Symptomatic vs. Disease-modifying treatments in neurological diseases: Where next?

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An optimal drug for chronic neurological disease would slow down disease progression in the long term, with short-term symptomatic benefits. This would shorten clinical development timelines and reduce the cost and risk level for drug developers. Henri Huttunen Chief Scientific Officer (CSO) at Herantis Pharma Plc explains

In Parkinson's disease (PD), the development of motor symptoms is associated with the degeneration of dopamine-producing nerve cells in the midbrain. For decades, motor symptoms of PD have been treated with levodopa, a precursor of dopamine, which helps to replenish dopamine levels in brain areas coordinating movement. Levodopa is an example of a symptomatic treatment as it improves symptoms but does not interfere with the underlying causes or progression of the disease.

As scientists and clinicians have gained more insight into the causes and mechanisms of central nervous system (CNS) diseases, the next goal has been to develop disease-modifying treatments, which would help to slow down or even stop the progression of the disease. In multiple sclerosis (MS), a disorder characterized by inflammation, demyelination, and degeneration of the CNS, there are now more than a dozen disease-modifying treatments available on the market, most based on interfering with the inflammatory processes that lie at the core of this disease. Recently, two amyloid immunotherapies, also potential disease-modifying treatments, have been approved for the treatment of Alzheimer's disease (AD).

While there has clearly been some progress, demonstrating a disease-modifying effect in a clinical trial with patients suffering from a neurodegenerative disease remains a massive challenge. A typical phase three clinical trial may require a thousand patients and one to two years of dosing and follow-up, costing tens of millions of euros per trial. Biomarkers linked to long-term outcomes could help to get early efficacy signals and derisk a drug development program, but often, this type of data or biomarkers is lacking.

From the regulatory and end-user (prescriber and patient) perspective, the product label of a drug contains the key information to guide the safe and effective use of a drug. Typically, the indication section of the product label should clearly state the treatment concept, i.e., distinguish between symptomatic, preventive, and curative treatments. However, a review of product labels of MS drugs approved in the US (Food and Drug

Administration, FDA) and EU (European Medicines Agency, EMA) has shown that the label information is not always aligned with regulatory guidance on labeling (Morant et al. Front. Med. 2019).

Why is this relevant? Practically, the data generated in clinical trials will dictate what can be claimed in the treatment concept section of the product label. The PD drug market, for example, is saturated with symptomatic drugs, but there is an unmet need for disease-modifying treatments. Thus, while most drug developers would aim for a disease-modifying product label, they struggle with the complexity, risks, and cost of clinical trials that could earn them that label.

But is it really so black and white?

The binary view of symptomatic vs. disease-modifying may be slowly changing among CNS drug developers. An increasing number of companies are developing treatments that target the underlying pathophysiology of the disease. These treatments are considered to be disease-modifying but could also have symptomatic effects.

Everything starts with the mechanism of action of the drug. A treatment may achieve a disease-modifying outcome by either inhibiting primary neurodegenerative events (neuroprotective) or boosting compensatory and/or regenerative mechanisms in the brain (neuro-restoration). While the ultimate goal of neuroprotective and neurorestorative treatments would be to slow down disease progression, in the short term, improved neuronal function could translate into symptom-alleviating effects. In PD, for example, a neuroprotective treatment that increases the number and functionality of dopamine neuron terminals in the midbrain would be expected to gradually start bolstering endogenous dopamine production, which would eventually reduce motor symptoms and the need for levodopa. In general, drugs improving neuronal health, enhancing synaptic function, and alleviating neuroinflammation could slow down disease progression but also provide early symptomatic effects.

As clinical trial designs aimed at demonstrating a disease-modifying effect are typically long and expensive, early symptomatic effects would be a particularly welcome feature for small biotechs and investors. How quickly these ‘early’ effects would become detectable in patients in a clinical trial likely depends on multiple factors, such as the mode of action of the treatment, disease stage, and efficacy of the treatment.

Another important aspect is the patient perspective. As a patient, how long would you remain on a medication that does not seem to affect the symptoms in the short term but may slow down the progression of the disease in the long term? For older patients suffering from a progressive CNS disorder, a key priority is the quality of life for the remaining years of life; they do not have the luxury of time to wait for the long-term benefits to slowly appear.

The long and winding road to registration

Neurological conditions are the leading cause of illness and disability worldwide (GBD 2021 consortium. Lancet Neurol, 2024). Aging-related chronic degenerative CNS diseases produce a significant burden to the public healthcare systems. Although we are finally entering the era of disease-modifying therapies with MS and AD leading the way, this is just the beginning. New innovative drug targets and treatment concepts need to be supported by improved clinical trial designs and regulatory paths that support success.

For a drug developer, the label of the drug can be a matter of life and death, particularly in the highly saturated market of symptomatic PD drugs. Eventually, the available clinical evidence will dictate what kind of treatment concept can be articulated on the label in a marketing authorization application of a new drug. In this regard, regulatory authorities should consider activities that are aimed at improving the consistency in product information terminology and description of treatment concepts, as well as increasing transparency on how indication wordings are assessed in the context of marketing authorization applications for new drugs.

In summary, the emerging paradigm shift in the classification of treatments for degenerative CNS disorders into either disease-modifying or symptomatic could facilitate triaging which drug candidates to take forward in early clinical development and designing phase two and three clinical trials with earlier readouts. As the field moves forward, we need to make sure that all stakeholders are aligned to remove unnecessary roadblocks on the way to new drug registration.

References

1. GBD 2021 Nervous System Disorders Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurol. 23(4): 344-381, 2024. https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(24)00038-3/fulltext
2. Morant AV, Jagalski V, Vestergaard HT. Labeling of Disease-Modifying Therapies for Neurodegenerative Disorders. Front. Med. 6: 223, 2019. https://www.frontiersin.org/articles/10.3389/fmed.2019.00223/full

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