Validity of Brain MRI as the Primary Outcome Criterion in Multiple Sclerosis Phase II Clinical Trials

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Brain magnetic resonance imaging (MRI), with and without gadolinium enhancement, has offered fascinating and unique insights into the pathogenesis of multiple sclerosis (MS) as well as increased diagnostic accuracy [1, 2]. As research tool, MRI has more than proven its value in MS clinical trials [3–5]. However, the recent proposal to use neuroimaging with MRI as the primary outcome measure in MS phase II clinical trials might reflect a disproportionate weighting of MRI [3]. The claim of the superiority of MRI in detecting "disease activity" over clinical criteria appears to be founded merely on the definition of silent disease activity by MRI itself [4]. We consider that our understanding of the significance of silent disease activity has not evolved to a stage where we can make MRI the primary outcome criterion in phase II clinical trials. The validity of the method is not bolstered by the following points, which are also acknowledged among MRI clinical researchers [5, 6]:

(1) Despite impressive long-term serial MRI observations [7, 8], frequent MRI monitoring, as proposed for phase II trials, has not revealed more than a nonsignificant association of area and frequency of gadolinium-enhancing lesions with clinical worsening [6].

(2) Spinal cord lesions and the pathological heterogeneity of the MS lesion have to be taken into account, in particular with regard to patient disability [5, 9]. Axonal loss and demyelination within the lesion as well as its strategic positioning in the brainstem and spinal cord are not revealed specifically by cerebral MRI. Moreover, could not downregulatory factors be present in "silent" lesions without altering their MRI appearance?

(3) According to current knowledge, gadolinium-enhanced MRI delineates breakdown of the blood–brain barrier, regardless of clinical signs. What would happen if a future treatment specifically targeted axonal loss, demyelination, or enhanced functional repair without altering blood–brain barrier permeability in the inflammatory lesion? MRI as the no. 1 criterion in phase II clinical trials might lead to the unwanted side effect of dismissing candidate compounds that successfully target demyelination, axonal loss, and regeneration without substantially altering the MRI picture, in favor of gaining "cleaner" and more objective study data.

MS remains enigmatic, since the most important questions about this disease remain open despite the advent of new molecular tools, progress in animal models, and novel neuroimaging techniques [10]. A "composite MS clinical and functional score" comprising progress in expanded disability status scale and other clinical scores, days of hospitalization, and recurrence rate as a primary outcome criterion in phase II clinical trials is at least worth reconsidering.

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Reply

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We agree with Drs Liedtke and Limmroth that clinical parameters remain the gold standard for the ultimate assessment of therapeutic trials in multiple sclerosis (MS). Unfortunately, the variability of the disease and the insensitivity of the commonly used rating scales makes the evaluation of clinical change difficult and often inaccurate. The majority at an international workshop on outcome measures in MS concluded that although clinical outcome measures such as

