Ups and Downs in MS Therapeutics

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Abstract

Over the past three decades, there has been a remarkable surge in the approval of drugs for treating Multiple Sclerosis (MS), with the number now exceeding 15 options, including various dosages and generics. However, while these treatments have primarily targeted the inflammatory activity underlying relapses, the progressive aspects of MS, characterized by a gradual worsening of disability without relapses, remain inadequately addressed. Siponimod and Ocrelizumab have emerged as crucial drugs approved for treating progressive forms of MS, particularly primary progressive and secondary progressive MS. Despite their benefits for patients experiencing clinical relapses or displaying disease activity in MRI scans, their use is limited to those with active disease as per regulators in the US and Europe. This leaves a significant treatment gap for patients with progressive MS lacking active disease. Addressing this gap, Jeremy Chataway and colleagues conducted a multi-arm phase 2b trial named the Multiple Sclerosis Secondary Progressive Multi-Arm Randomization Trial (MS-SMART), as reported in The Lancet Neurology. The trial selected three experimental drugs—amiloride, fluoxetine, and riluzole—based on an extensive systematic review of 532 potential treatment options. These drugs target axonal pathology and neuroprotection and boast a robust safety profile in humans, rendering them suitable candidates for testing in progressive MS. This study underscores the urgent need for more effective treatments to fill the existing gap in care for patients with progressive MS, particularly those without active disease.

Keywords: Drug abuse • Alcohol • Multiple Sclerosis

Introduction

Over the span of the past 30 years, there has been a remarkable increase in the number of drugs approved for treating multiple sclerosis. Initially, there were none, but now there are more than 15 options available, including various dosages and generic versions. Despite this significant progress, the current treatments for multiple sclerosis mainly target the inflammatory activity responsible for relapses, while the progressive aspects, characterized by a gradual worsening of disability without relapses, are not adequately addressed. Siponimod and Ocrelizumab are two drugs approved for treating progressive forms of multiple sclerosis, such as primary progressive and secondary progressive. They are particularly beneficial for patients experiencing clinical relapses or showing disease activity in MRI scans. When regulators in the US and Europe approved Siponimod for secondary progressive multiple sclerosis, they limited its use to patients with active disease. However, treatment options are scarce for patients with progressive multiple sclerosis who do not have active disease. Therefore, there is a need for more effective treatments to address this gap in care.

In an article published in The Lancet Neurology, Jeremy Chataway and colleagues address the challenge of treating secondary progressive multiple sclerosis with a multiarm phase 2b trial called the Multiple Sclerosis Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART). They selected three experimental drugs-amiloride, fluoxetine, and riluzole-based on an extensive systematic review of 532 potential treatment options. These drugs focus on axonal pathology and neuroprotection and have a strong track record of safety in humans, making them suitable for testing in progressive multiple sclerosis [1-6].

The primary outcome of the trial was to measure whole-brain atrophy, a commonly used endpoint in phase 2 trials for progressive multiple sclerosis. Despite meeting their target enrollment and achieving an excellent retention rate of 88% over 96 weeks, MS-SMART did not succeed in its primary objective. None of the three drugs tested showed a significant slowing of whole-brain atrophy compared to the placebo. Despite the trial's robust theoretical basis, well-designed experiments, and commendable execution, the desired outcome was not achieved.

These disappointing findings prompt a critical question: why wasn't a promising treatment identified to advance into phase 3 trials? The answer to this question remains unclear, but several possibilities warrant consideration. One potential factor is the inadequacy of the systematic review process for evaluating potential treatments. Another challenge lies in the incomplete understanding of the true pathophysiology of progressive multiple sclerosis. This lack of understanding compromises the accurate selection of drugs for testing.

In progressive multiple sclerosis, the involvement of white blood cells in the Central Nervous System (CNS) is less pronounced compared to relapsing multiple sclerosis. Instead, there is a shift towards innate immune mechanisms, which are isolated behind the blood-brain barrier. Additionally, factors such as mitochondrial dysfunction, metabolic dysregulation due to chronic demyelination, and possibly an exacerbated impact of normal aging and concurrent health conditions contribute to disease progression.

To address this gap in knowledge, researchers must intensify their efforts to uncover the genuine mechanisms driving multiple sclerosis progression. This understanding will facilitate the selection of more effective drugs. Importantly, this lesson likely extends to other neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease, highlighting the need for a deeper understanding of disease mechanisms to inform drug development efforts.

A deeper understanding of the mechanisms underlying neurodegenerative disorders will facilitate the validation of biological target engagement during clinical trials. Confirming that an investigative drug effectively interacts with its molecular or cellular target is crucial for determining the optimal dosage. In the context of relapsing multiple sclerosis, the necessity for biological target engagement has been less pressing because the presence of new lesions on MRI serves as a sensitive biomarker for treatment response, regardless of the intended biological target.

Biomarkers play various roles in clinical medicine, including assessing pharmacological responses to therapeutic interventions.

However, in progressive multiple sclerosis, the lack of validated biomarker outcomes in phase 3 trials underscores the heightened importance of target engagement. While whole-brain atrophy is commonly used as an endpoint, it has inherent limitations such as day-to-day biological variability, slow dynamic changes over time, limited granularity as a metric for full-brain assessment, and technical challenges associated with MRI acquisition and equipment variations during trials. Enhanced metrics from phase 2 trials can enhance trial efficiency by requiring fewer participants and shortening trial duration. Metrics like magnetization transfer imaging, cortical atrophy, and slowly expanding lesions show promise as more sensitive alternatives to whole-brain atrophy, although further validation studies are necessary. Additionally, efforts are underway to identify fluid-based treatment response biomarkers, with neuro-filament-light emerging as a leading candidate.

The MS-SMART trial sets a model for efficient trial design by comparing three active treatment arms with a placebo. Encouraging industry to adopt similar multi-arm designs could be beneficial, and collaboration between companies could be facilitated, potentially leveraging independent trial networks like NeuroNEXT or the Expert Consortium for Progression in Multiple Sclerosis Clinical Trials.

The negative outcome of MS-SMART, along with similar trials in neurodegenerative diseases, highlights the urgent need to reassess how we select and test experimental treatments for these conditions. Making informed choices about drugs requires a better understanding of disease pathology, accurate measurement of target engagement, and reliable treatment-response biomarkers. Global collaborative efforts, such as those led by the Progressive Multiple Sclerosis Alliance, will help coordinate and align individual scientific endeavors. These critical steps will enhance the identification of useful treatments more effectively and efficiently, reducing frustrating delays and disappointing dead ends for patients.

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