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LETTER TO THE EDITOR

Anti-IL-6R therapy on Graves' ophthalmopathy

KEYWORDS
Graves' ophthalmopahty;
Tocilizumab;
Remission

Dear Editor:

Since 1997, several authors like Molnár & Siddiqi have anticipated a role of IL-6 in the pathogenesis of GO (Graves' ophthalmopathy), stressing the fact that high blood levels of IL-6 were repeatedly found in GO. They suggested at that time that treatment with steroids could also act on IL-6 levels [1].

During decades, the standard treatment for GO has been surgery and radiation in order to decompress the orbit, with modest results and collateral risks. But in 1993, a challenge in the way of thinking came from Matzinger, who said: "there is a need for a nondestructive response to damaged tissues" [2]. These words were validated by specialists in the field, as R. Bahn that, in 2010 wrote: "the anti-interleukin-6 receptor antibody is an attractive potential treatment for Graves' ophthalmopathy." [3].

Biologicals open a new era in GO displacing the non-discriminatory steroids when it comes to act on immune system and specially the traditional harmful methods like surgery and radiotherapy.

There are some types of biological therapies that have been already tried in this setting: anti-TNF-alpha and the anti-CD20 monoclonal antibodies. Although some studies show that anti-TNF-α agents may worsen thyroid eye disease [4], there are also various published case reports showing the benefits of anti-TNF-α therapy in GO [5].

As to the anti-CD20 antibodies, besides affecting the autoantibodies' production by depleting B cells, it does down-modulate Th1 responses too, by suppressing B-cell induced activation of T-cells. Used in GO, it may contribute to normalizing abnormal autoreactive T-cell responses [6]. Here we report the clinical remission of GO by anti-IL-6R monoclonal antibodies (tocilizumab), given that the patient had negative anti-TSHR antibodies at that time. We suggest that anti-IL6R may be a more specific biological therapy for GO entity. To our knowledge, this is the first internationally documented case of GO treated with tocilizumab.

In 2008, a 52-year-old Caucasian woman was diagnosed with Graves' disease (GD) and bilateral thyroid-associated moderate-to-severe orbitopathy with chemosis, sensitivity to light, blurring and, most disabling for the patient, diplopia. The patient medical history was only relevant for supraventricular tachycardia, hypercholesterolemia and anxiety. The BMI was 19 and 46 kg weight. The patient used to smoke 15 cigarettes per day for almost two decades. The treatments received for GD were propiltiouracil (2008) and tiamazol. She was also treated with several pulses of methylprednisolone between 2009 and 2011 for her GO, without stopping the progression of the GO. The patient showed intolerance to steroids. No biological therapies were administered during this period, from 2008 to 2011.

From December 2008 to February 2010, blood tests displayed positive anti-TSHR antibodies but they turned negative in March 2010. Ophthalmologic examination documented symmetric bilateral affectation with NOSPECS class IV/VII TAO (left eye $\approx$ right eye). Her Mourits' Clinical Activity Score (CAS) was 6, on a scale of 0 to 10. A baseline orbitary CT in 2010 disclosed hypertrophy of both internal medial rectus muscles suggested that the patient had GO. The magnetic resonance imaging (MRI) of the orbits confirmed the ophthalmopathy. It showed a low-medium bilateral symmetric proptosis, and bilateral exophthalmos with retrobulbar adipose infiltration. The MRI also showed bilateral increase of extrinsic ocular muscle thickness. The maximum diameters of inferior rectus muscle in the transverse plane on T2-weighted sequences were 6.6 mm for the right muscle and 6.1 mm for the left muscle.

In 2011, the patient was referred to our Clinical Immunology Unit. As part of the immunological study, the following markers of acute inflammation were determined: CRP and ESR were negative, C3 and C4 were normal. Antinuclear (ANA), anti-DNA antibodies, anti-cytoplasm of neutrophils (ANCA), anti-thyroid (TSH-receptor, thyroglobulin peroxidase) antibodies were all negative. There were no alterations to total counts of T, B, NK cells, or to the CD4/CD8 ratio. T3 and T4 were in normal levels and TSH was less than 0.03 mUI/L. 25-hidroxi-vitamin D level was 19.1 μg/L. The Mantoux size was 13 mm. The chest x-ray showed no alterations.

The patient was treated with 3 cycles of tocilizumab (anti-IL-6R). The treatment lasted 3 months (at a dose of 480 mg, one intravenous infusion per month) as the standard

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schedule for rheumatoid arthritis (480 mg/infusion). No premedication was needed. Given the off-label use of tocilizumab for this indication, the patient had given written informed consent. Prophylaxis therapy for tuberculosis was performed.

The results and clinical evolution were: the Mourits' clinical activity score was reduced over time, from 6 to 0, with a decrease of both inferior rectus muscle diameters on MRI with 2-3 mm, from 6.6 mm right and 6.1 mm left. The initial physical appearance was regained. No adverse effects were observed besides mild asthenia 24 h after infusion. In more than 12 months since September 2011, no recurrence has been observed until now.

Conflict of interest statement

The authors report no conflicts of interest.

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