Natalizumab and multiple sclerosis

Natalizumabe e esclerose múltipla

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Multiple sclerosis, a demyelinating inflammatory and neurodegenerative disease of the central nervous system (CNS) that affects a young population, in their most productive life stage, had its development changed after the introduction of immunomodulatory drugs, such as preventive treatment of new outbreaks and disease progression in early 1990s. After more than 20 years using interferons and glatiramer acetate, an evolutionary improvement of patients treated with these drugs, as well as a better knowledge of its adverse effects and therapeutic response were observed.

Despite the proven efficacy of the immunomodulatory drugs, some patients (from 3 to 50%)[1] did not respond well to treatment, showing an unsatisfactory evolution, with increased number of outbreaks, increased brain lesion load, and progressive disability.

Monoclonal antibodies have emerged as a therapeutic option for the treatment of multiple sclerosis. Natalizumabe (NTZ) is a humanized monoclonal antibody that binds to integrin α4B1, with a relevant immunomodulatory effect[2]. After publishing two phase III studies, i.e. AFFIRM (NTZ in monotherapy compared to placebo) and SENTINEL (NTZ and Avonex compared to placebo and Avonex), which showed respectively a 68 and 55% reduction in the annual taxes of bouts, and a 42 and 24% reduction in the progression of disability along two years[3,4], the Food and Drug Administration (FDA) approved NTZ, in 2004, for treating relapsing-remitting multiple sclerosis (RRMS) with high disease activity. However, in 2005, with the identification of two cases of progressive multifocal leukoencephalopathy (PML), the medication was taken out of the market. In 2006, after additional security data, it was reintroduced with the FDA approval for specific indications and under surveillance[2].

PML is a rare demyelinating brain disease, caused by a human polyoma virus, the JC (JCV), which is found in healthy individuals, with a serum prevalence from 20 to 80%[5]. It is a severe sub-acute disease with behavioral and cognitive compromises, visual and motor dysfunctions, and may have a fatal outcome in three to six months. Clinical studies have shown that the risk of PML associated with NTZ was one case for every 1,000 patients; this risk was directly related to time and, in patients previously submitted to immunosuppressants, it would be increased in up to eight times[6,7]. Other mild adverse effects observed were those related to the infusion, such as headache, dizziness, and nausea. Hypersensitivity reactions may occur such as hives, rash, chills, and systemic reactions indicating discontinuation of the treatment.

NTZ proved to be a very effective drug in the treatment of severe cases of RRMS. However, it requires special care because it is a new drug and its serious adverse effects, which limit its use in Brazil and in other countries.

The group of MS experts, who met in this arduous task of assessing the adverse effects of NTZ in the Brazilian population, held a work of extreme importance, highlighting some features of these adverse effects in our population[8]. Given the very effective results with this new drug, in patients with more severe diseases, we are often induced to extend this treatment to a larger number of patients, or to amplify its time, even in groups at higher risk of complications, when presenting an evolutionary improvement of their disease. In this study, the adverse reactions observed in most patients (97%) out of 103 patients with RRMS, after 1,042 infusions of NTZ, were mild to moderate in the first 24 hours. Even so, two fatal cases were reported after the first infusion, due to acute myocardial infarction and massive respiratory infection that could be related to treatment with NTZ. The authors call attention, therefore, to other two adverse effects

to be observed: myocardial infarction and pneumonia in patients undergoing this treatment. They also emphasize the need to report moderate and severe adverse effects for increased pharmacovigilance so that experts can have access to this information. The orientation of this group of specialists is that treatment with NTZ should only be performed by multiple sclerosis specialized centers of treatment, with supervision programs.

NTZ is undoubtedly a medication that improved the prognosis of RRMS in its most severe presentations. We still need to be very attentive to their complications, and better understand its applicability in order to reduce risks. Citing Bernard Shaw, "the wisdom of men is not proportional to their experience, but to their ability to gain experience." Therefore, because of this ability, this group of expertise proposed us to work in teams so that our patients could be optimally benefited.

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