S0140-6736\(00\)02165-6](http://doi.org/10.1016/S0140-6736(00)02165-6).
18. Kahaly GJ, Roesler HP, Kutzner J et al. Radiotherapy for thyroid-associated orbitopathy. *Exp Clin Endocrinol Diabetes.* 1999; 107(suppl 5): S201-7. <http://doi.org/10.1055/s-0029-1212186>.
19. Ahn HY, Lee JK. Intravenous Glucocorticoid Treatment for Korean Graves' Ophthalmopathy Patients. *J Korean Med Sci.* 2020; 35(23): e177. <http://doi.org/10.3346/jkms.2020.35.e177>.
20. Kahaly GJ. Management of Graves Thyroidal and Extrathyroidal Disease: An Update. *J Clin Endocrinol Metab.* 2020; 105(12): 3704-20. <http://doi.org/10.1210/clinem/dgaa646>.
21. 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(1): 69-75. <http://doi.org/10.1530/EJE-07-0450>.
22. 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(5): 620-5. <http://doi.org/10.1089/thy.2012.0258>.
23. 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(6): 943-50. <http://doi.org/10.1111/j.1365-2265.2008.03279.x>.
24. Jagiełło-Korzeniowska A, Sokółowski A, Krzewska-Korek A et al. The efficacy of immunosuppressive treatment of Graves' orbitopathy is not affected by previous anti-thyroid drugs or by radioiodine therapy of Graves' disease. *Endokrynol Pol.* 2016; 67(6): 554-61. <http://doi.org/10.5603/EP.2016.0073>.
25. 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(9): 3464-70. <http://doi.org/10.1210/jc.2005-2813>.
26. Eckstein AK, Plicht M, Lax H et al. Clinical results of anti-inflammatory therapy in Graves' ophthalmopathy and association with thyroidal autoantibodies. *Clin Endocrinol (Oxf)*. 2004; 61(5): 612-8. <http://doi.org/10.1111/j.1365-2265.2004.02143.x>.
27. 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(4): 1033-9. <http://doi.org/10.3349/ymj.2013.54.4.1033>.
28. Gerding MN, van der Meer JW, Broenink M et al. Association of thyrotrophin receptor antibodies with the clinical features of Graves' ophthalmopathy. *Clin Endocrinol (Oxf)*. 2000 Mar; 52(3): 267-71. <http://doi.org/10.1046/j.1365-2265.2000.00959.x>.

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: 285-90.
30. Currò N, Covelli D, Vannucchi G et al. Therapeutic outcomes of high-dose intravenous steroids in the treatment of dysthyroid optic neuropathy. *Thyroid.* 2014; 24(5): 897-905. <http://doi.org/10.1089/thy.2013.0445>.
31. Le Moli R, Baldeschi L, Saeed P et al. Determinants of liver damage associated with intravenous methylprednisolone pulse therapy in Graves' ophthalmopathy. *Thyroid.* 2007; 17(4): 357-62. <http://doi.org/10.1089/thy.2006.0267>.
32. Marino M, Morabito E, Brunetto MR et al. Acute and severe liver damage associated with intravenous glucocorticoid pulse therapy in patients with Graves' ophthalmopathy. *Thyroid.* 2004; 14: 403-6.
33. Bartalena L, Krassas GE, Wiersinga W et al. European Group on Graves' Orbitopathy. 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(12): 4454-63. <http://doi.org/10.1210/jc.2012-2389>.
34. Cawood TJ, Moriarty P, O'Farrelly C et al. Smoking and thyroid-associated ophthalmopathy: A novel explanation of the biological link. *J Clin Endocrinol Metab.* 2007; 92(1): 59-64. <http://doi.org/10.1210/jc.2006-1824>.
35. Bartalena L, Veronesi G, Krassas GE et al.; European Group on Graves' Orbitopathy (EUGOGO). Does early response to intravenous glucocorticoids predict the final outcome in patients with moderate-to-severe and active Graves' orbitopathy? *J Endocrinol Invest.* 2017; 40(5): 547-53. <http://doi.org/10.1007/s40618-017-0608-z>.
36. Uddin JM, Rubinstein T, Hamed-Azzam S. Phenotypes of Thyroid Eye Disease. *Ophthalmic Plast Reconstr Surg.* 2018; 34(4S suppl 1): S28-S33. <http://doi.org/10.1097/IOP.0000000000001147>.
37. Smith TJ, Kahaly GJ, Ezra DG et al. Teprotumumab for Thyroid-Associated Ophthalmopathy. *N Engl J Med.* 2017; 376(18): 1748-61. <http://doi.org/10.1056/NEJMoa1614949>.
38. Bartalena L, Marcocci C, Tanda ML et al. Orbital radiotherapy for Graves' ophthalmopathy. *Thyroid.* 2002; 12(3): 245-50. <http://doi.org/10.1089/105072502753600223>.
39. Vannucchi G, Covelli D, Campi I et al. The therapeutic outcome to intravenous steroid therapy for active Graves' orbitopathy is influenced by the time of response but not polymorphisms of the glucocorticoid receptor. *Eur J Endocrinol.* 2013; 170(1): 55-61. <http://doi.org/10.1530/EJE-13-0611>.
40. Prummel MF, Bakker A, Wiersinga WM et al. A. 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(5): 491-5. <http://doi.org/10.1530/eje.0.1480491>.
41. Gharib S, Moazezi Z, Bayani MA. Prevalence and severity of ocular involvement in Graves' disease according to sex and age: A clinical study from Babol, Iran. *Caspian J Intern Med.* 2018; 9(2): 178-83. <http://doi.org/10.22088/cjim.9.2.178>.
42. Thornton J, Kelly SP, Harrison RA et al. Cigarette smoking and thyroid eye disease: a systematic review. *Eye (Lond).* 2007; 21(9): 1135-45. <http://doi.org/10.1038/sj.eye.6702603>.
43. Naselli A, Moretti D, Regalbuto C et al. Evidence That Baseline Levels of Low-Density Lipoproteins Cholesterol Affect the Clinical Response of Graves' Ophthalmopathy to Parenteral Corticosteroids. *Front Endocrinol (Lausanne).* 2020; 11: 609895. <http://doi.org/10.3389/fendo.2020.609895>.
44. Kahaly GJ, Douglas RS, Holt RJ et al. Teprotumumab for patients with active thyroid eye disease: a pooled data analysis, subgroup analyses, and off-treatment follow-up results from two randomised, double-masked, placebo-controlled, multicentre trials. *Lancet Diabetes Endocrinol.* 2021; 9(6): 360-72. [http://doi.org/10.1016/S2213-8587\(21\)00056-5](http://doi.org/10.1016/S2213-8587(21)00056-5).

#### Authors' contributions:

Agnieszka Jagiełło-Korzeniowska: conceptualization, analysis and interpretation of data, writing-original draft preparation. Andrzej Sokołowski: analysis and interpretation of data, writing-review and editing. Alicja Hubalewska-Dydejczyk: supervision, writing-review and editing. Bożena Romanowska-Dixon: supervision, writing-review and editing. Agata Bąldys-Waligórska: conceptualization, analysis and interpretation of data, supervision, writing-review and editing.  
All authors have made the final approval of the version to be submitted.

#### Conflict of interest:

None.

#### Financial support:

The study was performed under statutory grant of the Jagiellonian University Medical College No WŁ/470/KL/L.

#### Ethics:

The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.