Neurology Perspectives 1 (2021) 189–191

NEUROLOGY PERSPECTIVES

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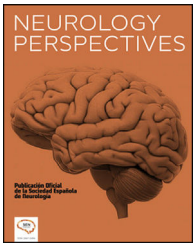

SCIENTIFIC LETTER

Benign multiple sclerosis, old age, and cognitive impairment: Is teriflunomide an appropriate treatment for this clinical triad?

Esclerosis múltiple benigna, edad avanzada y deterioro cognitivo: ¿una tríada clínica adecuada para el tratamiento con teriflunomida?

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Received 17 May 2021; accepted 19 May 2021
Available online 1 June 2021

Not all experts in multiple sclerosis (MS) acknowledge the existence of a benign progressive form of the disease.[1,2] We agree that it is difficult to classify as benign a condition that is characterised by its chronicity, a recurrent clinical course of neurological deficits, and a tendency to progress to disability with time (progression time). However, it is also true that the natural history of MS shows that some patients present an Expanded Disability Status Scale (EDSS) score ≤ 3.0 after 15–20 years of progression: these patients present no difficulty walking; therefore, we may speak about benign MS when patients do not need walking aids or wheelchairs. Today, we could consider this situation as a clinically benign condition presenting a clinically stable progressive course due to the early administration of specific disease-modifying drugs.[3]

However, the concepts "benign" (retrospective) and "clinically stable" are defined by a cut-off score on the EDSS scale, which the majority of neurologists consider to overweight motor aspects and possibly minimise cognitive symptoms. Cognitive impairment, to differing degrees of severity, may affect up to 50% of patients with MS; some even present full dementia, which interferes with their social and professional life and constitutes the main reason for unemployment in this population.[4–7]

Teriflunomide is an approved treatment for recurrent MS, considered a first-line treatment option with moderate efficacy in reducing relapses but with few adverse effects.[8,9]

In this sense, given the safety of this drug in terms of haematological alterations, it may be an ideal option when there is a need to modify injectable treatments for greater convenience in patients showing clinical and radiological stability, especially if they are older than 50 years, which is when the influence of immunosenescence should be considered.[10] Furthermore, teriflunomide has shown a significant effect in slowing brain atrophy,[11,12] and may play an essential role when considering disease-modifying treatments in clinically stable patients with long-standing MS and cognitive complaints confirmed with cognitive screening tests or more specific cognitive batteries.

We report the case of a 60-year-old woman with 28 years' history of MS with a progressive benign course (EDSS score = 2.5). The patient was receiving no disease-modifying drugs for MS and her main symptoms were cognitive complaints. Although no clinical or radiological signs had been observed for years, the patient always reported in her periodic assessments that "neurologists always tell me I am fine, that I should feel fortunate, but I feel that I am increasingly limited mentally to live a normal life." On January 2021, she took the written version of the symbol digit modalities test (SDMT), scoring 18. According to data from the NEURONORMA project, this corresponds to the percentile range from 11 to 18, after adjusting for education (primary education).[13] The SDMT is considered a useful tool for assessing MS progression; a decrease of ≥4 points is considered clinically relevant,

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https://doi.org/10.1016/j.neurop.2021.05.004
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especially in terms of employment and the ability to perform activities of daily living.[14]

A previous study of a series of patients with recurrent MS showed that SDMT scores are significantly correlated with progression time (r = −0.50, $P < .001$) and age (r = 0.58, $P < .001$).[7] Given the patient's age, she may concomitantly present MS and an early stage of a neurodegenerative disease such as Alzheimer disease; however, except for "slow thinking," the patient reported no alterations in other cognitive domains, and scored 28/30 on the Mini–Mental State Examination (2 incorrect answers in attention and calculation), and was independent for daily living. A brain MRI scan revealed no Sylvian, temporal, or hippocampal atrophy. Although no CSF determination of Alzheimer disease biomarkers was requested, we believe the reduced information processing speed was entirely due to MS, and aggravated by the long disease progression. Specific cognitive batteries (e.g., BICAMS, MACFIMS) would surely unmask other cognitive alterations typical of MS, but none was administered to our patient.

A brain MRI scan was used to determine two-dimensional measurements of brain atrophy,[7,15,16] corpus callosum index (CCI) and third ventricle width, which yielded values of 0.261 and 4.0 mm, respectively (findings suggestive of atrophy).

We also decided to study the effect of teriflunomide on the above-mentioned brain atrophy parameters in a sample of patients with MS. The sample included 46 patients (13 men and 33 women), with a median age of 50 years (range: 46–55), median progression time since diagnosis of 10 years (range: 6–22), and median duration of treatment with teriflunomide of 27 months (range: 20–45). Patients receiving this drug showed clinical stability as measured with the EDSS scale (2.43 ± 2.04 vs 2.51 ± 2.06), stable CCI values (0.341 ± 0.067 vs 0.335 ± 0.072), and a 14% increase in third ventricle width (4.07 ± 2.11 vs 4.64 ± 2.21, $P < .0001$), with a median follow-up time of 27 months (range: 12–63). Therefore, we have found teriflunomide to be effective in avoiding brain atrophy, based on CCI values, in actual clinical practice.

Considering the increasingly significant role of cognitive impairment in the selection of treatments for MS, our patient started treatment with teriflunomide, with a view to maintaining clinical stability (EDSS score) and improving her quality of life by slowing brain atrophy. Formal treatment for cognitive impairment in patients with MS would be exclusively based on cognitive rehabilitation, but we would like to suggest adopting a proactive approach, based on the above, with decreased SDMT scores considered as a marker of progression in MS. However, we are aware that the effects of treatments on brain atrophy are not the same as treating cognitive impairment, although promising evidence has recently suggested a positive effect of siponimod on cognitive impairment, as assessed with the SDMT, in patients with secondary progressive MS.[17]

Funding

This study has received no private or public funding of any kind.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2021.05.004.

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