

Challenges in developing new multiple sclerosis therapies

Michael K. Racke

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In the last 15 years, we have seen the therapeutic landscape for multiple sclerosis (MS) change dramatically. From a disease that essentially had no disease-modifying therapy, we have seen the approval of several drugs that have reduced relapses and altered the progression of disability in patients with MS. However, despite these advances, there is still no cure for the disease and the need for more effective and convenient therapies still remains.

While the cause of MS remains unknown, the major hypothesis regarding the effector mechanism for this disease is that the immune system attacks the myelin in the central nervous system (CNS), ultimately leading to destruction of axons and the permanent accumulation of disability in these patients [Frohman *et al.* 2006]. Thus, two major strategies would logically arise to treat this disease. One would be to inhibit the immune system from causing the damage that results in the clinical manifestations of the disease. The other would be to establish mechanisms where the CNS would be resistant to the deleterious effects of the immune response, a process often referred to as ‘neuroprotection’.

Currently, the major drugs used in the treatment of MS are referred to as ‘immunomodulatory agents’. They are thought to modify the immune response in some way to reduce the deleterious effects thought to be mediated by the immune system. Interestingly, the mechanisms by which these therapies exert their therapeutic

benefits are not well understood, particularly for interferon- β and glatiramer acetate [Zivadinov *et al.* 2008]. While these agents may also result in less subsequent damage in the CNS, it is not clear whether this is a primary or secondary phenomenon. Natalizumab, which significantly reduced relapse rate and MRI disease activity, was greeted with a great deal of enthusiasm, which was then dampened somewhat by the occurrence of progressive multifocal leukoencephalopathy (PML) in three patients receiving the drug [Khalili *et al.* 2007].

Immunosuppressive agents such as mitoxantrone have a significant effect on inflammatory parameters of the disease, but are limited in their usefulness because of their toxicity to other organ systems (cardiac toxicity and risk of leukaemia) and limited time for administration of the drug before risks far outweigh their potential benefits.

This issue with regard to toxicity is one that neurologists may have to continue to grapple with as new agents receive approval for use in treating MS patients. The success of clinical trials with agents such as alemtuzumab and rituximab suggests that the field is making great strides in identifying strategies that potentially provide much greater efficacy for patients with MS [Hauser *et al.* 2008]. Interestingly, several patients receiving alemtuzumab developed issues with bleeding as a result of a low platelet count, with one patient suffering a fatal intracerebral haemorrhage. Patients receiving rituximab (although not with MS)

Correspondence to:
Michael K. Racke, MD
Helen C. Kurtz Chair in
Neurology, Ohio State
University Medical Center,
Columbus, OH 43210,
Michael.Racke@
osumc.edu

have also been observed to develop PML. Thus, while we are seeing agents with enhanced efficacy, it appears that the risks associated with these agents are greater than previously observed with the earlier-generation immunomodulatory agents. However, these agents are teaching us important lessons regarding the pathogenesis of MS and perhaps will lead the way to new and improved methods for targeting the processes that underlie the formation of lesions in MS.

Combination therapy is another area where one could see progress in MS therapeutic development. Several small exploratory trials have examined the use of immunosuppressive agents with interferon- β . Oral agents such as atorvastatin are being tested in combination trials and may offer another therapeutic strategy with less systemic toxicity.

Perhaps as important as the development of new therapies for MS is the development of tools to help evaluate the disease. Perhaps nothing has been as influential as the use of magnetic resonance imaging (MRI) in helping make the diagnosis of MS and in helping evaluate the clinical response of various therapeutic agents. The recent revisions to the MacDonald criteria have clearly emphasized that disease activity demonstrated by MRI can be used to identify patients with clinically definite MS much more quickly than one could do by clinical criteria alone [Polman *et al.* 2005]. Perhaps even more importantly, MRI is now used as a surrogate marker for the evaluation of every new therapeutic agent that is being evaluated for the treatment of MS. It is probably also important to note that the initial FDA approval of interferon- β -1b was highly influenced by the significant effect that the drug showed on MRI disease activity. One of the major challenges that lies ahead is to develop MRI techniques that have better predictive value in terms of clinical outcomes.

In addition to the use of MRI in clinical trials, imaging is now being used by many clinicians as a surrogate for evaluating the efficacy of a therapy for MS. Many patients not only do not want to experience exacerbations, they want to hear from their neurologist that they have not had any new lesions appear on their MRI. However, much of that thinking has been the result of imaging performed on 1.5 Tesla magnets with single-dose gadolinium, often with the imaging performed without the suggested time period after

gadolinium administration to allow for optimal efficiency in detecting gadolinium enhancements. Imaging with higher field strength magnets (3 and 7 T) can detect lesions not appreciated previously with conventional strength magnets, although the clinical relevance of some of these lesions remains to be determined. As a field, have we been lulled into a false sense of security because our imaging suggested we were having a significant inhibitory effect on the pathophysiology of the disease, when in fact some level of pathology was still occurring when examined under the higher field strength magnets? While the burden of disease as measured by T2 lesion volume has been an outcome measure in several MS clinical trials, the correlation between T2 disease burden and clinical disability remains rather low. One explanation would be that the many processes represented by T2 lesions on MRI in MS are quite diverse and it would be processes such as axonal loss that would be most likely to contribute to permanent accumulation of disability. Perhaps this underlying pathology would help explain the paradox seen when an agent seems to have a profound effect on MRI, yet shows a more limited clinical effect.

Nonconventional MRI has also provided new insights into disease pathogenesis. Magnetization transfer imaging is a technique that measures the exchange of magnetization between bound and free protons in tissues such as the brain. When the tissue imaged is undergoing inflammation and oedema, the free proton pool increases resulting in a decrease in the MTR. Axonal loss and demyelination can result in an even greater loss in the MTR signal. Similar to the discussion regarding disease that may not be observed with conventional MRI, fluctuations in MTR histogram peak values in MS patients being treated with interferon- β -1b would suggest that inflammatory processes persist in lesions and/or normal-appearing white matter [Richert *et al.* 1998]. Magnetic resonance spectroscopy is a technique that allows one to measure the metabolites in the brain that is being imaged. This can give one an idea about the biochemical changes occurring in the lesions of MS patients. Perhaps one day these new imaging tools will allow us to monitor the changes that new therapies will bring about as a way of defining the success of a therapy for the individual patient.

Finally, imaging may also be the tool that helps to define a neuroprotective agent for MS.

Cerebral atrophy has long been recognized as a complication of MS, although there is also the issue of pseudo-atrophy caused by aggressive anti-inflammatory agents. Longitudinal studies of patients with MS have shown that accumulation of atrophy also occurs, even early in MS [Rudick *et al.* 1998]. Thus, would MRI provide an adequate surrogate marker for measuring the positive effects of a neuroprotective agent?

So, in this time of rapid clinical and diagnostic developments in MS, what challenges lie ahead? Are clinical trials going to move to active comparator rather than placebo-controlled trials because of the availability of agents that are known to affect the disease course? Will we develop biomarkers to help diagnose MS patients and identify which therapy patients will respond to best? Will MRI progress to a point that it will replace clinical outcomes in evaluating the outcome of clinical trials? Over the last 15 years, a great deal of progress has been made in understanding MS pathogenesis and producing therapies that significantly affect the MS disease process. Hopefully the next 15 years will see even greater strides made toward controlling one of the major causes of neurologic disability.

Conflict of interest statement

Dr Racke has consulted for Bristol Myers Squibb, Peptimmune Inc., and Teva Neuroscience. He is

on the Speaker's Bureau for Bayer, EMD Serono, and Teva Neuroscience.

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