Advanced MRI measures like DTI or fMRI should be outcome measures in future clinical trials: YES

Journal:	*Multiple Sclerosis Journal*
Manuscript ID	Draft
Manuscript Type:	Controversies in MS
Date Submitted by the Author:	n/a
Complete List of Authors:	Kapoor, Raj; Institute of Neurology, Neuroinflammation
Keywords:	
Abstract:	

Advanced MRI measures like DTI or fMRI should be outcome measures in future clinical trials: YES

Raj Kapoor

Queen Square MS Centre

National Hospital for Neurology and Neurosurgery

Queen Square

London WC1N 3BG, UK

r.kapoor@nhs.net

Neuroprotection and repair are two of the biggest unmet therapeutic needs in people with progressive MS. Despite recent positive trials of ocrelizumab and saponimod, the process of drug discovery for these needs remains painfully slow and difficult. This contrasts with the situation in relapsing MS, where there is an efficient pathway for discovering drugs to prevent relapse: the effects of candidate drugs on what has emerged as the dominant underlying pathology (inflammation) can be assessed with an MRI biomarker (lesion activity), which also correlates with meaningful clinical outcome (relapse)[1].

The situation is more complicated in progressive MS, because there are numerous mechanisms which contribute to neurodegeneration[2], and meaningful disability outcomes are still under discussion[3]. Increasingly sophisticated computational and phenotypic screens are likely to generate drug candidates acting on some of these mechanisms, including compartmentalized and innate immunity, energy failure, ionic imbalances and aspects of glial biology[2]. Comparison with relapsing MS suggests that drug development would be accelerated with rational pipelines that include biomarkers which are selected to measure the effects of drugs on specific injury and repair mechanisms.

For now, neurodegeneration is generally assessed using MRI techniques to measure atrophy, which integrates the end-stage consequences of diverse injury mechanisms. However, atrophy is affected by tissue hydration and by a complex interplay between volumes in multiple cellular compartments, limiting its sensitivity and responsiveness, as well as the interpretation of volume changes shortly after treatment is started. Furthermore, neural injury is likely to continue long after its cause is inhibited, leading to a therapeutic lag which could delay any response of atrophy to treatment by several years[4]. It remains to be seen whether these issues also place limits on more refined techniques for tissue microstructure and cellular integrity such as magnetization transfer ratio (MTR) and optical coherence tomography (OCT), which are outcomes in repair and progression trials reporting in the intermediate future. However, even with further technical refinements, measurements of tissue structure alone may not be sufficiently specific to enable shorter and smaller proof of concept trials in progressive disease.

Tissue fluid biomarkers for injury mechanisms offer greater pathological specificity, and include nitric oxide metabolites, chemokines associated with intrathecal B lymphocyte activity, and neurofilaments released by damaged axons. However, validation of these biomarkers has proved difficult, and they usually need to be measured in the spinal fluid.

Positron emission tomography (PET) offers highly sensitive and specific information about tissue cellularity and metabolism. PET radioligands are available for dissecting tissue metabolism, for myelin and neurons[5], and for activated microglia[6]. Despite its attractions for dissecting mechanisms in early stage proof of concept studies, however, wider implementation of PET as an outcome in clinical trials, especially multicentre studies, is likely to be limited by its expense and restricted availability, and by associated practical difficulties for establishing the validity of its outcomes.

OCT techniques are advancing rapidly, and in addition to providing sensitive measurements of neuronal and axonal compartments, they have the potential to study aspects of retinal metabolism. Despite correlations with CNS outcomes, however, acceptance of OCT outcomes may be limited by the ongoing debate about the extent to which results in the visual system can be related to processes in the wider CNS.

These limitations suggest that MRI techniques are likely to provide the most practical approach for developing biomarkers for drug pipelines in the intermediate future. The main attraction of MRI remains its ability to resolve structure, and MTR and diffusion based methods including tractography take this further than conventional imaging. However, advanced techniques show promise for differentiating disease mechanisms. Diffusion basis spectrum imaging[7] has the potential to resolve myelin, axons and inflammation; high field MRI can detect sub-surface abnormalities potentially driven by meningeal pathology[8]; and techniques which examine metabolic events in the injury pathway include sodium imaging[9], cerebral perfusion, and N-acetylaspartate as a mitochondrial signal. Functional MRI sits alongside these techniques because it offers the possibility of determining whether cerebral networks which are disordered by pathology can be renormalized by therapies which have restorative or repair potential[10]. Such functional changes would complement improvements in other outcomes for testing repair strategies.

Apart from being available widely, MRI also has the advantage of versatility: multiple structural, functional and metabolic measurements can be made in single subjects. Experience in other conditions including Alzheimer's disease suggests that multimodal imaging may provide a more robust biomarker with which to measure disease activity, and combined imaging of the spinal cord in MS using conventional and more advanced MRI techniques appears to support this view[11].

For all of these techniques, validation against disability outcomes and responsiveness to therapy need much further study. Longitudinal natural history studies are helpful, but validation is likely to be achieved more efficiently if selected measures are included as outcomes in placebo and treated groups in future clinical trials. Given restricted resources and a limited appetite for risk, should preference be given to developing techniques based on MRI over others? The distinction may ultimately be unhelpful: rather than choosing between MRI and PET, for example, it may be more relevant to evaluate the potential of specific techniques to measure the effects of treatments based on their ability to address a given mechanism of action, irrespective of modality.

In conclusion, this brief overview presents a case for developing rational pipelines for drug discovery to meet major unmet needs in progressive MS by validating a number of advanced biomarkers which show promise for quantifying specific cellular and pathological aspects of neurodegeneration and repair. It seems unlikely that any single modality will be sufficient to assess all of the mechanisms which underlie these processes, but MRI-based techniques are likely to predominate simply because the versatility and availability of MRI compared with other modalities makes it easier to implement.

Conflicts: no relevant conflicts

References

1. Sormani MP and Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomized trials. *Lancet Neurol* 2013; 12:669-676.

2. Salvetti M, Landesman D, Schwarz-Lam P, et al. Progressive MS: from pathophysiology to drug discovery. *Mult Scler* 2015; 21: 1376-1384.

3. Hulst HE, Thompson AJ and Geurts JJG. The measure tells the tale: clinical outcome measures in multiple sclerosis. *Mult Scler* 2017; 23: 626-627.

4. Giovannoni G, Cutter G, Sormani MP, et al. Is multiple sclerosis a length-dependent central axonopathy? The case for therapeutic lag and the asynchronous progressive MS hypotheses. *Mult Scler Relat Disord* 2017; 12: 70-8.

5. Freeman L, Garcia-Lorenzo D, Bottin L, et al. The neuronal component of gray matter damage in multiple sclerosis: a [^{11}C]flumazenil positron emission tomography study. *Ann Neurol* 2015; 78: 554-567.

6. Politis M, Giannetti P, Su P, et al. Increased PK11195 PET binding in the cortex of patients with MS correlates with disability. *Neurology* 2012; 79: 523-530.

7. Wang Y, Sun P, Wang Q, et al. Differentiation and quantification of inflammation, demyelination and axon injury or loss in multiple sclerosis. *Brain* 2015; 138: 1223-1238.

8. Mainero C, Louapre C, Govindarajan ST, et al. A gradient of cortical pathology in multiple sclerosis by *in vivo* quantitative 7T imaging. *Brain* 2015; 138: 932-945.

9. Petracca M, Vancea RO, Fleyscher L, et al. Brain intra- and extracellular sodium concentration in multiple sclerosis: a 7T MRI study. *Brain* 2016; 139: 795-806.

10. Tomassini V, Matthews PM, Thompson AJ, et al. Neuroplasticity and functional recovery in multiple sclerosis. *Nature Rev Neurol* 2012; 8: 635-646.

11. Gass A, Rocca MA, Agosta F, et al. MRI monitoring of pathological changes in the spinal cord in patients with multiple sclerosis. *Lancet Neurol* 2015; 14: 443-454.