Optic neuritis associated to treatment with infliximab

Treatments with anti-TNF-alpha (ATA) are commonly used for the treatment of certain inflammatory rheumatic diseases such as spondyloarthoritis, rheumatoid arthritis or psoriatic arthritis, and inflammatory bowel disease (IBD).

Among the different therapeutic classes available, there are, firstly, chimeric or humanized monoclonal antibody such as infliximab (Remicade®) and adalimumab (Humira®) and, secondly, etanercept (Enbrel®), competitively inhibiting the binding of soluble TNF-alpha to its receptors (soluble receptor).

Among the adverse events (AEs) associated with the use of this therapeutic family, the occurrence of iatrogenic autoimmune pathologies has been reported in the literature [1]. Neurologically, demyelinating events of the central nervous system [2,3] and demyelinating peripheral neuropathy [4] have been reported.

Observation

A 51-year-old female presented in December 2014 with a rapidly progressive decline in visual acuity of the right eye. In her past medical history was noted a rheumatoid arthritis diagnosed in 1990 and treated since 2008 by infliximab. There was no hypertension, no history of venous or arterial vascular thrombosis, no history of obstetric morbidity, no clinical criteria for an antiphospholipid syndrome.

She was hospitalized from December 11 to 17 in the Ophthalmology department. She presented central scotoma, eyeball pain and pain on palpation and mobilization of the right globe. Visual acuity was very low on her right eye (limited to light perception) and normal on her left eye. The fundus showed a slight papilledema and visual field showed a central scotoma (see figure 1). Clinical examination also noted metacarlophalangeal and interphalangeal arthritis. A right retro-bulbar optic neuritis was diagnosed. She then received intravenous corticosteroids (1 g/d) for 3 days which resulted in a progressive improvement in visual acuity. A brain MRI was performed revealing in Flair-weighted sequences 11 small subcortical frontal and parietal, 1 infratentorial and 3 periventricular hyperintensities without enhancement after gadolinium injection, suggesting demyelinating lesions with spatial dissemination (see figures 2-5). At the level of the optic nerves was noted in T2-weighted sequence a hyperintensity of the optic nerve of the right eye with enhancement after contrast injection compatible with optic neuritis (see figure 6).

A spinal cord MRI found on T2 and STIR-weighted sequences a cervical medullary hyperintensity at the C6 vertebral level without enhancement after contrast injection (see figure 7). Biologically, blood electrolytes were normal. Autoimmune assessment noted sedimentation rate at 18, antinuclear antibody (1/320, homonegenous) were positive, circulating anticoagulant, ANCA, anti-DNA, anti-ENA, anticardiolipin IgG antibodies were negative, anticardiolipin IgM antibody was weakly positive (26 mpl/mL), anti-ß2GP1 antibody was also positive for IgG (34 U/mL) and IgM (166 U/mL) thus clearly positive. Anti-NMO antibodies were negative, the dosage of the angiotensin-converting enzyme slightly increased to 71 (normal lower than 70). Lumbar puncture showed CSF protein level of 0.20 g/L, without cells, elevated IgG index (0.95; N < 0.7) and the isoelectric focusing was in favor intrathecal synthesis with an oligoclonal profile. No cells were noted.

The combination of clinical features (right retro-bulbar optic neuritis), of the biological data (inflammatory profile on CSF with intrathecal synthesis) and of radiological data (hyperintensities on brain MRI meeting the Barkhof and Tintoré criteria and Mac Donald 2010 criteria and on spinal cord MRI) was in favor of the diagnosis of a clinically isolated syndrome (CIS) at risk of progression to multiple sclerosis. Thrombotic lesions, even sequelae of an antiphospholipid syndrome, would have a different appearance on MRI.

This right retro-bulbar optic neuritis occurred in December 2014 while the patient was under treatment with infliximab. Infliximab therapy was discontinued immediately; the next injection date was scheduled for February which resulted at that time to change treatment for abatacept.

In December 2015, the patient had not presented any other clinical episode. A control MRI found some nonspecific subcortical hyperintensities in particular in left fronto-parietal area that seem to fade significantly compared to December 2014 MRI. Visual acuity was significantly improved with a visual acuity score in December 2015 of 9/10 in the right eye, 10/10 in the left one.

It was decided not to introduce immunomodulatory or immunosuppressive treatment for the demyelinating disease, but to maintain close neurological clinical and MRI monitoring every 6 months (the appearance of criteria of temporal spread that currently lack to make the diagnosis of clinically definite multiple sclerosis should lead to introduce immunomodulatory (interferon type) or immunosuppressant treatment).
We report the case of a patient who presented as an inaugural inflammatory optic neuropathy under ATA. A Spanish meta-analysis of randomized controlled trials and post-marketing studies found a prevalence of demyelinating events under ATA ranging between 0.05 and 0.20% [1]. The main clinical picture was a retro-bulbar optic neuritis, followed by multiple sclerosis (MS), and acute transverse myelitis. The time of occurrence of these events was variable, ranging from months to years after initiation of treatment. Other reported neurologic AEs were peripheral demyelinating neuropathies such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, and vasculitis. These events could be isolated or may be part of a systemic immune dysfunction-induced pathology.

The pathophysiology of neurological adverse effects in ATA is complex and poorly understood. A link between ATA and demyelinating diseases is suggested by several studies. Based on the TNF-alpha (TNF-a) overproduction in serum and cerebrospinal fluid of patients with MS [5], a double-blind, placebo-controlled trial in MS with lenenercept (ATA close to etanercept) has been conducted: unfortunately, this led to a worsening of the neurological condition [6]. Several publications have reported the occurrence of MS [7] or an aggravation under ATA [8], which led to contraindicate this pharmaceutical class in patients with MS or with a history of CNS demyelinating events. These studies suggest that ATAs may potentially initiate or unmask an underlying demyelinating disease.

In their literature review, Tristano et al. highlight the variability of the signal induced by the TNF-a depending on the type of receptor to which it binds [5]. There are two types of receptors TNFR1 and TNFR2 that induce respectively either a production of pro-inflammatory cytokines, or the induction of regulatory T-cells and remyelination processes, which would explain the unfavorable evolution of demyelinating diseases of the CNS under ATA. Also, some authors suggest the hypothesis of an inherent increased risk of occurrence of immune dysfunction disease in patients with active chronic inflammatory disease requiring use of second-line therapy [1]. Indeed, all these data must be tempered by cases of demyelinating diseases (MS) reported in patients with rheumatoid arthritis (RA) who were not receiving any ATA [9–11]. An argument against a direct role for ATA is that these cases are reported with a low incidence, below the natural incidence of MS in the general population,
Optic neuritis associated to treatment with infliximab

**Figure 2**
Hypersignal of the corpus callosum on sagittal Flair-weighted sequence

**Figure 3**
Periventricular and subcortical hypersignals on axial Flair-weighted sequence

**Figure 4**
Pons hypersignal on axial T2-weighted sequence

**Figure 5**
Subcortical hypersignal on sagittal Flair-weighted sequence
and they may represent coincidental events. These neurological syndromes could be a clinical manifestation of another autoimmune disease occurring in a patient with a propensity to develop MS due to common genetic background, suggesting that ATA treatment unmasks the demyelinating disease.

Epidemiological studies have also suggested an association between IBD and MS showing an increased prevalence of MS among IBD patients, but without accounting for ATA exposure. Recently, a large Mayo Clinic cohort study concluded that ATA biologics do not appear to impact the risk of developing idiopathic inflammatory demyelinating disease in patients with inflammatory bowel disease [12].

Another large population-based cohort designed to assess the risk of optic neuritis associated with ATA, the SABER Study concluded that Optic neuritis is rare among those who initiate ATA therapy and occurs with similar frequency among those with non-biologic exposure [13].

In patients with ATA related demyelinating events of the CNS, the prognostic value of the CSF study has previously been suggested in the literature [3]. In the analysis of three cases reported, two patients presented to the analysis of CSF oligoclonal bands, including one who presented during follow-up a remitting MS [3].

Little data is available in the literature concerning the characteristics of these events in MRI. In a review of the cases reported in the literature, Tristano highlights the diversity of radiological presentation [5]. MRI can sometimes show white matter hyper-intensities on T2 strongly suggestive of a demyelinating inflammatory process type of MS, or in other cases reveal abnormalities of the white matter of nonspecific appearance. The prognostic value of the initial MRI on the long-term evolution has not been studied in this specific situation [5]. The Barkhof and Tintoré criteria are considered the best prognostic markers conversion risk in MS after a first demyelinating event [14]. Their specific interest at the onset of demyelinating event under ATA has not been evaluated.

Our patient presented positive antinuclear antibodies. Autoimmunity is associated with anti-TNF-alpha treatments: the cumulative incidence of antinuclear antibodies was 56.8% after 24 months in a cohort of infliximab-treated Crohn's disease patients [15].

She also had positive anticardiolipin (ACL) and anti-β2GP1 antibodies, which could also evoke an antiphospholipid syndrome, but our patient had no clinical criteria nor lupus circulating anticoagulant (LAC) criteria for such diagnosis. Antiphospholipid syndrome is characterized by the occurrence of vascular thrombosis or pregnancy morbidity in the presence of antiphospholipid antibodies (APLs), which include ACL, anti-β2GPI, and LAC [16]. According to the revised Sapporo criteria, APS can be diagnosed by one clinical criterion and at least one laboratory criterion [16]. We believe that the presence of such antibodies in our patient was also probably secondary to the infliximab treatment as this has already been reported [17] although less frequently than for
antinuclear antibodies. Unfortunately, these antibodies were not quantified in our patient before beginning infliximab treatment. There are limited data regarding the induction of antiphospholipid antibodies (APLs) by ATA: two studies have reported antibody development in RA patients receiving ATA. Jonsdottir et al. [18] showed that up to 25% of such patients develop IgG or IgM ACL, while Ferraro-Peyret et al. showed that 21% developed APL positivity [19]. Ferraro-Peyret found no correlation between induction of autoantibodies (ACL or anti-β2GPI) and development of APS or lupus-like syndrome over a two-year period [19]. In our case, improvement in symptoms following the discontinuation of the drug (complete recovery from optic neuritis 12 months after infliximab withdrawal) could suggest a link between infliximab and the development of this neurological complication. Because of the level of evidence of the study and the lack of reintroduction sequence, that would not be ethical, we cannot conclude causality.

**Conclusion**

We report the case of a patient who experienced a first demyelinating event under ATA. The occurrence of this type of event requires the discontinuation of ATA. Careful clinical evaluation, including neurological examination, is needed before starting ATA. Patients with unexplained central nervous system involvement or signs of peripheral neuropathy, with past history or familial history of demyelinating disease, should not receive this treatment before complete neurological evaluation.

Patients being treated with ATA should be closely monitored for the development of ophthalmological or neurological signs and symptoms. If clinical evaluation leads to the diagnosis of optic neuritis or any other demyelinating event, discontinuation of the medication and initiation of steroid treatment should be a priority.

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**References**


3.1.2 Mise en page et graphiques

3.1.2.1 Mise en page

3.1.2.2 Graphiques

3.2 Références

3.2.1 Articles scientifiques

3.2.2 Précédents de recherche

3.3 Conclusion

3.3.1 Conclusion générale

3.3.2 Conclusion de la proposition

3.4 Discrétion

3.4.1 Discrétion des auteurs

3.4.2 Discrétion des destinataires

3.5 Références

3.5.1 Articles scientifiques

3.5.2 Précédents de recherche

4 Annexe

4.1 Tables

4.2 Graphiques

5 Conclusion

5.1 Conclusion générale

5.2 Conclusion de la proposition

5.3 Discrétion

5.3.1 Discrétion des auteurs

5.3.2 Discrétion des destinataires

5.4 Références

6 Références bibliographiques