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Long-term remission of steroid-resistant Graves' orbitopathy after administration of anti-thymocyte globulin

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Most cases of Graves' orbitopathy (GO) are benign and require no special treatment. In the active moderate-to-severe lesion, constituting 5–6% of cases, according to EUGOGO guidelines, an intravenous course of corticosteroids is the first-choice treatment, effective in about 70–80% of cases. The management of patients who are refractory to corticosteroid therapy is a major challenge and includes repeated courses of corticosteroids, orbital radiotherapy, cyclosporin A, and rituximab [1]. CD4+ cell infiltrates in orbital tissues play a central role in the molecular pathways leading to proliferation and differentiation of orbital fibroblast and the secretion of hyaluronic acid and the adipogenesis. GO patients are characterised by a low number of circulating Treg cells among peripheral blood mononuclear cells (PBMCs) with high CD4/CD8 ratios and abnormal cytokine expression [2]. In vitro, incubation of PBMCs obtained in GO patients with rabbit anti-thymocyte globulin (rATG) for 24 h substantially enhanced the expression of Treg cell markers FoxP3 and $CD3^+$ $CD4^+$ $CD25^+$ $CD127^{low}$ [2].

Thymoglobulin (rATG) is a polyclonal rabbit antibody that causes T-cell depletion, used in the induction after kidney transplantation (KTx) and treatment of acute rejection. In addition, it was shown that ATG in vitro can induce apoptosis of naive plasma B cells and plasma cells [3], inhibit the secondary immune response by memory B cells via T-cell modulation, and induce regulatory T cells during immune reconstitution [4]; thereby, it may suppress B cells and production of antibodies.

A 47-year-old woman with a 25-year history of Graves-Basedow disease, after subtotal strumectomy, two courses of radioiodine therapy, on thyroxine substitution, developed bilateral GO (conjunctival oedema, double vision, worsening of visual acuity). During glucocorticoid therapy (after 3–4 courses) according to the EUGOGO protocol, the patient developed symptomatic optic neuropathy treated with radiotherapy (20 Gy in 10 fractions) with continuation of methylprednisolone to a total dose 11 g with subsequent ineffective 14-week therapy with cyclosporin A. In July 2018, after obtaining acceptance of the therapy with rATG by the Bioethics Committee, we offered an experimental therapy with thymoglobulin (two doses of 1.5 mg/kg) with pretreatment with methylprednisolone 250 and 125 mg, paracetamol, and clemastine.

The clinical improvement in GO where noted at six-week examination and was maintained a year after rATG administration (Tab. 1). There was a significant improvement in the patients' clinical status, both subjective (GO-QOL EUGOGO questionnaire) and in the ophthalmologic tests: decrease in CAS from 5/7 to 0/7, subsiding of diplopia, improvement of best-corrected distance visual acuity - BCDVA (from 0.5 to 0.7 right eye — RE and from 0.5 to 0.9 left eye — LE), and colour vision recovery assessed with Ishihara colour plates (from 11/16 to 16/16 RE and 10/16 to 16/16 LE). Improvement was noted in the NOSPECS scale (from 2-b, 4-c, 6-a to 2-0, 4-b, 6-0), Donaldson's ophthalmopathy index (from 6/15 to 3/15), and Octo-

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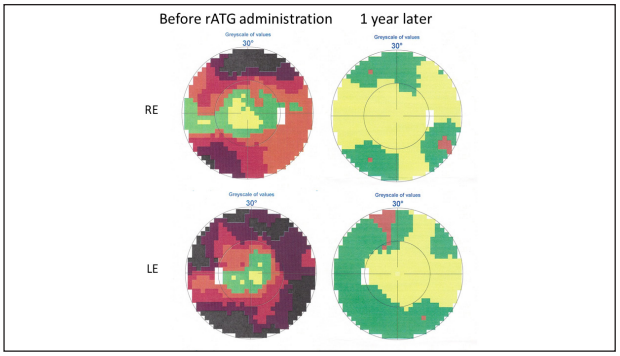

Figure 1. *Octopus static visual field of the right (RE) and left (LE) eyes before rATG administration and after the one-year follow-up period*

pus 1-2-3 static perimetry (Haag Streit, Switzerland), with complete reduction of absolute scotomata and decrease in relative scotomata (Fig. 1) and VEP Pattern, both in latency, which decreased (P100 latency after stimulation with 1° normalized and were delayed to 105% after stimulation with 15'), and amplitude, which increased (Tab. 1). In addition, there was only a transient decrease in TRAb titre and persistent improvement in CD4/CD8 ratio of peripheral blood T lymphocytes.

The presented case shows that patients with steroid-resistant GO may benefit from rATG therapy and that the obtained clinical remission is related to the long-lasting change in CD4 to CD8 ratio of peripheral blood T lymphocytes without disappearance of TRAb production. Our finding is not in line with the unique observation of the resolution of GO shortly after induction therapy with rATG (1.5 mg/kg/dose for five doses) with a triple immunosuppressive regimen (including glucocorticoids) in a kidney transplant recipient previously untreated for GO. The clinical improvement, in this case, was followed by the disappearance of TRAb after the procedure [5]. It should be stressed that in our patient glucocorticoid therapy, as well as RTH, were ineffective, and the available therapeutic options were exhausted.

Severe dysthyroid optic neuropathy (DON) in the course of GO is a sight-threatening complication [6]. In some individuals tension and lack of laxity of orbital septum prevent the eye globe from self-decompressing, resulting in severe DON, regardless of slight or no exophthalmos. This situation was present in our patient, whose colour vision loss and visual field loss were severely affected by compression neuropathy. A year after the rATG administration we observed significant improvement in functional visual tests, which can be explained by optic nerve decompression.

Therefore, we think that therapy with Thymoglobulin may be useful in the management of severe steroid-resistant GO. The effectiveness of this new therapy requires a larger number of observations.

Table 1. *Evolution of clinical findings during a year after thymoglobulin administration in a patient with Graves' ophthalmopathy*

	Before rATG		12 weeks		One year	
Clinical symptoms	Diplopia in every direction, abnormal acuity and colour vision		Without diplopia, significant improvement of visual acuity and colour vision		Periodic slight diplopia in every direction	
TRAb [IU/L]	> 40		> 40		> 40	
CD4/CD8 ratio	3.0		1.5		1.8	
DBCVA	RE 0.5 LE 0.5		RE 0.8 LE 0.9		RE 0.7 LE 0.9	
Exophthalmometry (Hertl)	RE 16 mm LE 18 mm		RE 16 mm LE 18 mm		RE 16 mm LE 18 mm	
Donaldson	6/15		1/15		3/15	
CAS	5/7		1/7		1/7	
NOSPECS	2-b, 3-0, 4-c, 5-0, 6-a		2-a, 3-0, 4-0, 5-0, 6-0		2-a, 3-0, 4-b, 5-0, 6-0	
Ishihara Colour Plates	RE 11/16 LE 10/16		RE 15/16 LE 15/16		RE 16/16 LE 16/16	
PVEP	RE	LE			RE	LE
1°						
P100	116	118			110	109
N75-P100	6.3	8.3			9.0	8.9
15'						
P100	136	128			130	130
N75-P100	6.9	4.8			9.9	10.1

CAS — Clinical Activity Scale; LE — left eye; MD — mean defect; MS — mean sensitivity; PVEP — pattern visual evoked potentials; RE — right eye; Classification of Graves' ophthalmopathy (NOSPECS): 0 — no signs or symptoms; 1 — only signs, no symptoms; 2 — soft-tissue involvement; 3 — proptosis; 4 — extraocular muscle involvement; 5 — corneal involvement; 6 — sight loss

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