Teriflunomide for Elderly Patients with Benign MS and Cognitive Impairment: Balancing Brain Atrophy Reduction with Safety Considerations

Priya Kumari* and Shivani Tomar

Department of Neuroscience, Meerut Institute of Medical Science, Meerut, India

*Corresponding Author**
Priya Kumari
Department of Neuroscience
Meerut Institute of Medical Science
Meerut, India
E-mail: 9105priya@gmail.com

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Abstract

Introduction

This study investigates Teriflunomide's potential to mitigate brain atrophy and its impact on cognitive function in MS patients.

Method

The study combines a case study and a cohort study. The case involves a 60-year-old woman with MS experiencing cognitive decline despite a stable EDSS score. The cohort consisted of 46 clinically stable Multiple Sclerosis (MS) patients who received teriflunomide treatment. Brain atrophy markers and cognitive function were evaluated.

Results

The case study patient showed signs of cognitive decline on the SDMT. The cohort study revealed teriflunomide treatment did not affect the corpus callosum index but resulted in a significant increase in third ventricle width, a potential indicator of brain atrophy.

Conclusion

Teriflunomide may offer benefits in mitigating brain atrophy in MS. The study proposes using declining Symbol Digit Modalities Test (SDMT) scores to proactively identify MS progression and suggests teriflunomide as a potential treatment approach. Further research is needed to confirm the link between teriflunomide and cognitive improvement.

Keywords: Benign MS • Clinically stable MS • Cognitive dysfunction in MS • Brain atrophy in MS • Progressive MS

Introduction

There exists a divergence among experts in the field of Multiple Sclerosis (MS) regarding the recognition of a benign progressive form of the disease. While some contend that labeling a condition as "benign" is challenging given its chronic nature, recurring neurological deficits, and tendency to advance towards disability over time, it's worth noting that the natural progression of MS reveals instances where patients maintain an Expanded Disability Status Scale (EDSS) score of ≤ 3.0 even after 15 years–20 years of progression [1]. These patients experience no difficulty walking, suggesting a state of benign MS where walking aids or wheelchairs are unnecessary. In contemporary discourse, we can interpret this scenario as a clinically benign condition marked by a stable progressive course, possibly attributed to the early initiation of specific disease-modifying medications [2].

Nevertheless, the terms "benign" (in a retrospective sense) and "clinically stable" are primarily delineated by a threshold score on the EDSS scale, a metric that many neurologists believe places undue emphasis on motor functions while potentially downplaying cognitive symptoms. Cognitive dysfunction, ranging in severity, can impact as many as 50% of MS patients; some individuals even experience complete dementia, significantly disrupting their social and occupational functioning and serving as a primary factor behind unemployment within this demographic [3].

Teriflunomide, an approved therapy for recurrent MS, is recognized as a first-line option with moderate effectiveness in reducing relapses and minimal adverse effects [4]. Given its favorable safety profile regarding hematological changes, it could be an optimal choice for transitioning from injectable treatments, particularly in patients demonstrating clinical and

radiological stability, particularly those aged 50 and above, when the impact of immunosenescence becomes relevant [5]. Additionally, Teriflunomide has demonstrated notable efficacy in decelerating brain atrophy, suggesting its potential importance in the consideration of disease-modifying treatments for clinically stable MS patients with long-standing disease and confirmed cognitive concerns through screening assessments or more specialized cognitive evaluations [6].

Some factors have strong evidence for involvement in MS, like long-lasting smoking, however, several other lifestyle factors, i.e. drug abuse and alcohol consumption have been associated with MS, but these associations have not been consistently confirmed [5].

Drug addiction, also known as substance abuse disorder is a chronic disorder characterized by compulsive drug use. Several drug classifications can cause addiction, such as opioids, stimulants, hallucinogens, and psychoactive drugs despite adverse consequences [6].

We present a case involving a 60-year-old woman with a 28-year history of MS, characterized by a progressively benign course (EDSS score=2.5). The patient had not been undergoing any disease-modifying treatments for MS, and her primary symptoms revolved around cognitive issues [7]. Despite the absence of clinical or radiological indicators for years, during her routine assessments, the patient consistently expressed her sentiments: "Neurologists always assure me that I am doing well and that I should feel fortunate, but I personally perceive an increasing mental limitation hindering my ability to lead a normal life." In January 2021, she underwent the written version of the Symbol Digit Modalities Test (SDMT) and scored 18. According to data derived from the NEURONORMA project, this places her within the percentile range of 11 year to 18 year, after adjusting for her educational background (primary education) [8].

The study indicated a significant correlation between SDMT scores and progression time ($r=-0.50$, $p<0.001$) as well as age ($r=0.58$, $p<0.001$). Given the patient's age, there's a possibility of concurrent MS and an early stage of neurodegenerative conditions like Alzheimer's disease. However, aside from experiencing "slow thinking," the patient reported no changes in other cognitive domains. She scored 28 out of 30 on the Mini-Mental State Examination (with 2 incorrect answers in attention and calculation) and maintained independence in daily activities. Notably, a brain MRI scan revealed no signs of atrophy in the Sylvian, temporal, or hippocampal regions [9]. Although no Cerebrospinal Fluid (CSF) analysis for Alzheimer's disease biomarkers was conducted, we attribute the reduced processing speed solely to MS, potentially exacerbated by the prolonged disease course. While more comprehensive cognitive assessments (such as BICAMS or MACFIMS) would likely reveal additional cognitive impairments common in MS, none were administered to our patient.

A brain MRI scan was utilized to obtain two-dimensional measurements of brain atrophy, specifically the Corpus Callosum Index (CCI) and third ventricle width, resulting in values of 0.261 mm and 4.0 mm, respectively, indicative of atrophy. Additionally, we opted to investigate the impact of teriflunomide on these brain atrophy parameters within a cohort of MS patients. This sample comprised 46 individuals (13 males and 33 females), with a median age of 50 years (range: 46 months–55 months), a median progression time since diagnosis of 10 years (range: 6 months –22 months), and a median duration of teriflunomide treatment of 27 months (range: 20 months–45 months). Patients prescribed teriflunomide exhibited clinical stability, as evidenced by similar EDSS scale scores (2.43 ± 2.04 *vs* 2.51 ± 2.06), stable CCI values (0.341 ± 0.067 *vs* 0.335 ± 0.072), and a noteworthy 14% increase in third ventricle width (4.07 ± 2.11 *vs* 4.64 ± 2.21, $P<0.0001$), over a median follow-up period of 27 months (range: 12 months–63 months). Thus, our observations indicate teriflunomide's efficacy in mitigating brain atrophy, as evidenced by CCI values, in real-world clinical settings.

Given the growing importance of cognitive dysfunction in guiding MS treatment decisions, our patient initiated Teriflunomide therapy with the aim of maintaining clinical stability (as measured by the EDSS score) and potentially enhancing her quality of life through the attenuation of brain atrophy. While formal treatment for cognitive impairment in MS typically revolves around cognitive rehabilitation, we propose a proactive approach grounded in the identification of declining SDMT scores as indicative of MS progression. It's worth noting that the effects of treatments on brain atrophy may not directly address cognitive impairment, although emerging evidence suggests a potential benefit of siponimod in ameliorating cognitive deficits, as assessed by the SDMT, in individuals with secondary progressive MS.

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