Multiple sclerosis therapeutics: opportunities, strategies and challenges

‘The unmet medical need in the multiple sclerosis field, natalizumab notwithstanding, is substantial, even for relapsing multiple sclerosis patients treated early.’

Not too long ago, multiple sclerosis (MS) was not only considered untreatable, but there was widespread skepticism that successful treatments were forthcoming. The challenges were delineated in a watershed international workshop on clinical trials in MS that was convened in Grand Island, New York, in the spring of 1982 [1]. This conference led to a concentrated effort to develop drugs to significantly slow the MS disease process, leading to another watershed event – approval in 1993 by the US FDA of subcutaneous interferon β-1b (Betaseron®) for relapsing–remitting MS (RRMS). Unequivocal reduction in the formation of new brain lesions detected by MRI scans contributed very significantly to the approval of interferon β-1b [2]. Within 5 years or so, regulatory authorities worldwide approved intramuscular interferon β-1a (Avonex®) [3], subcutaneous interferon β-1a (Rebif®) [4] and glatiramer acetate (Copaxone®) [5] for RRMS patients. These approvals were all based on Phase III registration trials, demonstrating an approximate 30% reduction in relapse rate in patients with established RRMS. Studies in patients with an initial clinical demyelinating episode presenting with multicentric brain lesions – so called clinically isolated syndromes at high risk for MS – demonstrated an approximate 50% reduction in the risk of a second relapse [6–8], suggesting that early treatment resulted in better efficacy. Studies of these agents in progressive forms of MS yielded negative or marginal benefits, further strengthening the rationale for early diagnosis and treatment. Theories about mechanisms of action were developed, published and debated. Sales of these drugs worldwide has grown to approximately US$6 billion.

In 2004, a monoclonal antibody to α-4 integrin, natalizumab (Tysabri®), was approved by the US FDA using an accelerated approval process based on the presence of an unmet need in the MS field, and on the observation that natalizumab reduced the relapse rate by 68% [9]. The use of natalizumab was suspended when two MS patients participating in a clinical trial were found to have progressive multifocal leukoencephalopathy (PML), a usually fatal CNS infection with an opportunistic DNA virus with tropism for oligodendrocytes. Natalizumab was reintroduced in the USA after a careful safety study quantified the risk of PML at 1:1000, and is now used worldwide, but with careful patient monitoring.

The unmet medical need in the MS field, natalizumab notwithstanding, is substantial, even for relapsing MS patients treated early. The explanation for this appears to be multifactorial:

- None of the available drugs completely stops the disease process, at least in populations of clinical trial patients;
- In many cases, MS progression is clinically silent for many years, at which time the disease is advanced and not highly responsive to treatment;
- None of the drugs has been shown to be effective in secondary progressive or primary progressive MS, a subtype affecting approximately 15% of MS patients in which inflammation appears to be less prominent;
- There is an underlying concern that inflammation may not entirely explain the progressive neurodegeneration that has been reported in MS patients, particularly later in the disease;
- It remains possible, maybe even likely, that MS is pathogenetically heterogeneous, yet personalized use of disease-modifying drugs has not yet developed in the MS field;
- None of the drugs trials have included children with MS, so it is unclear how to apply data from clinical trials to the pediatric population.

This Special Focus issue of Therapy takes a look forward at the field of MS therapeutics. Gary Cutter and Stacey Colfield discuss novel designs for Phase II trials in MS [10]. They discuss Bayesian designs (using information available from the past to assess the situation of the groups, and modifying the design as new information is collected during the trial); adaptive
designs (which can bridge between early development studies and registration studies, without the usual 1–2 year gap between study phases); treatment strategy designs (which include studies of treatment plans and drug combinations, for example); and futility designs (which are aimed at stopping trials early that have a low chance of success, making continuation of such trials futile). Cutter and Colfield discuss the advantages and promise of these and other alternative designs, and some MS-specific challenges.

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Manuel Comabella describes the evidence for heterogeneity in the MS disease process, which provides the basis for personalized medicine, and discusses the field of MS pharmacogenomics, still in its infancy [11]. Comabella reviews pioneering studies that have attempted to link interferon-β-induced gene-expression patterns to therapeutic response to interferon-β treatment. So far, results have been based on small samples and have been inconsistent. Genome-wide treatment response association studies are just now being contemplated, but hold promise for personalized MS treatments in the future.

Comabella and colleagues also provide short critiques on several recent research reports, each of which may lead to major new research directions in the future [12]. Genetic variations in the ecotropic viral integration site 5 (EVI5) gene were found to be associated with MS [13]. The EVI5 gene relates to a common site of retroviral integration that conceivably could tie endogenous virus together with immune dysregulation. Two other recent reports highlight two separate approaches to MS therapy – one nonspecific, the other more targeted. In a small study, a relatively nonspecific approach – high-dose cyclophosphamide – was reported to significantly reduce MS disease activity in severe RRMS [14]. In the more targeted approach, a monoclonal antibody to CD20 (rituximab [Rituxan®]) was shown to deplete B cells, and significantly reduce disease activity in RRMS patients [15]. The studies illustrate that multiple approaches are being used to suppress inflammatory activity in MS, and it is still unclear whether highly targeted approaches will prove to be better.

The rationale for clinical trials of new MS therapies is informed by understanding of mechanisms in animal models of the human disease. A novel therapeutic target – the endoplasmic reticulum (ER) stress response – is reviewed by Stephen Miller and colleagues [16]. The ER stress response is a cellular pathway that allows a cell to survive and recover from a stressful event. Miller and colleagues suggest that the ER stress response may be targeted to promote myelin survival and repair in the face of a CNS inflammatory insult. They further suggest that multifaceted therapies may be required, including inhibition of disease-inducing inflammatory cells, together with therapies that stimulate the ER stress response to promote survival of oligodendrocytes, and perhaps to stimulate remyelination by oligodendrocyte progenitor cells. However, translational research flows in both directions. Not only are clinical trial rationales based on studies in cell and animal model systems, but clinical trial results themselves can be used to learn about MS pathogenesis. In an interesting opinion piece, Michael Racke and Amy Lovett-Racke illustrate this concept by reviewing important lessons learned about MS pathogenesis from trials using natalizumab and rituximab [17].

Multiple sclerosis is increasingly recognized in children, yet the clinical, epidemiological, pathogenetic and therapeutic aspects of pediatric MS have been only sparsely described. This is changing, as described by Lauren Krupp, who provides a perspective on the special circumstances of children with MS, and particular issues related to therapy [18].

‘We believe that the future is bright because of progress in genetics, neuroscience, pharmacology, cell-based therapeutics, neuroimaging and clinical trial methodology.’

In his interview, Leslie Weiner provides unique insights into gene therapy and cell-based therapy, particularly stem-cell therapy for MS [19].

The future of MS therapeutics is bright, even though serious challenges remain. Is MS entirely driven by autoimmune-driven inflammation? Or is brain inflammation secondary to a poorly understood neurodegenerative process? If the latter is true, fully effective anti-inflammatory therapy will not entirely control the MS disease process. Can strategies be developed to screen neuroprotective and reparative therapy? Anti-inflammatory therapies have been developed using methods to detect brain inflammation and clinical relapse. Sensitive protocols suitable for screening therapies
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