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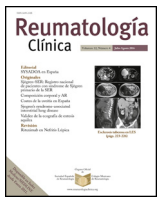

Review article

Biological Therapy and Neurological Manifestations. What do We Know?☆

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ABSTRACT

Biological therapy has changed the course of inflammatory rheumatic diseases. The safety is well documented in national and international studies. Neurological manifestations are uncommon and it is difficult to establish a clear causal relationship. The neurological signs and symptoms that may appear are multiple and sometimes mimic demyelinating neurological diseases and/or neurodegenerative diseases. Knowledge and disclosure of these cases is essential for a comprehensive management of biological therapy in our patients.

Terapias biológicas y manifestaciones neurológicas. ¿Qué sabemos?

Palabras clave:
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RESUMEN

La terapia biológica ha cambiado el curso de las enfermedades reumáticas inflamatorias. La seguridad de la misma está más que documentada en diferentes estudios nacionales e internacionales. La baja frecuencia de las manifestaciones neurológicas dificulta en muchas ocasiones el establecer una relación causal clara entre el tratamiento biológico y la clínica neurológica propiamente dicha. Los síntomas y signos neurológicos que pueden aparecer son múltiples, y en ocasiones simulan enfermedades neurológicas desmielinizantes y/o neurodegenerativas. El conocimiento y el reporte de los mismos es fundamental para realizar un manejo exhaustivo de la terapia biológica en nuestros pacientes.

Introduction

Since the commencement of the age of biological treatments, the prognosis of most inflammatory rheumatic diseases has improved significantly. Both the drugs that inhibit the proinflammatory cytokine, tumor necrosis factor alpha (TNFα), and those that inhibit other interleukins (IL) and cells that participate in the mechanism of inflammation, have definitively changed the course of many chronic rheumatic diseases.

At present, the safety of these drugs over the intermediate and long term is well-documented in different national and international studies, based mostly on patient registries that are followed prospectively. The outcomes in some of them are divergent, since the sample to be studied, the data collection and even the analysis, are far from being similar. However, in general, all coincide in that infections and hypersensitivity reactions are the most common adverse effects.

The biological drugs currently available in Spain are as follows[1,2]:

1. Drugs that act as TNFα inhibitors and can block the molecule itself *(infliximab, adalimumab, golimumab, certolizumab)* or its receptor *(etanercept)*.
2. Drugs that inhibit other IL: *tocilizumab*, inhibits IL-6, which participates in the inflammatory mechanisms and joint destruction;

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anakinra, which blocks the activity of IL-1 by competitively inhibiting its binding to the receptor IL-1R1; and *ustekinumab* (IgG1kappa monoclonal antibody, that inhibits IL-12/IL-23).
3. Drugs that interfere with the activity of certain cell lines: *abatacept* (which inhibits binding of CD28 and CD80, blocking the costimulatory signal of T cells); *rituximab* (depletion of CD20-positive B cells).

In this review, we will focus mainly on *anti-TNFα drugs* since there are nearly no cases of neurological involvement with the remainder, probably, among other things, because they have been available for less time. These neurological manifestations are uncommon during treatment with biological drugs, but this does not mean that they are less important. They can also be irreversible.

Since these agents are being utilized, a number of isolated events and series of cases have been published, although it is still hard to establish a definite cause-and-effect relationship.[3–5] The neurological finding most widely described in the literature is the demyelination of the central and/or peripheral nervous system, but others have also been reported: optic neuritis, acute/chronic inflammatory polyneuropathy, mononeuritis multiplex and Guillain-Barré syndrome, among others.[6–9] All of the guidelines on the use of biological therapy contraindicate their administration to patients with multiple sclerosis, and precaution when there is a family history of the disease.

However, the debate on whether biological treatment can disguise the development of a preexisting demyelinating disease, such as multiple sclerosis or, on the other hand, is responsible for inducing *de novo* demyelination in the central and/or peripheral nervous system.[9]

Epidemiology

In initial studies, it was reported that the risk of developing a demyelinating disease increased by 30% with the use of biological therapy.[10] According to the Spanish registry of adverse events in biological therapies in rheumatic diseases (BIOBADASER), the incidence is low, between 0.3 and 0.6 for each 1,000 person-years of exposure. In BIOBADASER, after a follow-up of 9256 patients (21,425 person-years), 9 cases were reported, meaning that the rate of demyelinating disease in patients treated with anti-TNFα was not greater than that expected in the general population.[3] The cases of demyelinating disease were more frequent among patients of more advanced age, men and those diagnosed as having psoriatic arthritis, although in no case were the differences statistically significant.[8]

Pathogenesis

The mechanism that leads a patient to be predisposed to develop a demyelinating disease or experience an exacerbation of that disease once the biological treatment has begun is unknown.

A number of hypotheses that have been proposed suggest that TNFα has a major role in the pathogenesis of multiple sclerosis.[11] It is a proinflammatory cytokine that participates in the acute phase of the disease and in the demyelinating process. On the other hand, TNFα also has immunosuppressive properties in the second phase of the disease. These properties are related to the TNFα receptors (TNFR1 and TNFR2), which measure different biological responses to TNFα itself.

In the central nervous system, TNFα is produced by microglia, astrocytes and other cells, such as the monomer precursor transmembrane protein (tmTNF). The TNFα converting enzyme disassociates from the cytoplasmic tail and releases soluble forms of TNFα (sTNF). To carry out its biological functions, the monomeric forms of tmTNF and sTNF should aggregate and form homodimers. Both TNF (tmTNF and sTNF) can bind to both TNFR1 and TNFR2; sTNF has a greater affinity to TNFR1, producing the inflammatory response and apoptosis. tmTNF binds mostly to TNFR2 and promotes cell activation and survival. Transgenic mice have been used to study how the isolated expression of tmTNF can avoid and suppress the progression of experimental autoimmune encephalitis, as it also maintains self-tolerance and resistance to infection. Thus, selective inhibition of the sTNF/TNFR1 signal could be used as a strategy to prevent relapses in multiple sclerosis.[11]

Taking this theory into account, 4 major hypotheses have been postulated to explain a potential biological relationship between TNF antagonists and demyelinating disease:

a) Anti-TNFα do not cross the blood-brain barrier, but they enhance the activity through an increase in the autoreactive peripheral T cells, that can penetrate the central nervous system.[12]
b) The necessarily reduced regulation of TNFR2 for the proliferation of oligodendrocytes and repair of the damage.[12,13]
c) Reduced regulation and production of cytokines like IL-10, and overproduction and regulation of IL-12 and interferon γ (IFN-γ) associated with the demyelinating process.[14,15]
d) Anti-TNFα could camouflage a latent infection that, in turn, could be critical to initiate a demyelinating autoimmune process.[16]

Kaltsonoudis et al.[9] conducted a prospective study in 77 patients with inflammatory rheumatic disease (36 patients with rheumatoid arthritis, 24 patients with psoriatic arthritis and 17 patients with ankylosing spondylitis) who began with anti-TNFα (infliximab, adalimumab, etanercept). All underwent a complete neurological examination, nuclear magnetic resonance of the brain and the entire spine, and a neurophysiology study before and more than 18 months after starting the biological therapy. In the initial scrutiny, they detected lesions compatible with demyelinating disease in magnetic resonance in 2 patients and, thus, decided against the biological treatment. At the end of the study, 4% of the patients (3/75) showed evidence of neurological involvement: peripheral demyelinating neuropathy (2 patients) and optic neuritis. In each case, the biological therapy was interrupted and the neurological disease was treated. The neurological symptoms remitted in all the patients.[9] The authors stress the importance of magnetic resonance and the neurophysiological study for the early detection of neurological involvement in these patients; however, to perform these ancillary tests in every patient who begins biological therapy would significantly increase the expense and would probably not be cost-effective.

Types of Neurological Involvement and Care Review

Nanau et al.[5] carried out a systematic review of the safety of TNFα inhibitors in patients with inflammatory rheumatic diseases.[5] They included the publication of clinical trials and case reports published between 2010 and 2014. The majority of the neurological adverse events were observed in patients with rheumatoid arthritis; 50.9% over a 10-year period, according to the authors. The most common finding was the involvement of the central nervous system, the spectrum of demyelinating diseases, optic neuritis and sensory and/or motor demyelinating peripheral neuropathy. The remainder of the neurological events, such as transverse myelitis or progressive multifocal leukoencephalopathy, were less common.[5,17]

In a French cohort, 33 patients with inflammatory rheumatic disease revealed evidence of demyelinating disease on magnetic