Curr Neurol Neurosci Rep (2011) 11:523–525
DOI 10.1007/s11910-011-0218-7

INVITED COMMENTARY

Personalized Treatment in Multiple Sclerosis

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Published online: 13 August 2011

Keywords Multiple sclerosis · Personalized treatment · Relapsing-remitting MS · Disease-modified therapies · Interferon · Glatiramer acetate · Natalizumab · Fingolimod · Responders · Nonresponders · Relapses · Disease progression · EDSS · MRI · Biomarkers · Clinical trials · PML · JCV antibody · Polymorphisms · Pharmacogenomics · Microarrays · Genome-wide expression

Multiple Sclerosis is a Heterogeneous Disease

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system evolving over decades that triggers abnormal immune mechanisms inducing myelin injury. Evidence exists indicating axonal damage closely associated with inflammation is present in early disease stages and is the pathologic substrate of residual disability.

Disease course is highly variable. The first episode of neurologic dysfunction, called clinically isolated syndrome, is important to identify because most patients will develop MS in the ensuing years. A total of 85% of MS patients begin with a relapsing-remitting pattern in which acute exacerbations are followed by periods of stability (remissions). However, in up to 50%, this pattern evolves to a secondary progressive form characterized by relentless neurologic deterioration over a period of years, with or without superimposed relapses. Ten to 15% of patients present primary progressive disease with sustained disability progression from onset. Additional MS categories are attributed to differences in disease severity: mild versus aggressive. Furthermore, pathology studies indicate the inflammatory component can be less prominent in some patients, whereas in others neurodegeneration or primary oligodendrocyte dystrophy can be the primary events, suggesting that, as occurs in many other chronic diseases, changes in multiple molecular pathways are involved. Thus, MS is a heterogeneous disease that presents in different populations with different clinical phenotypes, that seems to have different immunopathologic and immunogenetic backgrounds, which may account for differences observed in response to specific therapies. In consequence, clinicians who treat MS are not facing a single disease, but several clinical conditions, differing not only from patient to patient, but also in each individual case as the disease progresses.

Disease-Modifying Therapies, Responders, and Nonresponders

An expanding array of treatment options with different mechanisms of action have reduced both relapse rates and severity in relapsing-remitting MS, and have helped prevent or delay onset of secondary progressive forms. In different phase 3 clinical trials disease-modifying therapies (DMT) such as interferon-β (IFN-β), glatiramer acetate, fingolimod, and natalizumab (NZB) reduced both frequency and severity of clinical relapses, as well as subclinical features

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of disease activity measured on MRI. Current therapies are only partially effective however, and a number of DMT-treated patients continue to experience disease activity (20% to 50%). These patients are defined as nonresponders, suboptimal responders, or patients with breakthrough disease. Considerable variability in therapeutic response also has been observed between patients, further underscoring the need for new therapeutic strategies.

Although the armamentarium of available therapies for MS broadens, little is known about factors predicting individual patient response to treatment. Identification of subjects with poor response or tolerance to particular DMTs would allow switching patients to alternative treatment strategies before irreversible tissue damage occurs. Doctors have become aware that one of the great challenges for the 21st century is to delivery effective therapies tailored to the biological state of an individual, enabling so-called "personalized health care."

Clinical and Neuroimaging Markers

Guidelines to help identify treatment response on the basis of clinical markers (relapse rate, disability progression, or both combined) and MRI activity have been proposed in DMT-treated patients. Relapses are good markers of clinical activity. However, measuring relapses to predict treatment response remains controversial, and several studies have found no clear correlation between early relapses rates and subsequent degree of disability. Use of the Expanded Disability Status Scale (EDSS) to measure disability progression in MS patients can also exhibit significant fluctuations, making evaluation of changes difficult. A clear need for standardized and validated definitions of treatment response for daily use in clinical practice exists. One of the main concerns is that current literature evidence is based on short-term follow-up (<2 years). Thus, validation studies confirming treatment response definitions over longer periods of time are imperative.

In recent years, MRI has been used to evaluate DMT efficacy. Results of seminal studies support image-related quantification to define treatment options and strategies at the individual patient level. However, two major concerns in relation to use of this method are high intra- and interindividual heterogeneity of MS activity patterns, and influence of disease stage on MRI predictive value. Although helpful in early disease, lesion activity measured by MRI is less reliable in more advanced stages. Results from group studies indicate a significant prognostic value for measures derived from nonconventional MRI techniques such as magnetization transfer MRI; however, use for patient monitoring in a daily clinical practice setting remains at present inadvisable. Integration of appropriate clinical response criteria together with MRI findings are crucial for reliable management of patients undergoing DMT. Nevertheless, literature data on use of this approach remain insufficient at this time, and validation is lacking.

Biomarkers

Personalized therapy in MS will only be possible when biomarkers allowing reliable identification of therapeutically relevant subgroups of patients become available. Predictive markers present a major challenge because drug responsiveness may change overtime, a fact further complicated by use of varying definitions of treatment response. Ideal biomarkers have high sensitivity and specificity for disease activity, and are readily detected in body fluids. The idea of using genetic information to predict drug response is already widely accepted, and part of recommended prescription and dosing protocols for a number of treatments. Need of these approaches is more pressing for medications with high risk for adverse events and for progressive disorders such as MS.

Using predictive biomarkers to select specific treatments is not new in cancer medicine. Biochemical evaluation of estrogen and HER2 receptor expression to predict benefit from endocrine therapies and trastuzumab is now well established. Likewise, RAS and EGFR mutations are negative and positive predictors, respectively, of beneficial response to drugs inhibiting the epidermal growth factor receptor, a target in different solid tumor treatments.

Numerous biomarkers of different pathophysiologic processes in MS have been explored, such as ones reflecting alterations of the immune system, demyelination, and neuronal and glial damage. Additionally, novel candidate marker development has come from gene expression profiling, proteomics, and pharmacogenomics. Most transcriptional profiling studies related to MS treatment have investigated in vitro or ex vivo changes induced by IFN-β, reporting several induced and repressed genes. Representative studies include a pharmacogenomic analysis of IFN-β response in MS patients, which revealed drug responders had significantly different genotype frequencies of single nucleotide polymorphism (SNP) located on many genes including *glypican 5, collagen type XXVα1, hyaluronan proteoglycan link protein, calpastatin,* and *neuronal PAS domain protein 3*, compared with nonresponders. Many of these differences were associated with ion channels and signal transduction pathways, including glutamate and γ-aminobutyric acid receptors. The study also suggests that genetic variants in heparin sulfate proteoglycan genes may be of clinical interest in MS as predictors of response to therapy. Interestingly, microarrays for SNPs in genes previously considered pharmacogenomic candidates such as IFN-β receptors (*IFNAR1* and *IFNAR2*) or IFN-stimulated genes (eg, *LMP7, CTSS,* or *MxA*) were not

significant. Moreover, longitudinal analysis of gene pattern expression from IFN-β–treated MS patients identified nine sets of gene triplets whose expression, when tested before therapy, predicted response to IFN-β with up to 86% accuracy. Surprisingly, a pattern consistent with increased apoptosis proteins was observed in poor responders. This increase in pro-apoptotic transcripts in peripheral blood mononuclear cells from poor responders could be reflecting undesired elimination of certain regulatory cell populations needed to maintain homeostatic balance.

In another genome-wide expression study, monocytes from MS patients not responding to IFN-β showed selective increase in phosphorylated STAT-1 levels and surface expression of IFN receptor I at baseline, suggesting lack of drug response was related to perturbation of IFN-β signaling pathway in monocytes, predictable with up to 78% accuracy. Likewise, further observations demonstrated individuals with poor IFN-β treatment response had generally exaggerated biological response to type I IFNs. This particular response could identify a pathogenetically distinct subset of MS patients whose disease is driven in part by innate immunity.

Part of the unresponsiveness to IFN-β can be explained by the development of neutralizing antibodies, probably associated with a reduction in clinical and radiologic treatment effectiveness. However, the clinical impact of detection of such antibodies is controversial and guidelines for laboratory testing and clinical use are still being debated. Overall, results from different studies indicate that interindividual variations in pharmacologic responses to DMT are an intrinsic property of peripheral blood cells at baseline.

Biomarkers also may be relevant to monitor side effects of immunotherapies. For most novel agents, little information exists on side effects associated with long-term use. Thus, clinical care could be improved by treating patients not experiencing adverse events. In this regard, MS patients with the R92Q mutation of the tumor necrosis factor (TNF) receptor gene habitually present symptoms compatible with the autoinflammatory syndrome TRAPS (TNF receptor 1-associated periodic syndrome), and are more prone to side effects from various immunotherapies. Likewise, biomarkers may allow stratifying the risk of side effects in patients undergoing NZB treatment.

Progressive multiple encephalopathy (PML) generally occurs in severely compromised individuals as well as in some patients receiving certain immunosuppressive or biologic therapies such as NZB. Identification of patients at lower or higher risk for developing PML may allow more appropriate use of these therapies. Based on reports from confirmed PML cases, PML risk may increase beyond 24 months of treatment and in patients previously treated with chemotherapy, particularly mitoxantrone. Monitoring of the JC virus (JCV) DNA in blood or urine will not enhance the ability to predict PML. In contrast, JCV serology could be critical to stratify patients at lower or higher risk more accurately. Anti-JCV antibody detection using a two-step enzyme-linked immunosorbent assay may allow patient stratification into higher- (seropositive) and lower-risk (seronegative) groups. Data from different studies using NZB demonstrated 88% of PML cases occur in JCV serum–positive patients and 12% in serum-negative ones, reflecting PML risk of approximately 3/1000 for the former and 0.03/1000 for the latter. Clinical management of MS patients using or contemplating NZB use could be personalized using this assay.

Conclusions and Further Perspectives

Personalized medicine aims to use state-of-the-art genomics to tailor individual treatment, maximizing DMT efficacy while minimizing adverse drug reactions. Biomarkers have long been hailed as the key to better patient care and lower medical costs. Discovery of new biomarkers should the objective of a larger research network involving industry and experts in molecular biology, genetics, clinical trial design, epidemiology, statistics, regulation, and health care economics. Future clinical trials should not only address traditional end points pertaining to drug safety, pharmacology, and efficacy, but also consider including biomarker studies oriented toward identifying selected patient populations. Another practical and ethical concern is biomarker applicability across different ethnic groups. Polymorphisms associated with drug responses could differ considerably between populations, an issue that would need to be addressed in the application of biomarkers on a global scale. Because MS exhibits considerably heterogeneity, early patient selection and proof of concept in drug development may help minimize the risk of late and costly drug attrition, accelerate patient benefit by reducing morbidity, improve drug approval registration strategies, and result in more frequent and less costly drug approval.

Disclosure Conflicts of interest: J. Correale: has served on the board for Merck-Serono Argentina, Biogen-Idec Argentina, Novartis Argentina, and Merck LATAM; has been a consultant for Merck-Serono Argentina; has received honoraria from Merck-Serono LATAM, TEVA-Tuteur Argentina, and TEVA; and has received travel/accommodations expenses covered or reimbursed from Merck-Serono Argentina and Biogen-Idec Argentina.