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Monoclonal anti-TNFα antibody (infliximab) in the treatment of patient with thyroid associated ophthalmopathy

Zastosowanie przeciwciał anti-TNFα (infliximab) w leczeniu chorej z oftalmopatią tarczycową

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Summary: TNFα (tumor necrosis factor alpha) plays a central role in the development of thyroid associated ophthalmopathy (TAO). We describe and document by ophthalmic (CAS and NO SPECS scales) and radiological (MRI) evaluation a positive effect of anti-TNFα antibody (infliximab) administration on active TAO in a 58 years old woman with Graves' disease. The single dose of infliximab administration resulted in a dramatic reduction of inflammation studies and improvement of visual function as measured by MRI and CAS and NO SPECS scales, without noticeable short-term side effects. A randomized prospective study is needed to determine whether infliximab proves to be sufficiently effective in reducing the inflammatory symptoms of TAO, and whether it can be administered safely for a prolonged period without side effects.

Key words: TNFα, anty-TNFα, oftalmopatia Graves'a.
Słowa kluczowe: TNFα, anti-TNFα, Graves' ophthalmopathy.

Introduction

Graves' ophthalmopathy or thyroid associated ophthalmopathy (TAO) is an autoimmune disease of the orbit involving both the retroorbital connective tissue and the extraocular muscles, but the exact mechanism of the pathogenesis is still unknown (1). TAO is the most common cause of proptosis in adults and occurs in about 45% of patients with Graves' disease (2). Examination of retroorbital tissues in the initial inflammatory phase of TAO reveals an accumulation of hydrophilic glycosaminoglycans, increased fat volume, marked T and B lymphocytic infiltration, and presence of many pro-inflammatory cytokines and growth factors. Serum levels of pro-inflammatory cytokines released from T and B lymphocytes (IFNγ, IL-1β, IL-2, sIL--2R TNFα, IL-6) and antibodies of TSH receptor (TRAb) secreted from B lymphocytes are markers of the immune system activity (3,4). TRAb antibodies are thought to stimulate orbital fibroblasts to produce hydrophilic glycosaminoglycans and cause proliferation of adipocytes (4). Several studies suggest a fundamental role for TNFα in the acute phase of TAO with elevated levels of TNFα in orbital tissues and serum (2,3,4).

In the acute phase of TAO, oral (prednisone, dexamethasone) or intravenous corticosteroids (methylprednisolone) are the mainstay of immunomodulatory treatment but side effects limit their long-term use, and up to 35% of patients fail to respond (5, 6). The antioxidants, somatostatin analogs, orbital radiotherapy, orbital decompression are also used in the treatment of TAO in selected patients with severe disease, but results obtained with these treatment are often unsatisfactory. Recently it has been focused on the rationale for B lymphocyte depletion therapy in TAO using monoclonal anti-CD20 antibody therapy with rituximab (7,8). Therefore, the anticytokine therapy may also offer novel method of TAO treatment that targets the molecules involved in establishing and propagating orbital inflammation (2,9).

Aim

The aim of this pilot study was to present a patient with the acute phase of thyroid associated ophthalmopathy treated by infliximab (an anti-tumor necrosis factor alpha antibody).

This study was approved by the Local Ethical Committee of the Medical University of Lódź and accepted by a patient.

Material, methods and results

CASE REPORT

A 58-year-old female was referred to the Department of Clinical Endocrinology at the Medical University of Lodz with active TAO and mild hypertension (150/80 mm Hg) on April 15, 2006. Previously (October 15, 2005), she had been diagnosed as having hyperthyroid Graves' disease (without active TAO) and treated in another hospital with 18 mCi ^{131}I followed by 30 mg of prednisone daily for six weeks.

At the time of the admission to the Department of Clinical Endocrinology she was euthyroid with signs of active TAO (with increased blood concentrations of anti-TSH and anti-TPO antibodies) and, being on 50 μg of L-thyroxine daily substitution.

Medication: The patient received infliximab (Remicade, Schering-Plough – a chimeric human-mouse anti-TNFα – monoclonal antibody IgG1) as *i.v.* infusion in a one single dose of 300 mg (3.7 mg per kg body weight, administered during 2 hrs) after premedication with paracetamol 1g *p.o.* (60 min. before infusion of infliximab). Before (**I**), 5 days (**II**), 5 weeks (**III**), as well as 10 weeks (**IV**) after the treatment the biochemical, ophthalmic (with NO SPECS and CAS scale) and radiological (MRI) examinations were performed.

Ophthalmic examination

Full ophthalmic evaluation was performed before the beginning of the treatment with infliximab, and also 5 days, 5 weeks and 10 weeks following the treatment (Table I). Additional investigations included visual evoked responses and visual field analysis.

The patient presented with 3-month history of progressively increasing ophthalmic symptoms. She complained of pain and burning sensation around the eyes as well as constant double vision. The examination revealed signs of inflammatory thyroid associated ophthalmopathy. There was a marked lid lag and lid retraction, as well as lid and conjunctival oedema and redness. Visual acuities were reduced by two Snellen lines, and pupillary reactions including Relative Afferent Pupillary Defect (RAPD) were normal. Exophthalmometry readings were 25 and 26 mm, respectively. NO SPECS scale (5) was 12c3b4b for both eyes. Clinical Activity Score (CAS) (5) was 6 points for the right and 7 points for the left eye. Ocular motility function was severely compromised in all directions of gaze, but in particular for abduction and elevation for both vergences and ductions in both eyes. The patient complained of severe constant vertical double vision. There were 16 prism dioptres right over left hypertrophy. Visual fields were normal. Fundoscopy revealed no papilloedema. We performed visual evoked potentials analysis to exclude optic nerve involvement. We obtained normal pattern and flash responses. Slight reduction of best corrected visual acuity to the level of 0.8 was attributed to corneal tear film disturbance and irregular astigmatism caused by marked proptosis.

Ophthalmic evaluation was repeated 5 days after infliximab infusion. The patient's inflammatory symptoms increased slightly with CAS scores 6 and 8 points. There were no significant changes in any other symptoms. There was still pain, ocular discomfort, and burning sensation around the eyes. Double vision persisted accompanied by increased comparable restriction of ocular motility.

Five weeks following infliximab infusion there was a significant reduction in inflammatory signs and CAS score decreased to 3 points for both eyes. Subjectively, there was an improvement in pain and burning sensation. Redness and swelling of the eyelids and conjunctiva were no more noticeable. Visual acuities improved although reduction of eye movements, double vision and exophthalmos (23 and 25 mm) persisted. Vertical double vision was accompanied by 16 prism dioptries right over left hypertropia. NO SPECS score also improved, exept for increased restriction of ocular movements and was 12a3a4c for the right eye and 12a3b4c for the left. Ocular motility was decreased compared to initial examination, in spite of the marked reduction of all the inflammatory symptoms and exophthalmos. The above finding was attributed to increased fibrotic process of the extraocular muscles.

Ten weeks following infliximab infusion the patient was free from ocular pain and discomfort. She had moderate eyelid oedema but no lid or conjunctival redness. She was free from excessive lacrimation, photophobia and grittiness of the eyes. Exophthalmometry readings were 23 and 24 mm, respectively. Restriction of eye movements remained very stable compared to the examination performed 5 weeks earlier, with severe restriction in all directions of gaze, but in particular, restriction of elevation more marked on the right side and abduction restricted symmetrically on both sides. There was 20 prism dioptries vertical disparation right over left. Her double vision persisted but was well controlled with Fresnel prisms.

The MRI study

The patient underwent MR examination in 1, 5 T scanner Siemens, Vision+. The head coil was positioned according to the *nasion* point. Transversal sections were positioned parallelly to medial and lateral muscles, coronal ones perpendicularly to a course of the optic nerve what was tantamount to the long axis of the orbit.

The patient underwent both spin echo (SE) and STIR imaging with **T1** parameters: TR – 450 ms, TE – 14 ms, FA – 90º, FOV – 250 mm, number of layers – 15, thickness of layers – 3, dis. Factor – 0, 1, matrix – 192x512, number of acquisitions – 3, time 4 min 22 s, **STIR**: TR – 5300 ms, TE – 30 ms, TI – 150 ms, FA – 180º, FOV– 250 mm, number of layers – 15, thickness of layers – 3, dis. Factor – 0,1, matrix – 140x256, number of acquisitions – 2, time 3 min 38s as well as **multiecho T2** sequences: TR – 450 ms, TE – 15 ms, 75 ms, 135 ms, FA – 180º, FOV – 250 mm, number of layers – 11, thickness of layers – 4, dis. Factor – 0,1, matrix – 186x256, number of acquisitions – 2, time 4 min 10 s.

STIR images were quantified by measuring the signal intensity (10,11), and the multiecho sequence by calculation of T2 time (12,13,14).

Eyeball muscles' volume estimation

The coronal T1 images were used for the eyeball muscles` volume estimation.

For the purpose of image processing the open source ITK library [The Insight Software Consortium. The Insight Toolkit (ITK). http://www.itk.org/] was used. The algorithms employed were cubic spline re-sampling and Level Set segmentation. For the description of above-mentioned algorithms we refer to the ITK library reference manual [Ibanez, Schroeder, Ng, Cates **Internet**: http://www.itk.org/ItkSoftwareGuide.pdf].

In the first step of our workflow the radiologist roughly marked the position of the muscle on an MRI image. This operation created a mask image that was further on used as an initial condition for the Level Set segmentation algorithm. In the second step both the MRI and the mask images were re-sampled into 1x1x1mm isotropic voxel size by means of cubic spline re-sampling algorithm.

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	I. Before treatment	II 5 days following infliximab infusion	III. 5 weeks following infliximab infusion	IV. 10 weeks following infliximab infusion
NO SPECS scale RIGTH	12c3b4b	12c3b4b	12a3a4c	12a3a4c
NO SPECS scale LEFT	12c3b4b	12c3b4b	12a3b4c	12a3a4c
CAS SCORE RIGHT	6 points	6 point	3 points	3 points
CAS SCORE LEFT	7 points	8 points	3 points	3 points

Tab. I. Ophthalmic examination of the patient studied before and after infliximab administration.

All further processing was done on the re-sampled MRI and mask images. In the third step both re-sampled MRI and mask images were input into Level Set segmentation algorithm in order to obtain a segmented image, that is in fact a refined and more accurate position of the muscle. This step essentially classifies every voxel of an image into two classes – either containing the muscle or not. At the final fourth step of our workflow the volume of the muscle was estimated by multiplying the number of voxels in the area of the muscle by the volume of one voxel.

The first MRI examination carried out before the treatment revealed the enlargement of medial, inferior muscles of the right eye and superior, medial and inferior muscles of the left eye (Table II A). The increase in signal intensity (Table II B) as well as T2 time (Table II C) of these muscles was also observed. The next, after 5 days, examination did not reveal any significant changes both in the size and indexes of disease activity. Five weeks later there were still no differences in the size of the muscles, however T2 time values of affected muscles decreased evidently. That decrease was found to be continued in 10 weeks following infusion examination. Then reduction of the muscle volume was also found. Signal intensity of the muscles did not change at all throughout 10 weeks what proves the low value of this parameter in estimating the activity of pathological process in Graves's ophthalmopathy.

A. Volumes of eye ball muscles

	MS		MM		MI		ML	
	R	L	R	L	R	L	R	L
Exam I. Before treatment	480	1097	1523	2956	2210	2527	846	771
Exam II. 5 days after treatment	580	1132	1602	2832	2367	2479	845	790
Exam III. 5 weeks after treatment	665	1100	1640	2840	2380	2562	815	717
Exam IV. 10 weeks after treatment	580	957	1340	2300	2150	2025	780	790

B. Signal intensity in T2 images of eye ball muscles

	MS		MM		MI		ML	
	R	L	R	L	R	L	R	L
Exam I. Before treatment	480	669	647	690	910	873	420	434
Exam II. 5 days after treatment	443	694	792	698	918	877	475	378
Exam III. 5 weeks after treatment	630	765	765	782	883	706	514	489
Exam IV. 10 weeks after treatment	643	695	718	788	885	882	573	453

C. T2 time of eye ball muscles

	MS		MM		MI		ML	
	R	L	R	L	R	L	R	L
Exam I. Before treatment	108	162	170	152	268	190	113	121
Exam II. 5 days after treatment	110	202	170	166	251	197	121	97
Exam III. 5 weeks after treatment	120	174	134	140	239	128	94	116
Exam IV. 10 weeks after treatment	112	123	110	118	173	95	113	102

Tab. II. Radiological examinations (MRI). R – right, L – left, MS – superior muscle, MM – medial muscle, MI – inferior muscle, ML – lateral muscle.

Discussion

Many clinical trials have shown a beneficial effect of anti-TNFα treatment in Leśniowski-Crohn disease, rheumatoid arthritis, psoriasis, ankylosis spondylitis and, recently, acute uveitis (15).

Moreover, several studies suggest a key role of TNFα in the acute phase of TAO with elevated levels of TNFα in orbital tissues and serum (4,6)

The results of our study have clearly shown that the single dose of infliximab administration resulted in a dramatic reduction of inflammation and improvement of visual function as measured by MRI and CAS and NO SPECS scales without noticeable short-term side effects. Especially improvement was observed on the CAS scale which refers directly to the active inflammatory process. The good results of a single infusion of infliximab have also been noted in a patient with active TAO (2). In etanercept study of ten patients with Graves' ophthalmopathy (another anti – TNF drug administered twice weekly during 12 weeks) TAO signs also improved significantly (9). Therefore, we hope that TNFα antagonist may be a novel therapeutic option in selected patients with active TAO.

A randomized prospective study is needed to determine whether infliximab proves sufficiently effective in reducing the inflammatory symptoms of TAO, and whether it can be administered safely for a prolonged period without side effects.

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