ADDRESSING THE CHALLENGES IN RISK ASSESSMENT AND RISK MANAGEMENT IN MULTIPLE SCLEROSIS

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Therapy for multiple sclerosis (MS) has undergone multiple evolutions in the last 20 years. From the advent of the first US Food and Drug Administration (FDA)-approved therapy to the routine use of 4 different injectable medications, the field has come a long way in a relatively short period of time. With the re-release of natalizumab in 2006, patients with MS and treating physicians were faced with a new challenge in disease therapy—more intensive risk/benefit discussions. After experiencing a "honeymoon" period relative to the low risk associated with interferon and glatiramer acetate injection therapy, patients with MS and physicians were forced to determine what amount of risk they would be willing to endure in order to achieve substantially optimized disease-modifying effects (both clinical and radiographic).

Correspondingly similar challenges are increasing with the emergence of novel therapeutic capabilities, based on targeting mechanisms not heretofore characterized in medical immunobiology. The coupling of greater treatment efficacy with the observation of a broader diversity of associated adverse events (some of which can be life threatening), will no doubt prompt the FDA and similar agencies around the world to formulate more complex approval processes, which will likely result in a more protracted period of time between completion of phase III efficacy studies and the ultimate registration of these long-awaited advances on behalf of our deserving patients. After the recognition of potential life-threatening events with significant immunomodulation in patients with MS (in particular with progressive multifocal leukoencephalopathy [PML]), both practitioners and patients have become more risk aware when deciding amongst therapies. Yet, the ongoing risk of life-altering disability caused by MS persists, and these complexities weigh heavily on patients, families, and physicians.

On October 1, 2011, a meeting was convened in Philadelphia, PA, with approximately 50 academic and community-based neurologists who care for patients with MS, and who were appointed to serve as faculty in order to address the above-mentioned challenges that face the neurologist responsible for providing disease-modifying treatment for the patient with MS, commensurate with the intensity of the disease process, while taking into account the known risks of each of the considered treatments. The group considered data that would help clinicians risk stratify patients relative to their disease course and severity. The group considered whether there are features of a patient at diagnosis, or early in the course of the disease, that could be utilized to prognosticate about the risk of future disability. The participants also reviewed data about the currently available FDA-approved therapies and their reported efficacy and risks. Ultimately, participants worked through a series of real-world patient vignettes in order to practically operationalize the available evidence-based data and expert opinion for the purpose of illustrating how specific clinical circumstances can be translated into the rendering of specific and rational treatment recommendations.

A salient theme that was underscored by the par-

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ticipants throughout the meeting was that all therapeutic recommendations in the MS arena must be individualized. There are no amount of population data that will allow us to move patients through "cookie cutter" clinical management algorithms. Some patients are willing to take on more risk than others in order to optimize the chance of treatment-exacted remission and a disease-free status (at least by virtue of how we measure disease activity; eg, no attacks, progression, lesions, etc). The goals of treatment are quite heterogeneous, contingent upon what is of greatest priority to the patient. For instance, some patients are more concerned with preservation of cognitive capabilities relative to physical functioning. While the goals of disease-modifying therapy are principally focused on reducing and mitigating inflammatory demyelinating attacks and disease progression, confusion often arises when patients erroneously assume that such treatments are also intended to eradicate their existing MS-related symptoms such as fatigue, cognitive slowing, heat and exercise intolerance, or bladder and bowel dysfunction. Although these symptoms are likely a derivative of the disease process, they are already established and thereby require a separate process of multidisciplinary symptom management. Other factors that influence the type and intensity of treatment include patients who are considering pregnancy, while for others, adherence behavior will figure prominently in the ultimate choice of treatment. Collectively, these many variables are part of the complex decision-making process that both care providers and patients must confront: one that clearly corroborates the principle that there is definitely not a one-treatment-fits-all approach.

Notwithstanding the compelling need to personalize MS therapeutics, potentially useful tools could be developed to give patients and practitioners a way to assess the risk of the disease, the potential benefit of a therapy, and the relative risk of a serious adverse event while using a particular therapy. With a rapidly increasing therapeutic landscape for MS, a clinically practical "navigation" tool aimed at the application of "reasonable and safe" treatments that are tailored to each patient would represent a powerful advance for the clinical neurologist. It is with this primary thrust in mind that we organized the Philadelphia meeting, and upon which the framework of this monograph is based.

MS Clinical Outcomes

The most common form of MS is relapsing-remitting MS (RRMS), characterized by acute exacerbations, punctuated by variable lengths of remission. Most clinical trials for potential MS therapeutics have focused on reductions in annualized relapse rate (ARR) as the primary outcome measure of treatment efficacy. This outcome measure compares the ARR for the placebo arm of a trial to the ARR of the treated patient cohort. In fact, no matter how effective a disease-modifying therapy may be, unless there is active worsening in the placebo group of a randomized, controlled clinical trial, a therapeutic advantage cannot be established (eg, a false-negative or type II error). Alternately, if the placebo group exhibits worsening in excess of what would represent typical MS disease activity, the active treatment may appear to be erroneously more effective (eg, a false-positive or type I error).

While relapses cause disruption to patients' lives, lost time from work, and hardships for families, there has been a vigorous debate about their effect on the overall course of the disease. Alternatively stated, do relapses matter? The evidence systematically reviewed as part of the MS Think Tank meeting suggests that they do in fact matter greatly—particularly in the case of individual patients. First, data analyzed from the placebo arms of various randomized, controlled trials confirm that a significant number of patients have sustained accrued disability following MS exacerbations. In Lublin's carefully crafted and systematic examination of the impact of MS attacks on compromised functional capabilities across a broad and representative range of clinical investigations, in excess of 25% of patients will have a sustained 1-point change on the Expanded Disability Status Scale (EDSS) following a confirmed relapse (Figure).[1] Second, relapses represent ongoing disease activity not controlled by a therapy, and hence constitute a marker of ongoing disease progression. Beyond suppression of relapses, however,

Figure. Impact of Relapses in Multiple Sclerosis

Effects of Attacks on Disease Progression
- *N* = 224 patients with ≥1 exacerbation
  - 90 days after exacerbation
    - 41% had EDSS score residual deficit of ≥0.5
    - 40% had EDSS score residual deficit of ≥1
- Attacks can lead to permanent worsening

EDSS = Expanded Disability Status Scale.
Data from Lublin et al.

there are many goals in MS therapy, the most important of which is the maintenance of both physical and intellectual function in our patients over decades.

Multiple sclerosis is a heterogeneous disease of the central nervous system that has the potential to cause significant disability. Classically, the disability of MS has been measured using the EDSS, which rates patients 0 to 10 based on physical examination findings, and most particularly ability to walk. Although the EDSS score provides a metric for assessing disability in trials, it has several important limitations. First, the EDSS is heavily biased toward the physical domain of ambulation. Patients who are using a walker or wheelchair are scored similarly despite any other concomitant disability (eg, compromising cognitive dysfunction). Regardless of the presence or absence of comorbid MS symptom manifestations such as pain, fatigue, vision abnormalities, sensory disturbances, or cognitive slowing, 2 patients each using a walker would have the same score. Secondly, at low numbers on the scale (below 3) there is significant inter- and intra-rater variability. Such variability has been posited to be, at least in part, related to factors such as symptom fluctuations (widely recognized as a common phenomenon in MS, especially with changes in body and ambient temperature, time of day, the season, following exertion, and with psychological stress; the so-called Uhthoff's phenomenon) and the heterogeneity of assessment technique across different study examiners. Coupled with patient-reported subjective impressions of work performance, activities of daily living, and quality of life, such variability in the assessment of the neurologic examination over time powerfully underscores one of the most formidable challenges of ascertaining dynamic changes in disability. Unfortunately, when objectively trying to prognosticate for patients with MS, we are limited by the few validated domains of efficacy data collected and analyzed from essentially all of the pivotal phase III clinical trials—principally relapse rate, EDSS score, and radiographic measures of MS disease activity (magnetic resonance imaging [MRI] changes).

Clinical Factors Affecting Disease Risk

Multiple MS population studies have analyzed patient demographic information relative to long-term disability in an attempt to identify "high-risk" patients. These patients were more likely to have significant disability (quantified by the EDSS) over a 10- to 20-year period of time. Factors such as gender, age, ethnicity, and location of first attack have all been analyzed to determine their relative prognostic significance.[2] Likewise, the assessment of "early" disease activity, as measured by relapse rate, has received significant attention for its utility to identify patients at higher (versus lesser) predilection for precocious disability progression. Beyond demographic and clinical measures of disease activity, MRI metrics have been

Table 1. Demographics of Benign Multiple Sclerosis

	Ramsaransing and De Keyser, 2007			Sayao et al, 2007 (20 years)			Costelloe et al, 2008 (20 years)		
	Benign (151)	Non-Benign (345)	*P* Value	Benign (88)	Non-Benign (81)	*P* Value	Benign (53)	Non-Benign (88)	*P* Value
Age	30±8.8	35±11.6	.0008	27.5±8.1	31±9.26	.015	28.3±9.6	34±12.2	.004
% female	72.1%	66.6%	>.05	85.2%	72.8%	.047	88%	68%	.006
Pyramidal symptoms at onset	23%	46%	.0001	9.1%	8.6%		15%	40%	.001
Sensory change at onset	42%	48%	>.05	53.4%	50.6%		47%	36%	
ON at onset	37%	24%	.003	19.3%	14.8%		22%	20%	
Brain stem at onset	19%	16%	>.05	15.9%	14.8%		30%	24%	
EDSS at 5 years	1.8±0.9	4.4±1.8	<.0001	ND	ND				
EDSS at 10 years	ND	ND				<.0005			

EDSS = Expanded Disability Status Scale; ND = not done; ON = optic neuritis.
Data from Ramsaransing and De Keyser[1]; Sayao et al[3]; and Costelloe et al.[4]

extensively investigated with respect to similar prognostic capabilities. Ultimately, taken together, our clinical and radiographic assessments potentially serve to stratify patients relative to their disease state. The coordinated strategy of analyzing multiparametric clinical and paraclinical outcome data modeling should be validated with respect to being prognostically predictive of a lower versus a higher risk for disease-related disability. If confirmed, such models of assessment will potentially be integrated with novel information about individual patients (such as pharmacogenomic factors) that could be translated into corresponding and precisely individualized and predictably effective treatment recommendations—a heretofore unprecedented advance in contemporary neurotherapeutics.

Before, during, and following our meeting, several population studies were reviewed to determine what baseline clinical features were most associated with poor outcomes in MS. These included data from the Lyon MS cohort published by Confavreux et al in 2003; a meta-analysis of studies published by Langer-Gould et al in 2006; and studies of "benign MS" published by Ramsaransing and De Keyser in 2007, Sayao et al in 2007, and Costelloe et al in 2008.[2-6] The majority of data sets suggest that male gender, older age, African American ethnicity, and motor symptoms at onset are associated with worse outcomes in MS (Table 1). Furthermore, when early relapses were examined, more frequent relapses in the first 5 years,[4-6] and diminished time between events were associated with a higher likelihood of disability at epochs 10 and 15 years after disease onset. Nevertheless, these studies consistently underestimate the potential magnitude of accrued disability in MS because their outcomes and related conclusions are exclusively telescoped to a patient's EDSS score. Conspicuously, between 19% to 45% of patients designated as having so-called benign MS have been confirmed to exhibit evidence of cognitive dysfunction. Difficulties with attention, word finding, information processing speed, multitasking, parallel processing, and executive planning comprise the broad diversity of intellectual changes that can characterize "cognitive dysfunction" in MS, albeit despite being able to ambulate quite effectively and safely in many (ie, low EDSS). Thus, when considering the true level of disability from MS, clinicians and patients should be aware of the constellation of potential disease effects. Interestingly, in one study of cognitive impairment amongst "benign MS patients," there were in fact concomitant correlations with higher levels of disease burden as measured by MRI.[7]

MRI Factors Affecting Disease Risk

Magnetic resonance imaging has become a cornerstone of clinical investigation assessment protocols of patients with MS. Since its first application to a patient with MS in 1981, MRI has literally revolutionized our ability to diagnose and monitor the MS disease process over time. Innumerable technical and protocol refinements have markedly augmented the sensitivity and specificity of both brain and spinal cord lesional conspicuity, which has thereby facilitated the capability of the neurologist to utilize highly precise and reproducible information about the dynamics and ultimate disposition (eg, the fate and destiny of a plaque lesion to proceed toward tissue destruction and the appearance and persistence of a black hole) of central nervous system tissue injury. Balancing the mechanisms of inflammation, demyelination, remyelination, astrogliosis, axonal dysfunction (ion channel pathophysiology, perturbations in intermediate metabolic pathways in response to supply-demand mitochondrial energetic mismatch mechanisms, microtubular deconstruction, and neurofilament disassembly, among other intra-axonal and intraneuronal derangements), axonal transection, and neurodegeneration ultimately culminate in biasing the nervous system's risk of permanent injury versus the potential penchant for neuroprotection, and even perhaps neuro-restoration. Not withstanding the impressive and pervasive progress achieved in the development of novel imaging paradigms, there has been a long-recognized clinical-radiographic paradox in MS that has yet to be fully explained. There are countless documented cases of patients with relatively minimal MRI-identified pathology, but significant disability, whereas alternately there are patients with profound changes on MRI, albeit with relative preservation of neurologic functioning. Nonetheless, MRI has been shown to be informative about patient prognosis in several ways.

Fisniku et al published outcomes data from approximately 80 patients followed for 20 years, and noted that increased lesion load at diagnosis was an independent prognostic indicator for precocious and more severe long-term disability as measured by EDSS.[8] What has been more controversial is the predictive value of asymptomatic white-matter lesions over time relative to disability. Data were reviewed

indicating that nearly 100% of T2 hyperintense lesions were gadolinium enhancing at some point, thus one would expect the prognostic significance of new T2 lesions to be similar to those that are enhancing. Yet, when surveyed at the Philadelphia meeting, neurologists in the community were more concerned by the identification of gadolinium-enhancing lesions than with the presence of new T2 hyperintense lesions on routine surveillance MRIs. A meta-analysis of individual patient data from 2 large, placebo-controlled clinical trials of subcutaneous interferon β-1a in patients with RRMS or secondary progressive MS (SPMS) were analyzed separately and as pooled data to assess surrogacy for the number of new T2 hyperintense lesions. The number of new T2 hyperintense lesions correlated with the number of relapses over the follow-up period. The proportion of treatment effect on relapses accounted for by the effect of treatment on new T2 MRI lesions over 2 years was 53% in patients with RRMS and 67% in patients with SPMS.[9] Another study tested the validity of MRI surrogacy in MS studies on recently published trials of oral drugs.[10] Ninety-two percent of observed effects of oral drugs on clinical outcomes could be predicted by the presence of active lesions on MRI.[9] This further validates MRI surrogacy in MS, with important implications for individual patient management.

In a meta-analysis of 5 natural history studies and 4 placebo-controlled clinical trials involving 307 patients (RRMS = 237, SPMS = 70), Kappos et al found that neither gadolinium enhancement in the initial scan, nor in 6 subsequent monthly scans, was predictive of change in EDSS score at 12 or 24 months (admittedly a relatively short epoch of time compared to the overall risk during the life of a patient with MS).[11] The best predictor of relapse during the first and second years following diagnostic confirmation was change in the number of gadolinium-enhancing lesions on scans taken during the initial 6 months. Nevertheless, a recent meta-analysis study that included 23 randomized, double-blind, placebo-controlled trials in RRMS, for a total of 63 arms, 40 contrasts, and 6591 patients, showed that more than 80% of the variance in the effect on relapses between trials can be explained by the variance in MRI effects. Therefore, smaller and shorter phase II studies based on MRI lesion end points may also give indications on the effect of the treatment on relapse end points.[9]

Other Considerations in Risk Assessment

Two important characteristics about patients were repeatedly highlighted in the patient management sessions at the Philadelphia meeting. While duration of disease figured prominently in rendering disease-modifying treatment decisions for patients with MS, relapses or MRI changes occurring early in the course of the disease were considered more significant from a disease risk perspective than insidious changes occurring years into the course of the disease. This duration of disease-based impact upon prognosis has previously been quantified by the MS Severity Score, published in 2005 by Roxburgh et al.[12] Another important and influential factor with respect to treatment was a patient's baseline defining characteristics with respect to the level of clinical disability, and the MRI burden of disease. Those with pre-existing disability, large MRI burdens of disease, or lesions located in eloquent regions that represent harbingers for more substantial disability (eg, brain stem and spinal cord) were stratified into higher risk designations that justified a commensurate intensification of immune modulatory therapy, when compared to those classified into lower risk categories.

After reviewing the available data, neurologist participants in the MS Think Tank meeting applied the derived principles to real-world patient scenarios. Patients were risk stratified relative to their disease characteristics, followed by specific treatment recommendations for each respective patient. Although there was not a singular consensus approach in the management for each scenario (nor was this the objective of the meeting), several important and highly salient themes were codified within a treatment framework that will be underscored throughout the analysis of each patient vignette considered within this article. The proposed management for each patient with MS is based on identifying a disease-modifying therapy that would be anticipated to adequately suppress disease activity within a given patient, and based on differential and individualized considerations germane to balancing both efficacy and risk of the selected treatment.

Risk Assessment of FDA-Approved Therapies in MS

There are currently 8 FDA-approved therapies for RRMS (Table 2). Their approval was based on pivotal randomized placebo-controlled phase III trials that

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