Fluctuations in Multiple Sclerosis Therapeutics: Abundance or Scarcity

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Introduction

In the last three decades, the number of approved drugs for multiple sclerosis has increased significantly, from none to over 15, including various dosing options and generic versions. Despite this significant advancement, current treatments for multiple sclerosis tend to primarily target the inflammatory lesion activity associated with relapsing multiple sclerosis. As a result, the progressive aspects of the disease, characterized by gradual disability worsening without clinical relapses, remain largely unaffected.

Siponimod and Ocrelizumab are two agents that have received regulatory approval for progressive forms of multiple sclerosis (primary progressive and secondary progressive). These drugs offer the most benefits to patients experiencing clinical relapses or disease activity visible on MRI scans. Consequently, when regulators in the US and Europe approved siponimod for secondary progressive multiple sclerosis, they limited its use to patients with active disease. Patients with progressive multiple sclerosis who do not have active disease have limited treatment options available to them [1,2].

In The Lancet Neurology, a group of researchers led by Jeremy Chataway conducted an ambitious multiarm phase 2b trial with the aim of addressing the limited treatment options available for patients diagnosed with secondary progressive multiple sclerosis [3]. This groundbreaking study, known as the Multiple Sclerosis Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART), was meticulously designed and implemented to tackle the challenging aspects of the disease.

With great care, the team meticulously handpicked three promising experimental drugs (amiloride, fluoxetine, and riluzole) based on an extensive and systematic review of an astonishing 532 potential treatment candidates. These chosen drugs were specifically focused on targeting the intricate axonal pathobiology and providing neuroprotection to the affected individuals. Moreover, the selected drugs came with extensive evidence of prior use in human patients, boasting well-established safety profiles, which made them ideally suited for rigorous trial testing in the context of progressive multiple sclerosis [4].

To gauge the efficacy of the treatment approaches, the primary outcome measure meticulously selected by the researchers was the assessment of whole-brain atrophy, a crucial endpoint that has been widely adopted in phase 2 trials involving progressive multiple sclerosis. The trial saw remarkable success in achieving the targeted participant enrollment, and the retention rate over the astonishingly long 96-week duration was an impressive 88%.

Despite the exceptional theoretical underpinning, a rigorously designed experimental framework, and commendable efforts in execution, it is unfortunate to note that the MS-SMART trial did not achieve its primary objective. Somewhat disheartenigly, none of the three meticulously tested drugs demonstrated the desired ability to effectively slow down the progression of whole-brain atrophy when compared against the control placebo group.

The results of the MS-SMART trial, though disappointing, prompt a pertinent question: why was a promising treatment not identified to advance into phase 3 trials? The answer to this query remains elusive, but there are several potential explanations that warrant careful consideration [5].

One possible reason is that the systematic review process employed to evaluate potential treatments might have been insufficient. Given the enigmatic nature of the true pathophysiology of progressive multiple sclerosis, accurately selecting appropriate drugs for testing becomes challenging. Unlike relapsing multiple sclerosis, where leucocyte infiltration into the Central Nervous System (CNS) is prominent, progressive multiple sclerosis involves a shift towards innate immune mechanisms behind the protective blood-brain barrier [6,7]. Additionally, it is characterized by mitochondrial dysfunction, metabolic dysregulation due to chronic demyelination, and perhaps an amplified effect of normal aging and concurrent comorbidities. With limited understanding of these complex processes, the selection of effective drugs becomes hindered.

In light of these challenges, researchers must intensify their efforts to uncover the genuine mechanisms driving the progression of multiple sclerosis. By gaining deeper insights into these underlying processes, they can enhance the process of selecting drugs that have the potential to be effective. This lesson likely holds true for various neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease, underscoring the importance of advancing our understanding of these conditions to enable better drug selection and treatment strategies.

A more profound comprehension of the mechanisms underlying neurodegenerative disorders will facilitate the validation of biological target engagement during clinical trials. Verifying that the investigational drug effectively interacts with its specific molecular or cellular target is crucial for determining the optimal drug dosage. In the context of relapsing multiple sclerosis, validating biological target engagement has been less critical due to the presence of new lesions visible on MRI, which serves as a sensitive biomarker of treatment response, irrespective of the intended biological target. Biomarkers, in general, play diverse roles in clinical medicine, including assessing pharmacological responses to therapeutic interventions [8].

However, in progressive multiple sclerosis, the absence of biomarker outcomes with phase 3 trial validation elevates the importance of target engagement assessment. Whole-brain atrophy, the primary outcome measure used in the MS-SMART trial, has certain limitations, such as day-to-day biological variability, gradual changes over time, limited sensitivity as a full-brain metric, and technical challenges related to MRI acquisition and equipment variations over the trial duration. To improve trial efficiency, researchers aim to identify more robust phase 2 trial metrics that would require enrolling fewer patients and reduce the trial duration. Potential alternative metrics include magnetisation transfer imaging, cortical atrophy, and slowly expanding lesions, which exhibit promising sensitivity compared to whole-brain atrophy, though further validation studies are still necessary [9].

Moreover, researchers are exploring fluid-based treatment response biomarkers, with neurofilament-light emerging as a leading candidate. These biomarkers could provide valuable insights into the drug's impact on disease progression and treatment efficacy. Emphasizing the importance of target engagement validation and the pursuit of more sensitive and reliable

biomarkers, these advancements would greatly benefit not only multiple sclerosis research but also the broader understanding and treatment of neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease.

The MS-SMART trial sets a remarkable example of efficient trial design by comparing three active treatment arms against a placebo. Encouragingly, this model could be of great benefit to the industry, urging them to adopt similar multiarm designs. Such adoption could be facilitated through collaborations between companies and the utilization of independent trial networks, such as NeuroNEXT or the Expert Consortium for Progression in Multiple Sclerosis Clinical Trials. Embracing these innovative trial designs can enhance the effectiveness and speed of drug development, ultimately benefiting patients and advancing the field of neurodegenerative disease research [1-3].

The disappointing outcome of MS-SMART and several other trials in the domain of neurodegenerative diseases underscores the urgent necessity to reevaluate how we select and test experimental treatments for such conditions. Achieving informed drug selection requires an enhanced understanding of the underlying pathobiology of these diseases, as well as the development of effective methods for measuring target engagement and valid treatment-response biomarkers. Collaborative efforts on a global scale, as exemplified by the Progressive Multiple Sclerosis Alliance, play a crucial role in galvanizing and aligning individual scientific endeavors toward common goals [9].

By taking these essential steps, we can more effectively and efficiently identify promising treatments, sparing patients from enduring further frustrating delays and disappointing setbacks. The collective efforts of the scientific community, working collaboratively and driven by shared objectives, hold the key to unlocking new and useful treatments for neurodegenerative conditions. This collective effort will empower us to break through barriers and pave the way for hope and progress in the realm of neurodegenerative disease research and treatment.

References

1. Kappos, L., et al. "Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study." *Lancet* 391.10127 (2018): 1263-1273.
2. Montalban, X., et al. "Ocrelizumab versus placebo in primary progressive multiple sclerosis." *N. Engl. J. Med.* 376.3 (2017): 209-220.
3. Chataway, J., et al. "Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised placebo-controlled trial." *Lancet Neurol.* 19.3 (2020): 214-225.
4. Vesterinen, H.M., et al. "Drug repurposing: a systematic approach to evaluate candidate oral neuroprotective interventions for secondary progressive multiple sclerosis." *PloS one* 10.4 (2015): e0117705.
5. Salvetti, M., et al. "Progressive MS: from pathophysiology to drug discovery." *Mult. Scler. J.* 21.11 (2015): 1376-1384.
6. Biomarkers Definitions Working Group, et al. "Biomarkers and surrogate endpoints: preferred definitions and conceptual framework." *Clin. pharmacol. ther.* 69.3 (2001): 89-95.
7. Fox, Robert J., et al. "Phase 2 trial of ibudilast in progressive multiple sclerosis." *N. Engl. J. Med.* 379.9 (2018): 846-855.
8. Elliott, C., et al. "Chronic white matter lesion activity predicts clinical progression in primary progressive multiple sclerosis." *Brain* 142.9 (2019): 2787-2799.
9. Khalil, M., et al. "Neurofilaments as biomarkers in neurological disorders." *Nat. Rev. Neurol.* 14.10 (2018): 577-589.

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