

## BIOMARKERS AS A USEFUL TOOL IN MS RESEARCH: WHICH WAY TO GO?

D. Leppert

Department of Neurology, University Hospital Basel, Basel, Switzerland

Multiple sclerosis (MS) is a complex disease where several pathogenetic mechanisms of inflammation and neurodegeneration superimpose. The inflammatory processes are heterogeneous across individual patients with relapsing-remitting MS, but their initial clinical presentation does not allow concluding on the predominating molecular mechanism of disease. While the refinement of diagnostic criteria in recent years led to more reliable diagnosis of MS, and at earlier stages, they do not allow predicting the natural course of disease, nor the response to a specific therapy on individual grounds. The consequences of this are twofold:

a) For an individual patient, the standard diagnostic workup may not allow to indicate whether they should commence therapy. Moreover, in an era where a multitude of drugs with distinct modes of action is either registered or in late stage development, there are no established biomolecular criteria to choose the optimal therapy.

b) Given the pathogenetic heterogeneity of MS in trial cohorts, and hence the likely variability of treatment response to a specific mode of action, it is difficult to determine the therapeutic value of candidate drugs solely on clinical and MRI endpoints. With the approval of several new disease-modifying therapies this dilemma becomes more pronounced, as placebo-controlled trials will not be feasible any more. Novel compounds now need to be tested against an active comparator in phase III with inherently a smaller differentiating margin of treatment effect. In consequence, cohort sizes need to be larger and study duration will be longer to demonstrate improved efficacy of a candidate drug.

Biomarkers for drug efficacy are therefore an urgent development need in the field of multiple sclerosis, both to implement the requirement of individualized medicine, and to contrive novel, more effective therapies.

MRI has become in the last two decades the prominent biomarker to monitor disease course and drug response with regard to inflammatory aspects of MS; measures of lesion development and lesion load are now standard read-outs in MS trials. In contrast, MRI is less well established to capture features of neurodegeneration. The latter, however, is recognized more and more as the prevailing determinant for the long-term outcome of MS. Therefore the focus in biomarker development should be on measures that reflect neurodegenerative processes earlier, and hence are more sensitive than clinical readouts of disability, or brain volumetric measures in MRI. Moreover, to quantitate drug response these markers need to have a *sufficient dynamic measuring range*. This implies that biomarkers need to be validated by *correlation with clinical gold standards* of disability, and the establishment of *longitudinal* reference values is prerequisite for their use as surrogate markers. By nature, markers of *functional* character (e.g. NAA in MRI) are more likely to suffice these requirements than static (e.g. oligoclonal bands in CSF) or morphometric (e.g. brain volume) parameters.

The most promising fields of research to produce clinically applicable biomarkers that meet this profile are neurophysiology and transcriptomics. The combination of motor, sensory and visual evoked potential measures bears the potential to predict the course of neurodegeneration and prognosis of disease via non-invasive, standardized and relatively inexpensive methods, yielding numerical (mono-dimensional) primary read-outs.

Transcriptional measurement of gene expression has now been shown to address prominent clinical questions around interferon-beta therapy such as prediction of drug response and detection of neutralizing antibodies activity. These concepts undergo currently large-scale clinical validation.

The advent of more effective MS therapies coincides with an increased safety risk profile due to potentially lethal infectious diseases, and severe, drug-specific side effects. Although such adverse events may be rare, they may prevent the registration or the first-line use of these drugs. The development of biomarkers that identify patients at risk, based on pharmacogenetic (to prevent exposure) or pharmacogenomic (to monitor therapy) approaches is the most prominent biomarker need in the current therapy landscape. Such biomarkers may allow patients to keep having access to high efficacy drugs while containing the risk of severe adverse events.