

## SHORT COURSE CYCLOSPORINE TREATMENT IN GRAVES' OPHTHALMOPATHY

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### Abstract

*Glucocorticoid (GC) therapy and orbital radiotherapy represent the classic medical management of Graves' ophthalmopathy, either used separately or in association. Because of the lack of response for classic therapy, in some patients new immunosuppressive methods have been tried, one of them is cyclosporine, an selective immunomodulatory drug. This study has proposed to compare short time administration of cyclosporine with administration of iv methylprednisolone and combined therapy (methylprednisolone - orbital radiotherapy). In this comparative and prospective study we followed 127 patients with Graves' ophthalmopathy divided in 4 groups, treated with iv methylprednisolone, associated therapy (GC+RxT), cyclosporine and a control group. All patients were concomitantly treated with oral antithyroid drugs. At 0, 3 and 6 months, the patients were subjected to Hertel exophthalmometry, orbital ultrasonography, TSHR antibody and thyroid-peroxidase antibody assessment and to clinical activity score (CAS) calculation. Comparing the means of each parameter assessed in all 4 groups, a significant decrease of exophthalmia and of extraocular muscle thickness was observed in each group, with a better effect of cyclosporine comparing to iv methylprednisolone, but with a lower effect of cyclosporine comparing to combined therapy. CAS improved significantly in all patients. Cyclosporine has a poorly effect on TRAb and ATPO in contrast with GC or combined therapy.*

**Keywords:** ophthalmopathy, Cyclosporine, Methylprednisolone, orbital radiotherapy, TRAb.

## EFECTELE CICLOSPORINEI LA PACIENȚII CU OFTALMOPATIE GRAVES, ÎN ADMINISTRARE DE SCURTĂ DURATĂ

### Rezumat

*Tratamentul clasic al oftalmopatiei Graves cuprinde terapia cu glucocorticoizi și radioterapia orbitală, folosite individual sau în asociere. Datorită lipsei de răspuns la terapia clasică, s-a încercat folosirea altor metode imunosupresoare, printre care și Ciclosporina, preparat cu efecte imunomodulatorii selective. În acest studiu ne-am propus evaluarea administrării Ciclosporinei pe termen scurt, comparativ cu pulsterapia cu Metilprednisolon și terapia asociată (Metilprednisolon - radioterapie orbitală). Studiul a urmărit comparativ și prospectiv un număr de 127 de pacienți cu oftalmopatie Graves, împărțiți în 4 loturi supuse pulsterapiei cu Metilprednisolon, terapiei asociate, Ciclosporinei și un lot martor. Toți pacienții au fost tratați concomitent cu antitirodine de sinteză. La 0, 3 și 6 luni au fost efectuate aprecierea evoluției exoftalmiei, ecografie orbitală, dozări de anticorpi anti-receptor TSH și anti-tiroperoxidază, s-a notat scorul de activitate clinică a oftalmopatiei (CAS). Rezultatele au demonstrat o ameliorare semnificativă a protruziei și a diametrului mușchilor orbitari la fiecare lot, Ciclosporina a avut efecte mai bune comparativ cu Metilprednisolonul, însă mai reduse comparativ cu terapia combinată. De asemenea,*

*CAS scade semnificativ la toți pacienții. Ciclosporina are efecte minime asupra anticorpilor TRAB și ATPO, spre deosebire de Metilprednisolon și terapia asociată.*

**Cuvinte cheie:** oftalmopatie, Ciclosporină, Metilprednisolon, radioterapie orbitală, TRAB.

### Introduction

Graves' ophthalmopathy is an autoimmune process causing retro orbital tissue inflammation, being mediated by cytokines such as IL-1 and TNF $\alpha$ , and leading to orbital accumulation of nonsulfated glycosaminoglycans and hyaluronic acid [1,2,3]. Graves' ophthalmopathy occurs in 40% of patients, with large variability [4,5,6].

Orbital radiotherapy and glucocorticoids used individually or as an association, are the most common therapies of this disease. They can act synergistically, combining the prompt action of glucocorticoids with the sustained effect of radiotherapy [4,7,8,9,10,11,12]. Associated therapy proved itself as a method of preventing the transitory exacerbation of orbital inflammatory process which occurs in the first week of radiotherapy, and as useful in decreasing the frequent recurrence after steroid withdrawal [13,14,15,16].

Because of the lack of adequate response of some patients to this treatments, some new immunosuppressive methods have been proposed in patients with active ophthalmopathy: cyclosporine, ciamexone, ciclophosphamide, methotrexate, plasmapheresis, intravenous immunoglobulin, which produced at most some contradictory results [4,6].

Cyclosporine A has an selective immunomodulatory effects which inhibits the induction of T helper cell proliferation, prevents activation of T cytotoxic lymphocytes and allows activation of T suppressor cells, forbidding the production of specific cytokines [6,17,18,19,20]. It has a T-cell independent inhibitory effect on immunoglobulin production by B lymphocytes [6]. These effects led to the application of this treatment in Graves' ophthalmopathy, the studies showing an improvement of proptosis, visual field, and visual acuity, a decrease of soft tissue inflammation and an improvement in extraocular muscle swelling. Other studies didn't confirm the benefits or superiority of this treatment, and the debate on its usefulness is still ongoing [19,20].

The aim of our prospective interventional study was to compare the efficiency of three different therapeutic schemes in patients with Graves disease and ophthalmopathy, related to the evolution of clinical ophthalmologic parameters and of thyroid antibodies levels. As a secondary objective we assessed the difference in antibody levels between treated groups and a control group without eye disease.

### Patients and Methods

We recruited 127 patients with Graves' disease, admitted to the Cluj-Napoca Endocrinology Hospital in years 2005-2009. Patients were divided in 4 groups: A, B, C and D. Each group was subjected to a different therapeutic approach: group A – methylprednisolone 500 mg/day for 6 days or 1g/day for 3 days, in consecutive or alternative administration; group B – methylprednisolone in the same doses associated to orbital radiotherapy (10 Gy/orbit); group C – cyclosporine 200 mg/day for 2 months; group D – no treatment. Group A and B comprised 40 patients, group C 15, and group D 32 patients. All patients were treated concomitantly with oral antithyroid drugs.

Including criteria in treated groups were: women and men of all ages with at least Werner II, NOSPECS 3 Graves' ophthalmopathy, smokers or non-smokers, on antithyroid drug therapy. The laboratory tests included: TSH (thyroid stimulating hormone, ECLIA, Roche Diagnostics GmbH, Mannheim, Germany), FT4 (free thyroxine, ECLIA, Roche Diagnostics GmbH, Mannheim, Germany), TRAB (thyroid stimulating hormone receptor antibody, ELISA, DRG International Inc., SUA), ATPO (thyroid peroxidase antibody, ECLIA, Roche Diagnostics GmbH, Mannheim, Germany).

Patients were assessed at baseline and at 3 and 6 months. Besides personal medical history, we performed at each visit a thyroid ultrasonography, an orbital ultrasonography with maximal extraocular muscle diameter measurement (lateral rectus and medial rectus), and a Hertel exophthalmometry (at admission and at discharge from the hospital). Proptosis was defined as exophthalmia more than 16 mm and/or extraocular muscle diameter greater than 4 mm. Orbital and thyroid ultrasonography and the hormonal tests were performed at each point before medical treatment. Each patient signed a written informed consent according to the protocol approved by the University of Medicine of Cluj-Napoca.

For each variable, the statistical analysis took into account the mean and standard deviation. Function of data distribution, the comparison between variables of different study groups used the *t* test for independent variables corrected by Levene's test for equality of variances, or the Mann-Whitney U test. The comparison between variables of the same group was performed using the paired samples *t* test, or Wilcoxon test. For multiple data comparisons ANOVA or Kruskal-Wallis test were used. In each situation, *p*<0,05 value was considered as statistically significant. The statistical analysis was carried out through SPSS 14.0 for Windows software (SPSS Inc. Chicago, IL, SUA).

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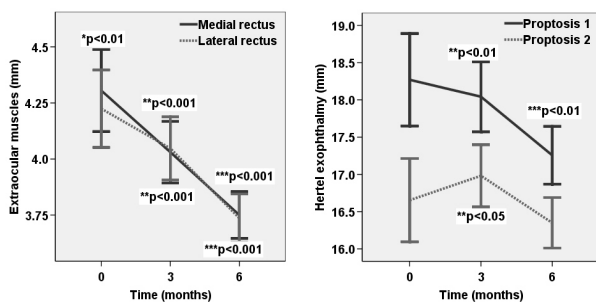
## Results

The patients groups were relatively homogeneous at the beginning of the study (month 0/basal). There were no meaningful difference between the means of different followed up parameters, excepting the TSH and FT4 between group A and C ( $p<0.05$ , ANOVA test). The values of the followed parameters are represented in table I.

**Table I.** Clinical and biological parameters at 0, 3 and 6 months - mean  $\pm$  standard deviation (CAS = clinical activity score, total volume = total volume of the thyroid, Hertel hospitalization = Hertel exophthalmia at the admission to the hospital, Hertel discharge = Hertel exophthalmia at discharge out from the hospital).

	Group A	Group B	Group C	Control group
Age	40.48 $\pm$ 11.67	43.48 $\pm$ 11.56	43.63 $\pm$ 8.48	44.16 $\pm$ 9.96
TSH 1 (mUI/l)	0.57 $\pm$ 0.85	0.7 $\pm$ 1.8	1.57 $\pm$ 2.18	1.68 $\pm$ 4.42
TSH 2 (mUI/l)	1.01 $\pm$ 1.07	1.22 $\pm$ 2.15	2.03 $\pm$ 1.18	1.17 $\pm$ 1.77
TSH 3 (mUI/l)	1.44 $\pm$ 0.84	1.63 $\pm$ 2.26	1.57 $\pm$ 1.42	1.61 $\pm$ 1.33
FT4 1 (pmol/l)	45.41 $\pm$ 28.15	34.8 $\pm$ 22.47	21.62 $\pm$ 14.27	39.89 $\pm$ 34.6
FT4 2 (pmol/l)	29.55 $\pm$ 16.17	21.14 $\pm$ 10.24	24.24 $\pm$ 17.29	27.30 $\pm$ 15.77
FT4 3 (pmol/l)	22.6 $\pm$ 10.39	18.29 $\pm$ 7.63	16.74 $\pm$ 4.66	21.16 $\pm$ 5.3
TRAb 1 (UI/l)	14.96 $\pm$ 11.78	15.47 $\pm$ 12.26	15.62 $\pm$ 12.16	13.32 $\pm$ 12.61
TRAb 2 (UI/l)	12.45 $\pm$ 10.43	13.32 $\pm$ 11.56	13.18 $\pm$ 10.17	11.33 $\pm$ 11.67
TRAb 3 (UI/l)	9.3 $\pm$ 8.3	9.88 $\pm$ 9.23	10.48 $\pm$ 8.6	9.98 $\pm$ 8.67
ATPO 1 (UI/l)	138.74 $\pm$ 147.09	186.47 $\pm$ 182.86	109.63 $\pm$ 86.58	102.98 $\pm$ 107.11
ATPO 2 (UI/l)	114.18 $\pm$ 120.46	122.18 $\pm$ 134.22	75.24 $\pm$ 62.17	85.24 $\pm$ 52.87
ATPO 3 (UI/l)	95.92 $\pm$ 103.138	84.32 $\pm$ 84.14	54.42 $\pm$ 34.01	79.93 $\pm$ 79.06
Total thyroid volume 1 (ml)	24.33 $\pm$ 10.71	20.37 $\pm$ 11.13	25.48 $\pm$ 7.62	10.71 $\pm$ 4.4
Total thyroid volume 2 (ml)	20.77 $\pm$ 9.8	19.48 $\pm$ 10.43	18.54 $\pm$ 9.8	8.15 $\pm$ 3.9
Total thyroid volume 3 (ml)	19.78 $\pm$ 9.14	17.81 $\pm$ 9.28	17.9 $\pm$ 8.08	7.54 $\pm$ 3.5
CAS 1	4.78 $\pm$ 0.76	4.75 $\pm$ 0.67	4.67 $\pm$ 0.61	1.66 $\pm$ 0.6
CAS 2	4.3 $\pm$ 0.51	4.15 $\pm$ 0.7	3.93 $\pm$ 0.59	1.41 $\pm$ 0.56
CAS 3	4.03 $\pm$ 0.57	3.48 $\pm$ 0.64	3.33 $\pm$ 0.48	1.16 $\pm$ 0.36
Hertel admission 1 (mm)	18.23 $\pm$ 1.9	20.18 $\pm$ 2.25	19.93 $\pm$ 1.99	15.85 $\pm$ 0.95
Hertel admission 2 (mm)	18.06 $\pm$ 1.5	19.32 $\pm$ 1.83	20.21 $\pm$ 1.82	15.64 $\pm$ 0.88
Hertel admission 3 (mm)	17.25 $\pm$ 1.21	18.17 $\pm$ 1.14	18.76 $\pm$ 1.21	15.42 $\pm$ 0.77
Medial rectus 1 (mm)	4.29 $\pm$ 0.55	4.81 $\pm$ 0.74	4.93 $\pm$ 0.53	3.53 $\pm$ 0.26
Medial rectus 2 (mm)	4.03 $\pm$ 0.44	4.63 $\pm$ 0.62	4.76 $\pm$ 0.48	3.5 $\pm$ 0.26
Medial rectus 3 (mm)	3.75 $\pm$ 0.32	4.19 $\pm$ 0.33	4.4 $\pm$ 0.46	3.48 $\pm$ 0.23
Lateral rectus 1 (mm)	4.22 $\pm$ 0.52	4.79 $\pm$ 0.74	4.89 $\pm$ 0.63	3.52 $\pm$ 0.25
Lateral rectus 2 (mm)	4.04 $\pm$ 0.45	4.61 $\pm$ 0.61	4.75 $\pm$ 0.52	3.5 $\pm$ 0.25
Lateral rectus 3 (mm)	3.73 $\pm$ 0.33	4.14 $\pm$ 0.31	4.36 $\pm$ 0.42	3.48 $\pm$ 0.23

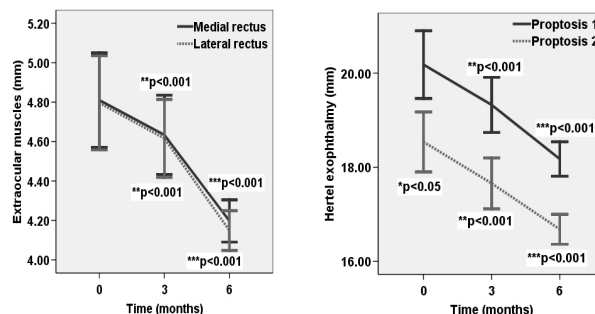
In group A, between 0-3 months, extraocular muscles decrease in size with 0.2 mm ( $p<0.01$ ), and between 3-6 months with another 0.3 mm ( $p<0.001$ ), total 0.5 mm ( $p<0.001$ ). Proptosis decreased at hospitalization between 3-6 months with 0.8 mm ( $p<0.01$ ) with a total decrease of 1 mm  $p<0.01$  in 6 months (figure 1).



**Figure 1.** Evolution of extraocular muscles and proptosis at 0, 3 and 6 months in patients treated with iv Methylprednisolone (\*= time period 0-3 months, \*\*= time period 3-6 months, \*\*\*= time period 0-6 months; proptosis 1= proptosis at the hospitalization, proptosis 2= proptosis at the discharge from the hospital).

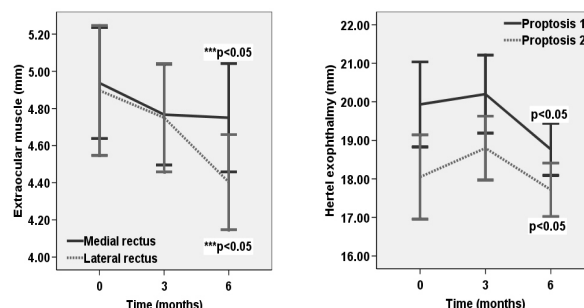
In group B, in time period 0-6 months, medial rectus decreased with 0.7 mm ( $p<0.001$ ) and lateral rectus

with 0.6 mm ( $p<0.001$ ). Between 0-3 months, proptosis has a inclination to decrease by 0.8 mm at hospitalization ( $p=0.06$ ); between 3-6 months the hospitalization proptosis decreases by 1.2 mm ( $p<0.001$ ) totally between 0-6 months with 2 mm ( $p<0.001$ ) (figure 2).



**Figure 2.** Evolution of extraocular muscles and proptosis at 0, 3, and 6 months in patients treated with combined therapy (\*= time period 0-3 months, \*\*= time period 3-6 months, \*\*\*= time period 0-6 months; proptosis 1= proptosis at the hospitalization, proptosis 2= proptosis at the check out from the hospital).

In group C, in time period 0-3 months there is no improvement in ocular changes. Between 3-6 months proptosis decreases with 1.4 mm at hospitalization ( $p<0.05$ ); extraocular muscles thickness improve with 0.3 mm medial rectus ( $p<0.05$ ), and lateral rectus with 0.4 mm ( $p<0.05$ ) (figure 3).



**Figure 3.** Evolution of extraocular muscles and proptosis in patients treated with Cyclosporine (proptosis 1= proptosis at the hospitalization, proptosis 2= proptosis at the check out from the hospital).

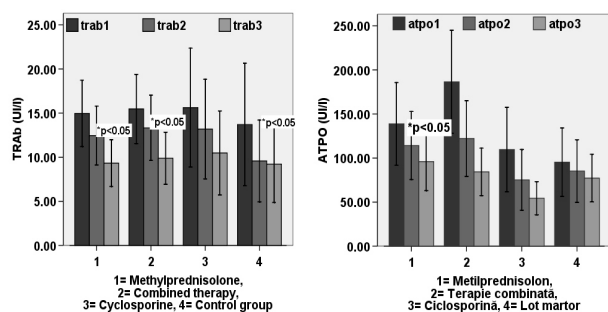
We compared ophthalmopathy's evolution in group A and B with the patients from group C over 6 months. The basal proptosis degrees for group A at hospital admission (2.1 mm), as well as the extraocular muscle's thickness (0.8 mm medial rectus and 0.6 mm lateral rectus) were significantly lower than group C ( $p<0.05$ ); after 3 months group A vs. group C shows a greater degree ( $p=0.001$ ) of proptosis in group C (18 mm against 20.4 mm) at hospital admission; extraocular muscles thickness was 4.7 mm in group C and 4 mm in group A ( $p=0.001$ ). This difference is also significant after 6 months for both lateral and medial rectus ( $p<0.05$ ); 4.4 mm against 3.1 mm. In all evaluation

time, cyclosporine produces a decrease in proptosis with 1.1 mm while glucocorticoids alone produce a decrease with 0.9 mm, in the same period of time. Lateral and medial rectus thickness decreases with 0.5 mm after cyclosporine, this improvement being the same after glucocorticoids.

Comparison between group B and C does not reveal a basal differences; after 3 months there seems to be a tendency in decrease of proptosis ( $p=0.09$ ); at 6 months in group B lateral rectus is significantly lower (4.1 mm against 4.4 mm,  $p=0.05$ ), while medial rectus also has a tendency in decrease comparing with group C (4.1 mm against 4.4 mm,  $p=0.07$ ).

The evaluation of TRAb titres shows a decrease in group A after 6 month from 14.6 UI/l to 9.3 UI/l ( $p<0.05$ ) and in group B from 15.5 UI/l to 9.8 UI/l ( $p<0.05$ ) (figure 4). There's no decrease in TRAb titres after 3 month from the initiation of the therapy. ATPO values showed a decrease in the first 3 months in group B from 186.4 to 122.1 UI/l ( $p=0.07$ ); after 6 months there's an improvement of ATPO titres from 186.4 to 84.3 UI/l ( $p<0.01$ ) in group B. In group A there are no differences after 6 months. In group C we didn't register any improvement of TRAb and ATPO titres for all 6 months. In control group TRAb decreased between 2nd-3rd hospitalization ( $p<0.05$ ), while ATPO titres had no changes in all 6 months. The comparison between groups A, B and C shows significantly greater ATPO values in group A (95.92 UI/l against 54.42 UI/l) after 6 months ( $p<0.05$ ). Comparing group A, B and C with control group we found greater basal ATPO values in group B (186.47 UI/l, 102.98 UI/l,  $p<0.05$ ), but this difference is no longer evident after 3 and 6 months.

There was no significant improvement in ophthalmopathy's CAS over all 6 months. In group A, between 0-3 months CAS decreased from 4.7 to 4.3 ( $p<0.01$ ) and between 3-6 months from 4.3 to 4 ( $p<0.05$ ), totally for 6 months from 4.7 to 4 ( $p<0.001$ ). In group B, CAS improved from 4.7 to 4.1 ( $p<0.001$ ) in the first 3 months, and from 4.1-3.4 ( $p<0.001$ ) next 3 months, totally from 4.7 to 3.4 ( $p<0.001$ ). In group C, in the time period 0-3 months CAS decreased from 4.6 to 3.9 ( $p<0.01$ ) and from 3.9 to 3.3 ( $p<0.01$ ) between 3-6 months, totally 4.6 to 3.3.



**Figure 4.** Evolution of TRAb and TPO antibodies at 0, 3 and 6 months for all 4 groups (Methylprednisolone, Combined Therapy, Cyclosporine and Control group; \* $p=p$  at 6 months).

Comparing CAS in group A with group C we registered significant differences at 3 and 6 months ( $p<0.05$  and  $p<0.001$ ) on behalf of group C. There were no differences regarding CAS between group B and C.

In control group CAS improved between 3-6 months from 1.4-1.1 ( $p<0.05$ ) and comparing all groups we found significantly lower values ( $p<0.001$ ) in control group than group A, B, C after 3 and 6 months.

## Discussion

Orbital radiotherapy (RxT) and glucocorticoids (GC) are usual therapies used in Graves' ophthalmopathy used as a single therapy or combined [4,5,6,11,12,13,14]. The choice of the therapy has not been yet established by a precise international guide, the choice of the therapy is made using a more or less subjective clinical evaluation of the disease activity [4,5,6]. Studies regarding cyclosporine showed an positive effect in patients with Graves disease, decreasing proptosis, improving orbital inflammation, CAS and visual acuity [5,6,7,18,19].

Clinical trials evaluated the effect of cyclosporine administration in patients with Graves' ophthalmopathy with contradictory results [27,28,29,30]. In most of the cases they observed an improvement regarding subjective complains and less effect on objective changes. Most of the patients were pretreated for the ophthalmopathy with glucocorticoids or radiotherapy and this thing could have brought an influence upon the results. There was no correlation found between the response and duration of the disease, except Karlsson et al. [31], who noted that patients with shorter duration of the disease had a better response for therapy. They concluded that cyclosporine had a limited effect in management of Graves' ophthalmopathy [31]. In our patients treated with cyclosporine there were no changes in ocular complains in the first 3 months, but in the next 3 months we registered a significant improvement in eye changes. There for the effects were visible after the retreat of the therapy. The existing data and the results from clinical trials on cyclosporine, show that it's effects depend on duration and the used doses [28,31,32], although in some autoimmune diseases like Sjogren syndrome, cyclosporine's effect seems to be evident sooner (3-5 weeks) [33].

There are few clinical trials which compared cyclosporine with other therapies. Prummel et al. compared cyclosporine alone with prednisone. This study was performed for 12 weeks period of time. It is possible that this short period of time to follow up the patients in Prummel's study [34] should be the explanation for the short number of responsive patients.

Kahaly et al. [35] treated patients with prednisone or a combination of prednisone and cyclosporine. They noted a decrease in CAS and were better able to maintain a favorable effect after therapy was withdrawn. There was no rebound phenomenon as far as 6 months after completion of the cyclosporine therapy and the authors concluded that

cyclosporine has a positive role for patients with Graves' ophthalmopathy with class IV-VI and 9-12 months duration of the disease [35]. Our patients treated only with cyclosporine, without any associated therapy, guarantees exclusive effect of this therapy on ophthalmopathy. The patients from our study had a short duration of the disease, between 2-8 months. It wasn't any improvement of the disease in the first 3 months, but between 3-6 months there was a significant decrease in proptosis as well in extraocular muscles thickness. The patients treated with glucocorticoids had also a positive development with significant lower values after 6 months, but cyclosporine determined a greater decrease of proptosis, as compared to group A. In group B, proptosis evaluation at 3 and 6 months shows an improvement, with a greater therapeutic response for group B in both proptosis and extraocular muscles thickness. Our study shows that cyclosporine, even as a single therapy has benefic effects in Graves' ophthalmopathy, like glucocorticoids alone, but not as good enough as associated therapy (GC/RxT). It's possible that association between cyclosporine and glucocorticoids, to have better results on eye changes but the mean of this study was to evaluate the cyclosporine as a single therapy comparing it with classical therapy in use for Graves' disease [36,37].

Cyclosporine has positive effects on CAS, causing a significant improvement after 3 and 6 months. CAS comparison in group A and C does not reveal any difference between basal score, but evaluation at 3 and 6 months shows significant lower score for patients treated with cyclosporine. Our data differs to other studies, who revealed a greater improvement in patients treated with GC [6,34,35].

The evolution of TRAb and ATPO in patients treated with cyclosporine had no basal differences comparing to non treated group. TRAb and ATPO values decreased dramatically in Methylprednisolone's group and associated therapy's group after 3 and 6 months. Laurberg et al., in 2008, obtained a 80% remission rate of TRAb after 18 months of antithyroid therapy in 48 patients with Graves' disease recently diagnosed [38]. Smith et al. observed normalization of TRAb values in youth and teenagers after 2 years of antithyroid therapy and the conclusion was that the young patients need a longer period of time than adults for antibodies values normalization [39]. The impossibility to withdrawn antithyroid therapy is a fact that limited the possibility to evaluate the role of anti-inflammatory and immunosuppressive therapies upon TRAb values [39,40,41].

There were no correlations regarding basal TSH and FT4 values with TRAb and ATPO, possible because of the antithyroid treatment already in course at the beginning of the study.

Our study describes the effect on Graves' ophthalmopathy in a short period of time – 6 months, providing information regarding proper therapy in

accordance with the precocity of the wanted effects. For a better characterization for the results of the different therapies in Graves' disease, more extensive and rigorously managed studies are needed, to follow patients evolution on a longer period of time, the results based on evolution of an autoimmune disease with a large variability inter- and intra-individuals are not guaranteed.

### Conclusions

Cyclosporine as a single treatment in Graves' ophthalmopathy may be as effective on objective measurements of disease activity as intravenous corticosteroid treatment, but is less effective than combined therapies. Cyclosporine improves ophthalmopathy's clinical activity score but has a poorly effect on thyroid antibodies titres on a short time evaluation, comparing to classic therapies.

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