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Real-life clinical practice studies in multiple sclerosis

Estudios de práctica clínica real en esclerosis múltiple

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It has been called "the disease of a thousand faces" on account of its clinical and radiological variability and the difficulties inherent in predicting its response to treatment. It is also the first non-traumatic cause of disability in young adults. Yes, we are referring to multiple sclerosis (MS), an increasingly prevalent condition that affects nearly 2.8 million patients worldwide, of whom 1 million are European[1].

It is usually diagnosed between the ages of 20 and 40, although pediatric and late-onset forms are becoming increasingly common. Nearly 85% of patients start off by experiencing flares, in what is known as the relapsing remitting form of the disease. If appropriate treatment is not provided within 15-20 years, up to 80% of these patients will face a sustained worsening of their symptoms, with a rapid progression of disability, regardless of the presence of relapses. This type of evolution is known as secondary progressive multiple sclerosis. Finally, the remaining 15% of patients experience a sustained worsening of their function from the onset of symptoms. This form of MS is known as primary progressive and is more usual during middle age[1,2].

The causes of MS remain unknown. The existing scientific evidence suggests that a series of environmental factors (vitamin D deficiency; certain types of viruses, particularly those of the herpes family; obesity during adolescence; smoking; and substantial microbiome changes) could affect a genetically predisposed immune system and cause a pathological reactivation of T lymphocytes against antigens in the central nervous system, particularly myelin antigens. Nonetheless, we know that the disease is not merely a demyelinating condition. Axonal damage, gliosis and neurodegeneration are also present from the onset of symptoms and play an important role in the physical and cognitive disability that characterizes the disease[3].

In MS patients, disability typically results in a progressive loss of autonomy, a worsening of work performance, and a deterioration of family and social relationships. It also leads to stigmatization and a significant reduction of quality of life. This is particularly significant when considering that the disease tends to present in the early stages of life, when individuals are starting to be productive and useful to society.

Although there is currently no cure for MS, few neurological conditions have experienced such a great expansion of therapeutic possibilities. Diagnostic techniques like magnetic resonance imaging (MRi), cerebrospinal fluid (CSF) flow measurements, optical coherence tomography and neurofilament light chain serum tests, for example, have greatly improved our understanding of the disease. Patients can now be treated early and in a more personalized way before an irreversible change occurs. They also enjoy a higher quality of life and can live longer without the burden of disability.

At present fifteen agents have been approved by the European Medicines Agency as MS-modifying drugs, the last three having been authorized between the end of last year and the beginning of this one. Moreover, there is a huge number of phase III clinical trials in the process of recruiting patients with the different forms of the disease, which certainly bodes for a promising immediate future for these patients.

One of these drugs is dimethyl fumarate, a drug in use in since 1994 in the context of refractory psoriasis. In Spain, it was approved in 2015 for patients with relapsing-remitting MS. It is believed that it has a dual mechanism of action, with anti-inflammatory and cytoprotective effects. Its approval was based on two phase III randomized clinical trials: DEFINE and CONFIRM[4,5], which included nearly 1,600 patients in the different treatment arms. Patients receiving dimethyl fumarate exhibited a reduction between 44 and 53% of their annualized flare rate and a decrease between 85% in the development of new T2-lesions and gadolinium-enhancing lesions. Subsequently, evaluation of the drug continued with the ENDORSE extension trial. An overall follow-up of 13 years (considering the three trials) confirms the drug's safety and efficacy[6].

The most common side effects found in these trials included gastrointestinal disturbances (45%), lymphopenia (41%), and flushing (34%). Moderate to severe prolonged lymphopenia seems to increase the risk of progressive multifocal leukoencephalopathy (LMP) in patients on dimethyl fumarate. However, LMP has also been observed in patients with mild lymphopenia. Another risk factor in patients on dimethyl fumarate, observed during the post-marketing period, is age as most cases of LMP occurred in patients > 50 years[7].

There is no doubt that clinical trials are the gold standard in terms of generation of clinical evidence about the effects of a drug in specific populations under ideal conditions. However, they are never fully representative of the general MS patient population as they do not consider factors such as extreme age, comorbidities, interactions with other drugs, etc. In this regard, post-marketing observational studies are of the essence as they allow long-term follow-up of large numbers of patients in real-life conditions: patients belonging to a wide range of age groups, with multiple conditions and receiving multiple treatments, pregnant and breastfeeding women, and situations where the drug of interest is administered in the midst of a pandemic like the one the world is experiencing right now. The results of these studies can help neurologists select the right therapies and, particularly, tailor treatment to the needs of each patient.

Nevertheless, even if observational cohort analyses are superior to prospective randomized studies in terms of the possibility to generalize their results to standard clinical practice and their longer follow-up periods, they too are subject to multiple biases. It is up to the authors of each study, and they must be particularly strict in this respect, to mitigate such risks to ensure that their results are robust and can be considered valid[8].

In this regard, the Multiple Sclerosis Data Alliance (MSDA), was created in 2019 under the auspices, among others, of the European Charcot Foundation (ECF) to bring together researchers, physicians, holders/applicants of marketing authorizations, health technology assessment organizations, MS patients/patient associations, and MS register representatives[9] with a view to:

- Raising awareness on the importance of research by providing real-life data on MS.
- Building an MS data ecosystem available to all stakeholders.
- Promoting reliable and transparent practices for using the data.
- Classifying existing and emerging MS data sources.
- Supporting local harmonization efforts and developing and promoting the adoption of a common MS-specific data model.
- Constructing a federated ecosystem to allow local access to cohorts and registers, ensuring the autonomy and rights of ownership of data sources.

Several analyses are now available, by both Spanish and foreign authors, on large cohorts of patients treated with dimethyl fumarate in standard clinical practice[10-13]. In this issue of the *Revista*, the hospital pharmacy team of Pontevedra Hospital will present one of those studies, which included 55 patients and had a median duration of treatment of 23 months in conditions of real-life clinical practice. The article found that lymphopenia was the most common adverse reaction in those patients and proposed that a decreased lymphocyte count during the first 6 months of treatment could constitute a predictive factor for the development of grade II/III lymphopenia by the end of follow-up[14]. These findings are in line with those of other studies in the literature[15].

In short, MS is an increasingly prevalent disease that is apt to cause severe impairment in young individuals, and where early treatment is of the essence to prevent progression to disability. We are fortunate to have several drugs, each with their own mechanism of action, capable of preventing such disability. Approval of those drugs by regulatory agencies is contingent on the outcomes of randomized clinical trials. However, the data provided by observational studies, conducted in the context of ordinary clinical practice, has shown itself to be increasingly useful not only because it exemplifies the effect of the drug of interest on different populations, but also because it makes it possible to follow-up criteria such as potential adverse events, tolerability, and drug-to-drug interactions in the long term.

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