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Controversies in Multiple Sclerosis

Advanced MRI measures like DTI or fMRI should be outcome measures in future clinical trials – Commentary

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A number of paraclinical outcome measures have been used in multiple sclerosis (MS) clinical studies in addition to clinical endpoints to monitor disease progression and treatment efficacy. In this context, magnetic resonance imaging (MRI)-based measures are of paramount relevance due to their sensitivity in detecting and quantifying the focal and diffuse pathology occurring in MS.[1] Indeed, MRI measures of white matter lesional activity (i.e. new/enlarging T2 lesions or Gd-enhancing T1 lesions) and those of brain atrophy (i.e. percentage of brain volume change) have shown to be valid surrogate endpoints for clinical outcomes and have been accepted as endpoints in the most recent pharmacologic clinical trials.[2]

In addition to these MRI measures, newer and more tissue-specific MRI measures able to assess the microscopic tissue damage (e.g. magnetization transfer imaging (MTI), diffusion tensor imaging (DTI)) and the functional cortical reorganization (i.e. functional magnetic resonance imaging (fMRI)) occurring in the brain of MS patients have been proposed. In these controversies in MS, Kapoor advocates that these advanced MRI metrics should be outcome measures in future clinical trials, while Matthews counters that, at present, they have limited practical utility and are far from being 'clinical trial ready'.

As correctly indicated by Kapoor, while we have efficient MRI biomarkers able to surrogate MS relapse and the related inflammation (i.e. active lesions), the situation looks much more confused when the aim becomes the assessment of disease progression and the related neurodegeneration. In this context, we agree that measurement of brain atrophy is not and cannot be the solution, as this represents a sort of global measure of various mechanisms of tissue injury that is influenced by a complex interplay across multiple cellular compartments. Biomarkers that are specific for tissue injury and repair are therefore necessary to provide more pathologically specific endpoints. The main question is: can MRI provide these biomarkers in the near future?

There is no doubt that most of the advanced MRI methods, including DTI and fMRI, are powerful research tools that have shed a new light into MS and its pathogenetic mechanisms (i.e. altered brain connectivity and changes in functional reorganization). We may also agree, as stressed by Kapoor, that these MRI techniques are likely to provide the most practical approach for developing biomarkers for drug pipelines in the intermediate future. However, despite their extensive application in research settings, their value for the assessment of treatment effects in the clinical trials has yet to be achieved. This is clearly stated by both Kapoor and Matthews, but the latter makes a strong case on the need of 'biomarker conservatism' in clinical trials[3] that, in our opinion, cannot be underestimated. In general, to be used in clinical trials a given biomarker should be sensitive to treatment-related changes, specific to disease features, reproducible across different centres and users and clinically meaningful. We are afraid that this cannot be established, at present, for most of the advanced MRI measures in the MS scenario. In these circumstances, the risk is to use these measures improperly and thus jeopardize their correct implementation in the future.

Indeed, only scattered data are reported on the use of MTI, DTI, fMRI and even magnetic resonance (MR) spectroscopy in multicentre settings. In rare occasions, these measures were used as exploratory endpoints in ancillary, smaller studies of much larger clinical trials.[3–5] Some effort has been spent to set up and standardize the acquisition of these sequences in a multicentre setting.[6–9] In addition, advanced MRI techniques have also been explored as outcome measures in small, single-centre clinical trials of pharmacological and non-pharmacological treatments. Improved white matter microstructural integrity,

assessed by DTI, was demonstrated after upper limb motor rehabilitation[10] and training with a balance board system.[11] Similarly, a few single-centre studies have explored the potential of fMRI measures (i.e. assessing the role of neuroplasticity and functional recovery in limiting the clinical consequences of tissue damage) to monitor pharmacological and motor and cognitive rehabilitative treatments in MS.[12–14]

We can conclude that, while there is scientific evidence that advanced MRI techniques still keep the promise of providing practical and pathologically specific measures, it is not yet time to use them as main endpoints of large, multicentre clinical trials. They should be used, however, as exploratory endpoints, particularly when the clinical trial aims at exploring drug potentials for neuroprotection and tissue repair. Indeed, the use of DTI and fMRI in this setting should be strongly promoted, as this represents the only way to provide new and definite evidence on whether these measures can be 'clinical trial ready' in the intermediate future.

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