

SHORT THESIS FOR THE DEGREE OF DOCTOR OF
PHILOSOPHY (PHD)

New aspects in the differential diagnosis
and treatment of endocrine orbitopathy

by Annamaria Erdei

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New aspects in the differential diagnosis and treatment of endocrine orbitopathy

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The Examination takes place at the Conference room of Department of Preventive Medicine, Faculty of Public Health, University of Debrecen, on May 16, 2018, at 11 a.m.

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The PhD Defense takes place at the Lecture Hall of Bldg. "A", Department of Internal Medicine, Faculty of Medicine, University of Debrecen, on May 16, 2018, at 1 p.m

1. Introduction

The most common orbital disease with exophthalmos is Graves' orbitopathy (GO), which is the extrathyroidal complication of Graves' disease (GD). Graves' orbitopathy usually appears simultaneously with or soon after the development of thyrotoxicosis; however, rarely it may precede hyperthyroidism. The clinical features of Graves' orbitopathy are upper eyelid retraction, edema, and erythema of the periorbital tissues and conjunctivae, proptosis, dry ocular sensation, photophobia, double vision, and pressure sensation behind the eyes.

The pathogenesis of GO is only partially understood; GO is probably initiated by autoreactive T lymphocytes reacting with one or more antigens shared by the thyroid and orbit. The most probable shared thyroid-orbital autoantigens are the thyrotropin receptor and the IGF-I receptor. After reaching the orbit and recognizing the shared antigen(s), T lymphocytes trigger a cascade of events, including secretion of cytokines. These cytokines stimulate the proliferation of orbital fibroblasts, expansion of adipose tissue, and production of hydrophilic glycosaminoglycans. B cells are involved as antigen-presenting and autoantibody-producing cells.

Besides detailed ophthalmological examination (best-corrected visual acuity, color vision, pupillary examination, ocular motility, Hertel's exophthalmometry, intraocular pressure, adnexal examination, slit-lamp examination, dilated fundus examination) laboratory parameters that are necessary to confirm the diagnosis

include: measurement of serum thyroid stimulating hormone, free thyroxin, and TSH receptor antibody levels. In euthyreoid Graves' orbitopathy, TSH receptor antibody level is elevated without any thyroid function abnormality.

The diagnosis of Graves' orbitopathy in most patients is obvious; however, exophthalmos can also be present in patients with lymphoproliferative disorders of the orbits, idiopathic orbital inflammatory syndrome, orbital myositis, severe obesity, Cushing's syndrome, histiocytosis, granulomatosis with polyangitis, and IgG4-related orbitopathy (IgG4-rd). Orbital magnetic resonance imaging, orbital computed tomography and/or single photon emission computed tomography and histology (if necessary) can help to distinguish between the underlying causes.

Treatment of severe, active GO remains a therapeutic challenge.

Rituximab, a chimeric anti-CD20 antibody and is approved for treatment of B-cell lymphoma in adults. It is used in autoimmune diseases including immune thrombocytopenic purpura, systemic lupus erythematosus, myasthenia gravis and rheumatoid arthritis. CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35) is a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD. The antigen is expressed on the surface of pre-B and mature B lymphocytes, but not on stem cells, pro-B lymphocytes, and plasma cells. CD20 regulates early steps in the activation process for cell cycle initiation and differentiation. Three different mechanisms have been proposed for the elimination

of B cells by anti-CD20: complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and stimulation of the apoptotic pathway. Anti-CD20 has become a clinically relevant treatment option in selected cases of GO. Some authors have shown, in preliminary work, that anti-CD20 has affected the clinical course of GO positively by binding to the CD20 receptor on B lymphocytes. The mechanism by which anti-CD20 influences the clinical course of GO is largely unknown. In addition to influencing the cytokine production in the orbit by inducing depletion of antigen presenting B-cells, the action of anti-CD20 therapy may also involve autoreactive T cells. Phagocytes and other inflammatory cells not only remove anti-CD20-opsonized B cells, but at the same time remove autoreactive T cells interacting with them in peripheral lymphoid organs. That could be the explanation for the unexpected efficacy of anti-CD20 in the treatment of predominantly T helper cell mediated autoimmune diseases, including rheumatoid arthritis.

2. Aims

- Create an algorithm to distinguish between GO and IgG4 orbitopathy
- Study the short-term effect of anti-CD20 treatment in severe, treatment-resistant GO
- Study the long-term effect of anti-CD20 treatment in severe, treatment-resistant GO

- Study the effect of anti-CD20 treatment on the autoimmune process and hyperthyroidism in GD patients
- Study the short and long-term side-effects of anti-DC20 treatment

3. Patients and methods

3.1. Patients

Five patients, four women and one man, aged 31-64 year (47.8±12.2) were entered in the study. All had severe, treatment-resistant, active GO. The study protocol required either no improvement or worsening of clinical activity of the disease after a recent course of intravenous methylprednisolone totalling at least 3 grams within the 6 weeks preceding initiation of rituximab therapy. The combination of the steroids with 20 Gy retrobulbar irradiation by a linear accelerator was allowed for entry. Inclusion criterion was the activity of GO confirmed by three independent techniques: clinical activity score (CAS) [23], ^{99m}Tc-labeled diethylene-triamine-pentaacetic-acid (^{99m}Tc DTPA) single photon emission computed tomography (SPECT), and orbital magnetic resonance imaging (MR) [24]. Disease activity criteria for inclusion were as follows: CAS ≥ 4, DTPA uptake ≥ 20 % above normal on orbital SPECT, and T2 relaxation time ≥ 20% above normal in at least one muscle on MR. Patients were ineligible if they had hypothyroidism, severe hyperthyroidism, previous orbital decompression surgery, fever,

previous treatment with any other monoclonal antibody, allergy that needed continuous medication, pregnancy, breast-feeding, or operation in general anaesthesia in the last four weeks.

Four patients were smokers and one patient was ex-smoker. At the time of anti-CD20 therapy, patients were euthyroid or mildly hyperthyroid, one on propylthiouracyl, two on methimazole combined with L-thyroxine, and two patients on L-thyroxine after previous thyroidectomy. Thyroidectomies were performed one and two years before anti-CD20 treatment in patients 3 and 4, respectively. TSH receptor antibody (TRAb) level was elevated in all patients. All patients had received methylprednisolone, 3 grams or more, within the 6 weeks preceding initiation of anti-CD20 therapy, and two of them also underwent retrobulbar irradiation 3 months earlier than anti-CD20 treatment was given.

3.2. Study design

Before anti-CD20 treatment, thyroid function tests, TSH receptor antibodies and B lymphocyte counts were measured in all patients. Initial disease activity parameters were assessed within the last 2 weeks before anti-CD20 treatment. All laboratory parameters were repeated at 1, 3, 6, 12 months after the first anti-CD20 infusion. Thereafter thyroid function tests and TSH receptor antibody levels were measured if required by health-conditions changes, but at least in once on a yearly basis. The mean follow-up period was 67 months (range: 58 to 81 months). Visits included detailed ophthalmological examination. CAS was calculated in order to monitor the clinical

improvement of the patients. Orbital DTPA SPECT and MR T2 relaxation time measurements were performed before the first RTX infusion and 3 and 12 months thereafter. Changes of T2 relaxation times of the muscle with the longest T2 relaxation time at study entry in each orbit were separately analyzed.

Anti-CD20 was a chimeric human–mouse monoclonal antibody by Hoffman La Roche, Basel, Switzerland (rituximab, MabThera). The therapeutic protocol was the one established for treatment of patients with B cell lymphoma: anti-CD200 was given as weekly infusions of 375 mg/m² body surface area for 4 weeks. One hour prior to anti-CD20 infusion, paracetamol (500 mg), metimazolnatrium (500 mg) and calcium gluconat (5 ml) were administered orally and methylprednisolone (80 mg) intravenously to prevent possible allergic reactions. During the infusion, heart rate and blood pressure were monitored. Patients left the clinic 2 hours after completion of the treatment session. All 5 patients received a full anti-CD20 course and were included in the analyses.

The Hungarian National Review Board and the Institutional Ethics Committee approved the study protocol and ensured that written informed consent was obtained from all patients.

3.3. Biochemical and immunological measurements, cytofluorimetric analysis

Serum TSH, fT4, fT3 concentrations were measured using the electrochemiluminescence immunoassay technique (ECLIA) on the Modular Analytics E170 analyser (Roche Diagnostics,

Mannheim, Germany). TSH receptor antibodies, detected as TSH binding inhibitory immunoglobulins, were measured using I^{125} labelled competitive radio-receptor assay (BRAHMS TRAK human RIA, Henningsdorf, Germany) on the Ria-mat 280 analyser (Stratec, Birkenfeld, Germany). Reference ranges were as follows: TSH: 0.3-4.2 mIU/L, fT4: 12-22 pmol/L, fT3: 2.4-6.3 pmol/L, TRAK: <1 IU/L.

CD20⁺ cells were counted using anti-CD20 FITC-conjugated monoclonal mouse anti-human reagent (BD Biosciences, Erembodegem-Aalst, Belgium) on the BD FACSTM brand flow cytometer. BD CellQuest software was used for data acquisition and analysis (BD Biosciences, Becton, Dickinson and Company, San Jose, California, USA).

3.4. Imaging techniques

3.4.1. MR

MR of the orbits has been performed in a conventional 1.5 T MR unit (GE Excite, General Electric, Milwaukee, USA). Following STIR, T1 and T2 weighted coronal images, sagittal and axial non-contrast T1 weighted fast spin echo images were also taken. All scans were acquired consecutively with 3 mm slice thickness. Axial and sagittal planes were chosen to be parallel with the course of the optic nerve. Additionally, multisection-multiecho T2 weighted sequences were prepared in the coronal plane (TR=2020 ms; TE= between 12-180 ms using 14 echos) with 4 mm slice thickness. To avoid inaccuracies resulting from rectus and

orbicularis muscle contraction, the subjects were asked to keep their globe in a neutral position and to close their eyes gently.

T2 relaxation maps were calculated on pixel-by-pixel by using a linear least squares curve-fitting monoexponential algorithm. T2 relaxation time of ocular muscles was measured on T2 relaxation time maps using region-of-interest (ROI) assignment.

3.4.2. SPECT

Shortly, 7MBq/kg ^{99m}Tc -DTPA (PromtCarry, Szeged, Hungary) was administered intravenously. After 20 minutes, a Nucline X-Ring four headed SPECT device (Mediso, Budapest, Hungary) was used for imaging. One hundred twenty-eight frames were acquired in step-and-shoot mode. After iterative reconstruction and absorption correction, coronal and sagittal slice sets were generated perpendicularly to the transversal plane, covering the entire orbital area. To quantify DTPA accumulation in the orbits, regions of interest were drawn on the transversal slices, outlining areas corresponding to the right and left orbits. The sum of the six transaxial slices containing the entire orbital region was used in uptake calculations. The DTPA uptake was the fraction of the injected dose taken up by the selected regions of interest. DTPA uptake activities obtained by SPECT before and after treatment were compared.

3.5. Statistical analysis

Statistical analyses were performed using the SAS for Windows 8.2 (Cary Inc., SAS Institute Inc. USA) statistical package. Descriptive statistics were given as the mean±standard deviation (SD). The changes of serum TSH receptor antibodies, CAS values and DTPA uptakes were analyzed by ANOVA (post-hoc Scheffé and Newman-Keuls tests). To compare the T2 relaxation time values before and after treatment, we used a paired sample t-test. The $p \leq 0.05$ probability level was accepted as significant.

4. Results

4.1. Effects of anti-CD20 treatment: B-cell depletion

The proportion of CD20⁺ lymphocytes was 3.62±1.45 % at the beginning of the study. All patients attained peripheral B-cell depletion with anti-CD20 treatment; CD20⁺ cell number dropped to 0 % after anti-CD20 infusions. CD20⁺ cell counts started to increase after 6 months (0.19±0.2 %) and failed to reach the pre-treatment values at 12 months (1.74±0.87 %) in any of the patients.

All patients tolerated anti-CD20 treatment well. A minor side effect (localized skin erythema) was detected in one patient during the first infusion. The infusion was continued and the erythema disappeared within 1 hour.

4.2. Effect of anti-CD20 treatment on the activity and course of GO

In all patients treated with anti-CD20 antibody, a definite clinical improvement of GO has been observed. The mean CAS before therapy was 6.5 ± 1.72 and decreased to 3.4 ± 1.58 by 1 month and remained unchanged afterwards (3.2 ± 1.75 at 12 months, $p < 0.05$). No further CAS change, in either direction, was detected during the yearly follow up visits.

On the SPECT images, the mean DTPA uptake before therapy was 16.52 ± 4.51 MBq/cm³, which decreased to 13.30 ± 2.06 at 3 month, and further to 11.97 ± 2.36 MBq/cm³ at one year (ANOVA, $p < 0.002$).

The mean of T2 relaxation times on MR images (n=40 muscles) before therapy was 96.91 ± 17.61 ms and decreased to 84.29 ± 9.41 ms by the end of one year follow-up period (t-test, $p < 0.001$). We studied separately the most severely involved external eye muscles in each orbit (10 muscles in 5 patients). In these muscles, the mean of T2 relaxation time was 112.80 ± 14.38 ms before anti-CD20 treatment and dropped to 83.99 ± 12.66 ms by the 12th month ($p < 0.01$).

4.3. Effects of anti-CD20 treatment on thyroid autoantibodies

After anti-CD20 treatment, a decline of TRAb level was noted in all patients: the mean serum TRAb level was 7.44 ± 3.36 U/L before therapy, 5.6 ± 4.5 U/L at the 1 month control visit and 1.68 ± 1.52 U/L at one year. The difference between the 0 and 12 months values is statistically significant (Scheffe test; $p < 0,004$). No correlations between changes of TRAb and activity parameters

(CAS, DTPA uptake, T2 relaxation time) were found. TRAb values remained low in 4 of 5 patients throughout the 5 years follow up.

Before anti-CD20 treatment, patients were either euthyroid or mildly hyperthyroid, one on propylthiouracyl, two on methimazole combined with L-thyroxine, and two patients on L-thyroxine after previous thyroidectomy. Methimazole and propylthiouracyl treatment could be terminated during the first six months after anti-CD20 treatment ($2.6 \pm 2,1$ months). The serum TSH level was 0.24 ± 0.16 mU/L before anti-CD20 therapy and 0.81 ± 0.91 mU/L 12 months later. Serum fT3 was 5.88 ± 1.24 pmol/L before therapy and 5.04 ± 0.99 pmol/L at 12 months; serum fT4 was 21.52 ± 6.54 before therapy and 21.10 ± 6.16 at 12 months. While we did not detect relapse of hyperthyroidism in any of the patients at the one year follow up visit, in one patient TRAb positivity and relapse of hyperthyroidism occurred at 3 years.

5. Discussion

The diagnosis of Graves' orbitopathy in most patients is obvious; however, exophthalmos can also be present in patients with lymphoproliferative disorders of the orbits, idiopathic orbital inflammatory syndrome, severe obesity, Cushing's syndrome, histiocytosis, granulomatosis with polyangitis, and IgG4-related orbitopathy. Orbital magnetic resonance imaging, orbital computed

tomography and/or single photon emission computed tomography with histological examination (if necessary) can help to distinguish between the underlying causes.

IgG4-rd is a recently described and increasingly recognized entity which may present with involvement of the eyes, termed IgG4-related orbitopathy. IgG4-rd usually affects more than one organ, typically the orbits, salivary glands, lungs, pancreas, biliary ducts and retroperitoneal tissue. Orbital involvement most frequently includes the lacrimal glands and extraocular muscles, however, infraorbital and supraorbital nerve enlargement may also be detected. In a series of 1014 orbital lymphoproliferative disease cases, the incidence of IgG4-related orbitopathy was found to be 21.6 %. Features of IgG4-rd include tumor-like swelling of involved organs, lymphoplasmacytic tissue infiltration enriched in IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis. The number of IgG4-positive plasma cells per high-power field (HPF) that is regarded as consistent with or suggestive of IgG4-rd varies somewhat from tissue to tissue. Generally, the minimum for making the diagnosis for most tissues is from 30 to 50 IgG4-positive cells/HPF. However, in the lacrimal gland, 10 IgG4-positive plasmacells/HPF may be sufficient for the diagnosis. Storiform fibrosis and obliterative phlebitis are more typical of the systemic pathology; however, they are not always present in the orbital disease. A specific autoantigenic target has not been identified; furthermore, it is not clear whether the IgG4 antibodies are pathogenic. In 2009, diagnostic criteria for IgG4-rd were proposed,

and comprehensive diagnostic criteria are currently in use. In patients with typical clinical features and organ involvements both measurement of serum IgG4 levels and tissue biopsy are recommended. Elevated serum concentrations of IgG4 are found in 60-70 percent of patients with IgG4-rd, but this finding is not specific, as it can also be associated with Churg-Strauss syndrome, sarcoidosis and allergic diseases.

All patients with symptomatic active IgG4-rd require treatment. Glucocorticoids are the first-line agents for remission induction. Following a successful course of induction therapy, certain patients benefit from maintenance therapy. Repeated glucocorticoid courses are indicated in patients who relapse following successful remission induction. Most patients respond to glucocorticoids within several weeks, typically with symptomatic improvement, reduction in the size of masses or enlarged organs, improvement in organ function, and a decrease in serum levels of IgG4. In those who are resistant to glucocorticoids, or have side effects or contraindications to glucocorticoid therapy, anti-CD20 is another therapeutic option.

Neither the natural course nor the prognosis of IgG4-rd is well-understood. Spontaneous improvements can be seen, but the disease often relapses if left untreated. Symptoms respond dramatically to glucocorticoids, but relapses are common following discontinuation of therapy. Significant organ dysfunction may arise from uncontrolled and progressive inflammatory and fibrotic changes in affected tissues. Currently, it is uncertain if there is an increased risk of malignancy in patients with IgG4-related disease, however,

lymphomas occur more frequently in patients with IgG4-related disease.

The prevalence of the disease could be more frequent than it is diagnosed. There is enhanced attention towards IgG4-related orbitopathy in Japan, as well as few published cases in Europe.

The most typical manifestations of IgG4-related orbitopathy are the usually easily detectable dacryoadenitis, swollen eyelid and involvement of extraocular muscles. The external eye muscle involvement pattern on MRI is distinct from Graves' orbitopathy, where the inferior and medial rectuses are the most frequently involved muscles. In IgG4-related orbitopathy these muscles are often spared, as seen in our case. Less commonly, compressive optic neuropathy secondary to mass effect from inflammatory lesions may result in visual loss, afferent pupillary defect, or visual field defects. Mass effect can particularly occur in patients with infraorbital nerve enlargement, which is defined as the infraorbital nerve being greater in diameter than the optic nerve. Infraorbital nerve enlargement is significantly correlated with elevated serum IgG4 levels. Sensory loss is extremely rare. Other less common manifestations are frontal nerve and perioptic nerve lesions. Involvement of the nasolacrimal duct system can cause epiphora. In rare cases of IgG4-related orbitopathy causing scleritis, patients may present with conjunctival and scleral injection with blurred vision.

Data on the association of IgG4-rd and Hashimoto's or Riedel's thyroiditis exist, but similar association with Graves' disease has

not been described. Notably, one group found elevated IgG4 levels in 6.4 % of 109 patients with Graves' disease. This subgroup of patients was significantly older, their symptoms were manageable with small doses of antithyroidal drugs and they were prone to be hypothyroid after treatment. It has recently been shown that IgG4 levels may be elevated in newly diagnosed Graves' disease patients compared with euthyroid subjects and in the presence of Graves' orbitopathy compared with the absence of Graves' orbitopathy. However, the IgG4 rise in IgG4-rd is more marked. Corticosteroid treatment is the standard therapeutic option for both Graves' orbitopathy and IgG4-related orbitopathy, but unlike in Graves' orbitopathy, marked response to low corticosteroid doses is typical in IgG4-related orbitopathy.

IgG4-related orbitopathy may easily be mistaken for Graves' orbitopathy. All patients with suspected euthyroid Graves' orbitopathy in whom TSH receptor autoantibodies are not present have to be evaluated for IgG4-related orbitopathy. Once IgG4-related orbitopathy is proven, other manifestations of IgG4-rd have to be searched for; lifelong follow up is required. Immunoglobulin G4-related disease is an increasingly recognized syndrome of unknown etiology. IgG4-rd could affect many organs and tumor-like swelling of the involved organs is common. Several of the manifestations typically occur in the same patient. The diagnosis of IgG4-rdis based upon biopsy findings (IgG4 positive lymphoplasmacytic infiltration and tissue fibrosis). Serum IgG4 level should be measured, and isolated elevated levels support the

diagnosis, although it is not fully diagnostic without histological examination. Due to various manifestations of this new entity, a multidisciplinary approach is warranted.

Corticosteroid resistant, progressive GO remains a therapeutic challenge. In the present series, we found that anti-CD20 monoclonal antibody had beneficial effect on disease activity in all five patients with treatment-resistant, severe, active GO. The immediate decrease in disease activity parameters CAS and DTPA, at 1 and 3 months, respectively, in patients who failed to respond to conventional therapy, was striking. The positive effect remained permanent for 5 years. To our knowledge, this is the longest published follow up of anti-CD20 treatment in GO.

The initially elevated TRAb levels were reduced at 12 months after anti-CD20. Thyroid function of those patients who had required antithyroid medication, returned to the normal range within 6 months. Relapse of hyperthyroidism was detected in one of the 3 medically treated patients at the 3 year follow up visit.

Effective anti-CD20 treatment in severe active GO has also been reported by other groups. However, the effect on TRAb levels and the outcome of Graves' hyperthyroidism has been controversial. We found that anti-CD20 administered in a high dose compared to doses used in the majority of previous studies, divided over a 4 week period, significantly reduced TRAb levels, and was able to influence the course of Graves' hyperthyroidism with a comparative effectiveness to conventional medical therapies.

However, as the cost of anti-CD20 is substantially higher than that of antithyroid drugs, we think that anti-CD20 treatment is not suitable option for unselected cases of Graves' hyperthyroidism. It is tempting to speculate that the more favorable outcome of anti-CD20 in this respect may be the consequence of the therapeutic protocol we used: in our series, the full lymphoma dose has been administered, i.e. 375 mg/m² anti-CD20 infusions were given weekly for 4 consecutive weeks. Of the studies detailed above, one group used the same regimen in their two works and in fact, their findings are nearly identical. The schedule used by another groups, 1.0 g anti-CD20 given twice 2 weeks apart, failed to result in any reduction in the TRAb levels. Neither in their, nor in our study did CAS changes correlate with TRAb levels. This could mean that the favorable effect of anti-CD20 in GO is not a direct consequence of the declining TRAb production, this speculation is supported by the fact that beneficial effect of anti-CD20 treatment on GO was observed in very low dose and with intraocular use.

The limitation of our study is that some of the favorable orbital changes seen after anti-CD20 treatment may be related to the recent administration of intravenous corticosteroids, or to the use of corticosteroid as premedication before anti-CD20 infusions. Additionally the slowly developing effect of irradiation in 2 of the patients as well as the spontaneous fluctuations during the natural course of the disease may have contributed to the clinical effect. Similarly, previous thyroidectomy in 2 patients may have had a positive effect on both GO course and TRAb level. However, the

fact that improvements occurred within 30 days after anti-CD20 administration in patients who had shown no response to high dose corticosteroids, and the effect remained stable for 5 years, strongly supports the notion that anti-CD20 exerts its effect at one or several factors of the pathogenesis of GO. Another limitation is the low number of patients studied. With improving endocrine care and early detection of GO, severe therapy resistant cases are infrequent; it took 19 months to recruit five patients with steroid resistant GO for the study. In spite of the small number of patients, the improvement of all three disease activity parameters followed were statistically significant.

We detected only one minor side effect (localized skin erythema) of anti-CD20 in one patient during the first infusion. Benign infusion related adverse events are common. El Fassi reported articular adverse events and gastrointestinal symptoms in GD patients who received anti-CD20. Others investigated mortality associated with rituximab use in autoimmune diseases and they found the mortality rate of 2.4 % in patients with autoimmune disease treated with anti-CD20. Among them, 75 % died from infections. In the case of GO patients, anti-CD20 should be restricted for the most severe cases.

We believe that all patients with conventional therapy resistant Graves' orbitopathy are candidates for anti-CD20 treatment administered according to the lymphoma protocol. This may prevent disease progression and help to avoid orbital decompression surgery. In addition to reporting that anti-CD20 administered according to the

lymphoma protocol is effective in severe GO, we provided proof of its efficacy by three independent methods, CAS, MR and SPECT. If severe active GO is present, anti-CD20 may be a useful therapeutic choice if conventional therapies, including steroids and irradiation fail.

6. Summary of the new results

- We worked out an algorithm for the differential diagnosis of the endocrine orbitopathy and IgG4 orbitopathy
- We administrated anti-CD20 therapy for treatment of endocrine orbitopathy first time in Hungary. The treatment improved the clinical signs and the activity of the disease rapidly and this effect was stable during the 5 years follow-up.
- Decrease in TSH receptor antibody level was significant at 12 months follow-up; however improvement in orbita process was mark able at 1 month after the treatment. Our resultssuggest that effect of anti-CD20 therapy is not due the decrease of TSH receptor antibody level. Anti-Cd20 treatment influenced favorably the autoimmune process against thyroid and the hyperthyroidism.
- We did not detect severe side effect beside the anti-CD20 treatment.

7. List of publications



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Candidate: Annamária Erdei

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List of publications related to the dissertation

1. Erdei, A., Steiber, Z., Molnár, C., Berényi, E., Nagy, E. V.: Exophthalmos in a young woman with no Graves' disease: a case report of IgG4-related orbitopathy. *BMC Ophthalmol.* 18 (1), 1-6, 2018.
DOI: <http://dx.doi.org/10.1186/s12886-018-0672-y>
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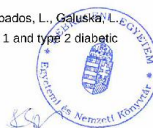
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8. Appendix

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