

Therapeutic Considerations for Disease Progression in Multiple Sclerosis

Evidence, Experience, and Future Expectations

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In the management of patients with multiple sclerosis (MS), providers are all faced with the highly formidable challenge of ascertaining whether, and to what degree, disease-modifying therapy is effective in the individual patient. While much has been learned in randomized, controlled clinical trials, we cannot simply extrapolate the outcomes of these initiatives and apply them to the care of a single patient. In the future, the application of pharmacogenetic techniques, proteomics, and microarray analysis will yield novel profiling information on individual patients that will substantially refine the specific therapeutic questions of relevance: (1) What is the best treatment for an individual patient? (2) Which patients require intensive therapeutic combination regimens to optimize control of the disease process? (3) What are the appropriate drug dosing targets for an individual patient? and (4) Which patients will be predisposed to the development of drug-related adverse events? Such data may provide a novel variable of drug responsiveness that will mandate its inclusion into the process of covariate analyses for clinical trials.

In the management of individual patients, subjective judgments will, no doubt, be made in trying to determine whether treatment should be changed or intensified. Relevant to the process of analyzing for breakthrough disease is the consideration of different treatment effects, such as control of relapse rate, disability, and magnetic resonance imaging (MRI) measures of disease activity. Each of these domains of efficacy will be determined by a number of highly relevant factors that

potentially dictate how and when we commence the process of therapy reassessment. For example, what is the latency period between treatment inception and the onset of significant effects on these various domains of disease activity? Phase III clinical trials do provide us with some level of evidence-based outcomes on which to make some preliminary assumptions. Nevertheless, in formulating a treatment strategy for an individual patient, additional information is required to address particular disease characteristics. Pharmacogenomic approaches are needed to assist clinicians in understanding the factors that underlie differences in treatment response. This appears to be particularly important in MS given the heterogeneity of the potential clinical and radiographic phenotypes.

ASSESSMENT OF DISEASE ACTIVITY

Patient Adherence

It is important to recognize that the fidelity of treatment adherence achieved by pa-

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tients in a clinical trial does not necessarily equate with behavior in general practice. In a clinical trial, patients frequently visit the study site, receive substantial support and education, and are accountable for the return of the medication vials as well as unused medication. Clear expectations are outlined to patients in the study about the conduct of the trial and the specific responsibilities expected of patients. It is also patently clear that patients with MS are a highly motivated group of trial participants.

Adherence rates have been very high in the context of well-designed clinical trials. In contrast, there is little data to suggest that these drug usage rates can be simply extrapolated to the expected use in clinical practice. We have found that when we actively query patients during each visit or during calls to the clinic about their use of injectable disease-modifying agents, up to one third of our patients admit to frequent nonadherence. This underscores the importance of assessing treatment adherence and compliance as part of any strategy to diagnose breakthrough disease in MS. Education, support, and accountability (eg, use of administration logs) to ensure the suggested use of medications may be one strategy to improve patient adherence.

Neurological Examination

The periodic assessment of the neurological examination continues to represent an important cornerstone of tracking changes in disease progression. Repeat evaluation will frequently reveal definitive changes that are not necessarily appreciated by our patients. One of the most formidable challenges faced by clinicians relates to which examination techniques should be included. Certainly, the routine neurological examination is standard practice in the periodic assessment of patients with MS. Recently, a number of ancillary techniques have been used in clinical trials that have been validated as useful instruments to detect meaningful change in discrete functions. These include the MS Functional Composite that combines a timed 25-foot walk, the 9-hole peg test (a measure of upper extremity function), and the paced serial auditory addition test (a measure of information processing speed).¹ While apparently useful as outcome measures in clinical trials, we lack data to corroborate the usefulness of these techniques to follow changes in the clinical course of our individual patients with MS in response to individually tailored therapy regimens. The same argument could be made for the use of the Expanded Disability Status Scale (EDSS) in clinical practice. While this disability assessment technique has been of use in clinical trials, most clinicians do not have sufficient time or staffing to perform the complete neurological examination, including the attempted 500-m walk, at every clinic visit. Many neurologists who treat MS can, however, routinely measure the 25-foot timed walk. This measure does correlate with the ambulation index and EDSS, and it provides us with a useful serial assessment strategy for following up gait mechanics and safety.²

Even when neurologists are equipped with adequate resources to perform these assessments, there are still a number of confounders that must always be considered when evaluating patients with MS: (1) What is the time

of day? (2) Is the patient being examined at the same time at each visit (which is unlikely)? (3) What is the weather like (as physical function does change in patients with MS in response to temperature variations)? and (4) Does the patient have an infection or fever, or are they having a particularly stressful day? There is a high degree of variability relating to the conditions under which we routinely follow up patients in the clinic. Despite these limitations, the astute neurologist is capable of translating routine assessments over time into a judgment concerning disease stability or instability. This judgment is refined by integrating information concerning relapses, MRI activity, and even the patient's subjective report of their "own examination" (analysis of activities of daily living, work performance, etc).

Patient's Examination (Activities of Daily Living)

The office-based examination is a highly stereotypic and standardized (as well as very artificial) approach to objectively documenting meaningful change in neurological capabilities. The inherent strength of this approach has been obvious and highly useful in the context of clinical trial initiatives. Despite these strengths, the "real" examination takes place where patients live their lives. In the assessment of breakthrough disease, patients should be asked about toileting, showering, dressing, ambulation, and eating. How are they functioning at work? Are they having more difficulty driving? Are cognitive changes occurring? Does depression cloud this assessment? A very important area of inquiry concerns the level of our patient's physical conditioning. The deconditioned patient with MS often perceives that his or her disease course has deteriorated. Correspondingly, the physician may likewise document a change in the course of disease progression secondary to breakthrough disease when a reduction of exercise tolerance may have compromised the patient's activities of daily living.

DEFINING BREAKTHROUGH DISEASE

Breakthrough disease may be characterized by unacceptable clinical or radiographic evidence of disease activity that is not sufficiently controlled by current treatment intervention. Detection of such activity is, in reality, not necessarily a true reflection of the actual level of disease activity. Defining breakthrough is contingent on the sensitivity of the assessment strategies being used to detect disease activity. As such, inherent limitations of subjective evaluations (clinical examination, patient self-report of activities of daily living) and even information derived from quantitative studies (MRI, immunological profiling, physiological examination) will continue to make the establishment of threshold limits for the confirmation of constitutive disease activity in MS inadequate. Hopefully, the use of newly emerging MRI applications, including magnetic resonance spectroscopy, magnetization transfer, and diffusion tensor imaging, will help to refine our ability to generate more realistic burden-of-disease measurements that can be used to monitor the disease process and to detect treatment effects in controlled clinical trials.

Patient Name	Date	Date	Date	Date	Date	Date
DMA*						
Drug name						
Drug name						
Drug name						
MS subtype						
2 y RR, No. of attacks per y						
1 y RR, No. of attacks per y						
EDSS score						
T-25, s						
9-HPT score						
PASAT score						
Patient's examination†						
QOL VAS score or QOL-54 score						
Fatigue scale score						
Depression scale score						
ADLs†						
MRI lesions‡						
MRI lesion volume‡						
MRI BH§						
MRI atrophy§						

Figure. Recording instrument used for assessment of patients with multiple sclerosis (MS). 9-HPT indicates 9-hole peg test; ADL, activity of daily living; BH, black hole; DMA, disease-modifying agent; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; PASAT, paced serial auditory addition test; QOL, quality of life; RR, relapsing-remitting; T-25, timed 25-foot walk; and VAS, visual analog scale; asterisk, compliance should be rated as high (H), moderate (M), or low (L); dagger, results should be rated as stable (S), better (B), or worse (W); double dagger, MRI lesions should be rated as grade 0 for stable, grade 1 for 1 to 3 lesions, grade 2 for 4 to 10 lesions, or grade 3 for more than 10 lesions; section mark, results should be rated as present (P), absent (A), stable (S), better (B), or worse (W).

Progression, whether clinically or radiographically evident to the physician or patient with MS, likely represents an ongoing process that, while modifiable with treatment intervention, is not currently amenable to a confirmable therapy-induced remission. Insights from sophisticated imaging and histopathological investigations in brain and spinal cord tissue samples from patients with MS indicate that a very active constitutive process of molecular and cellular events operates within the microenvironment of the central nervous system (CNS), generally without interruption throughout the course of the disease.²⁻¹¹ Disease activity may be escalated or mitigated depending on yet to be elucidated “driving” or “braking” factors or treatment interventions. What constitutes breakthrough activity in one patient might be considered adequate control in another. The features that characterize the pretreatment level of disease activity may be important to consider when formulating reasonable expectations to be derived from therapy intervention in the individual patient. For many (if not most) patients, some level of ongoing disease activity might be expected.

Despite the substantial and inherent limitations in defining breakthrough disease in MS, it does appear reasonable to begin the process of ascertaining changes in disease activity across multiple domains and comparing such changes over time with respect to baseline and pre-baseline measures. For instance, ascertaining the number of bona fide relapses in the preceding year or 2 years before treatment initiation may constitute an important benchmark from which to compare relapse rate after treatment inception (even though subclinical relapses often go undetected). While there is certainly no magic number of relapses that should be considered as a threshold for altering therapy, control over the disease process with

drug therapy should be attempted to limit the number and severity of attacks.

In an attempt to codify the global assessment of our patients with MS, one of us (E.M.F.) has designed a simple recording instrument that is integrated into the medical record (**Figure**). Incorporated in this device are a number of fields of assessment for each clinic visit that can then be easily compared serially across visits to render subjective opinions about disease stability or breakthrough.

EFFECTS OF PHARMACOTHERAPIES ON DISEASE PROGRESSION IN MS

We review here the clinical evidence for approved and experimental agents that are commonly used in clinical practice. A controlled trial that would provide the answer for every therapeutic question that the neurologist asks has not been conducted. Often, clinicians have to apply appropriateness criteria in deciding on a particular treatment approach for an individual patient. Notwithstanding this approach, repeated observation of efficacy in an uncontrolled fashion should eventually lead to the design of a controlled trial to confirm the efficacy of a treatment approach in a larger representative population of patients with a similar disease phenotype.

APPROVED DISEASE-MODIFYING THERAPIES FOR MS

Interferon Beta

Interferons (IFNs) were originally thought to increase the resistance of tissues, including those of the CNS, against viral infections. There is currently no data to suggest

that viral inhibition underlies IFN- β effects on MS in any way. Several mechanisms of action have been described. Interferon β increases levels of vascular adhesion molecule 1 in the sera of patients with MS.¹² In 1996, 2 studies^{13,14} showed that the migration of activated T lymphocytes across an artificial blood-brain barrier was partly mediated by metalloproteinase-9, and that IFN- β treatment reduced the production of metalloproteinase-9 by activated T cells as well as the migration of the T cells in vitro. It was also shown that IFN- β down-regulates IFN- γ -inducible major histocompatibility complex class II expression on nonprofessional CNS antigen-presenting cells such as astrocytes¹⁵ and microglial cells,¹⁶ and it may therefore reduce T-cell activation in the CNS. Furthermore, production of the proinflammatory cytokine tumor necrosis factor α by T cells activated by microglial antigen-presenting cells was also significantly decreased by IFN- β .¹⁷

Evidence. The first study to show that a pharmacotherapeutic intervention could improve the clinical course of MS was published in 1993, when IFN- β -1b (Betaseron; Berlex Inc, Montville, NJ) reduced the rate of exacerbations of relapsing-remitting (RR) MS in a multicenter trial.^{18,19} Furthermore, the number and frequency of lesions on brain MRI were decreased in the high-dose-treated patient population.^{18,19} There was a trend to less disability, though it was not statistically significant. The results of another multicenter placebo-controlled trial using IFN- β -1a (Avonex; Biogen Idec Inc, Cambridge, Mass) administered intramuscularly once weekly demonstrated that IFN- β -1a significantly delayed the time to sustained clinical disability in RRMS. A reduction in the exacerbation rate and time to sustained change in clinical disability was also seen.²⁰ Yet another preparation of IFN- β -1a (Rebif; Serono Inc, Rockland, Mass) was also shown to decrease the number of clinical exacerbations, to decrease the percentage of T2 active MRI scans, and to delay sustained disease progression.¹⁷ In that particular multicenter, placebo-controlled trial, the relapse rate was significantly lower at 1 and 2 years with both a low dose (22 μ g, 3 times per week) and a high dose (44 μ g, 3 times per week) of IFN- β -1a than with placebo. A recently published study²¹ indicates that IFN- β -1a (Avonex) has significant beneficial effects for patients with RRMS with regard to cognitive function.

In 1999, a double-blinded, placebo-controlled trial²² conducted in Europe revealed a highly significant delay of progression in patients with secondary progressive (SP) MS who were treated with IFN- β -1b. Unfortunately, a second SPMS trial in North America showed no statistically significant benefit of IFN- β -1b as compared with placebo.²³ Findings from a study^{24,25} of IFN- β -1a (Rebif) in SPMS were also disappointing. In a study²⁶ using IFN- β -1a (Avonex), a significant reduction in disability was demonstrated. The inconsistency with regard to the outcome of these trials may be partly owing to differences in the patient populations, both with regard to disability and disease activity.

Future Perspectives. Clearly, the effect of IFN- β on disease progression is only modest. This may be owing to the

fact that our current dosing is insufficient, or that IFN- β given as monotherapy is simply not effective enough in significantly slowing the natural course of MS. Combination therapy with other approved or experimental agents may greatly improve the effect of IFN- β on disease progression.

Role of IFN-Neutralizing Antibodies in MS Progression

The use of biotherapeutic agents is frequently associated with the generation of antibodies. Interferon β is a first-line treatment for RRMS, and occurrence of antibodies against IFN- β were described in several clinical trials.^{18,20,27-29} While binding antibodies were found in as many as 78% of patients treated with IFN- β , the frequency of neutralizing antibodies (NABs) has varied from 2% to 42%.

Evidence. Neutralizing antibodies hamper the biologic response to IFN- β and have a detrimental effect on the treatment response after 18 to 24 months of therapy.³⁰⁻³² In the pivotal trials of the 3 commercially available IFN- β preparations (Betaseron, Avonex, and Rebif), all of the 3 studies found initially no relationship between NABs and clinical efficacy in a 2-year study period.^{18,20,33} However, in the trial of IFN- β -1b (Betaseron), NABs occurred in approximately 35% of the patients; between 13 and 36 months of treatment, the exacerbation rate in NAB-positive patients was similar to that seen in placebo-treated patients. Further, the number of active lesions on MRI increased significantly in NAB-positive patients.³⁴ In the extension phase of the Prevention of Relapses and Disability by Interferon- β -1a Subcutaneously in Multiple Sclerosis study,³⁵ NABs to IFN- β -1a caused a significant reduction in efficacy during treatment years 3 and 4. Patients who were positive for NABs experienced a significantly higher relapse rate than NAB-negative patients (relapse rate, 0.81 vs 0.50, respectively; $P = .002$). The disease burden on MRI decreased by 9% from baseline to year 4 in NAB-negative patients whereas it increased by nearly 18% in NAB-positive patients ($P < .01$). In a recent Danish study³⁶ of IFN- β -1a and IFN- β -1b products, the presence of NABs was studied in 541 patients with RRMS treated with IFN- β , and an evaluation of different concentrations of NABs on the treatment effect was assessed. It was found that across all of the IFN- β treatments, even moderate concentrations of Nabs caused a significant difference in the relapse rates. The yearly relapse rate was 0.64 during NAB-positive periods as compared with 0.43 in NAB-negative periods, yielding an odds ratio of 1.53 (95% confidence interval, 1.31-1.92) for having relapses during NAB-positive periods. Patients who were positive for NABs showed an increase in the mean EDSS score after 48 months, though the difference between the 2 groups did not reach statistical significance. Time to confirmed progression of 1 point on the EDSS sustained for at least 6 months showed a trend in favor of NAB-negative patients ($P = .14$).

Future Perspectives. The biologic activity of IFN- β can be assessed in vivo by analyses of MxA gene expression.³⁷ Measurement of IFN- β bioactivity in all of the pa-

tients with MS who receive IFN- β therapy might be the future method for detecting antibody-mediated hampering of treatment effect, specifically with regard to disease progression.

Glatiramer Acetate

Glatiramer acetate (GA) is a random, synthetic, basic copolymer of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, the most prevalent amino acids in myelin basic protein.³⁸⁻⁴⁰ This agent is administered as a daily subcutaneous injection that is well tolerated by most patients.

Evidence. In 1995, a multicenter, randomized, 2-year study⁴¹ demonstrated that the clinical benefits in GA-treated patients were similar to those demonstrated in the IFN- β -1b trial. The frequency of clinical MS attacks was reduced by 29%. After approximately 6 years of evaluation, GA showed sustained efficacy in reducing the rate of clinical exacerbations in patients with RRMS.⁴² Magnetic resonance imaging studies of a cohort of patients included in the original trial were performed, and they demonstrated that GA treatment significantly decreased the percentages of annual MRI lesion volume and loss of brain tissue.⁴³

Future Perspectives. The effects of GA on disease progression seem modest. Future trials should assess the effects of GA in combination with other approved or experimental agents.

Mitoxantrone

Mitoxantrone is an antineoplastic agent that intercalates DNA, resulting in DNA strand breaks and inter-strand crosslinks. The major limitation associated with the use of mitoxantrone is related to potential cardiotoxic effects. Mitoxantrone can produce a vacuolar cardiomyopathy, producing a reduction in ejection fraction. Further, there is an increased incidence of leukemia associated with this agent that should be completely discussed with candidate patients before commencing therapy.⁴⁴ Most MS specialists primarily use mitoxantrone for patients who exhibit either inflammatory demyelinating syndromes not responding to corticosteroids or plasma exchange, and for those patients who exhibit neurological deterioration and progression in disability despite first-line therapy interventions.

Evidence. Based on the results of a phase II trial⁴⁵ and a phase III trial,⁴⁶ mitoxantrone was the first drug approved for the treatment of SPMS with worsening relapsing and progressive relapsing disease course. In the phase III trial, the greater of 2 mitoxantrone doses (12 mg/m²) resulted in a 64% reduction in sustained disease progression and a 69% reduction in the number of treated relapses as compared with the placebo control group.

Future Perspectives. Like all of the other approved medications, mitoxantrone should be assessed in combination with other approved or experimental agents in

controlled clinical trials. Similarly, studies are underway to determine whether a strategy is effective in reducing the risk of cardiotoxic effects when administering this agent.

Natalizumab

Natalizumab is a selective adhesion molecule inhibitor used for the treatment of relapsing forms of MS, and it had only recently been approved by the Food and Drug Administration in November 2004. Biogen Idec Inc and Elan Corp, Dublin, Ireland, the manufacturers of natalizumab, then announced the voluntary withdrawal of this agent from the market because of the development of progressive multifocal leukoencephalopathy in 2 patients who had been treated with a combination therapy of natalizumab and IFN- β -1a (Avonex). In addition, the companies have stopped using the drug in clinical trials. It is unclear when and whether this agent will be reintroduced for MS therapy.

EXPERIMENTAL ANTI-INFLAMMATORY AND IMMUNOMODULATORY AGENTS

Currently, clinical trials for numerous pharmacological agents are in the planning stage or are under way. This review will only discuss agents that are already commonly being used in clinical practice. There is no definitive evidence that any of these medications alter the natural course of MS. Particularly, it is unknown whether any of these agents slow disease progression. This point underscores the enormous need for a broader number of randomized, controlled trials to carefully and systematically assess the use of these agents in the management of MS.

Corticosteroids

During the past 2 decades, the use of glucocorticosteroids to treat MS relapses has gained increasing acceptance. There is general consensus that intravenous (IV) methylprednisolone (MP) (administered usually as 500-1000 mg daily for 3-5 days) hastens recovery from MS relapses.^{47,48} It has been found that short-term treatment with IVMP reduces tissue damage and promotes lesion recovery in patients with RRMS.⁴⁹ Moreover, it has been suggested that pulsed IVMP could favorably affect events responsible for early preenhancing lesion formation.⁵⁰ Different mechanisms may explain this hypothesis. There is evidence showing that IVMP restores the blood-brain barrier by down-regulating adhesion molecule expression, inhibits proinflammatory cytokines, reduces matrix metalloproteinase secretion, induces lymphocyte apoptosis, and promotes remyelination.⁵¹

Evidence. There is some suggestion that MP treatment may change the natural course of RRMS.⁵² Results of the Optic Neuritis Treatment Trial⁵³ suggested that IVMP delays development of clinically definite MS following optic neuritis in the long run. However, it was unclear whether the results could be generalized to clinically isolated syndromes other than optic neuritis, or to patients

with RRMS. A randomized, controlled, single-blind, 5-year, phase II clinical trial of IVMP in patients with RRMS demonstrated that prolonged treatment with pulsed IVMP slowed the development of destructive lesions (T1 black holes), the rate of whole-brain atrophy progression, and the development of sustained physical disability.⁵⁰ A phase II, double-blind, dose-comparison study of bimonthly IVMP pulses in patients with SPMS showed no significant improvement related to difference in primary outcome, which was the proportion of patients with sustained disability worsening over 24 months.⁵⁴ However, a beneficial effect was detected with the high-dose IVMP regimen as measured by the preplanned secondary analysis, a comparison of time to onset of sustained progression of disability. Both studies^{50,54} demonstrated that prolonged use of pulsed IVMP was safe and well tolerated, and they concluded that phase III trials of corticosteroids in RRMS and SPMS are warranted to more definitively establish the role of pulsed IVMP as a disease-modifying therapy, either alone or in combination with other agents.

A randomized, double-blind, placebo-controlled pilot study of IV immunoglobulins (IVIgs) in combination with IVMP did not demonstrate superiority of IVMP-IVIg in the treatment of moderate-to-severe acute relapses in MS.⁵⁵

Future Perspectives. Two recently published studies^{55,56} investigated the effect of glucocorticosteroids as add-on therapy to standard disease-modifying therapy in patients with MS. Two other multicenter combination trials have been launched to investigate the efficacy of IVMP as an add-on therapy to standard treatments. The Avonex Combination Therapy study will assess the benefit of IFN- β -1a (Avonex) combined with bimonthly IVMP in patients with RR breakthrough disease. Another double-blind, controlled trial will evaluate the efficacy of IFN- β -1b (Betaseron) alone or in combination with bimonthly IVMP in patients with SPMS.

IVIg

Some patients fail to respond to standard treatments and continue to worsen over time, with the occurrence of additional relapses associated with neurological deterioration and no apparent effect of the immunomodulatory treatment. Other groups of patients who are not suitable for standard treatments include (1) patients who develop intolerable adverse events, (2) patients who are non-compliant to self-injections or are reluctant to take injectable medications, and (3) female patients who are contemplating becoming pregnant.

Intravenous Ig modulates the immune system by various mechanisms, such as macrophage Fc receptor blockade, idiotypic-anti-idiotypic networking, decreasing T-cell activation, and enhancing remyelination in virus-induced experimental encephalomyelitis, which are all relevant to MS.

Evidence. Intravenous Ig treatment has been described to be beneficial for patients with RRMS.⁵⁷⁻⁶⁰ Relapse rate, relapse severity, progression of disability, and disease activity evaluated by brain MRI were all found to be posi-

tively affected by IVIg treatment. Four double-blind trials^{61,62} in RRMS have demonstrated that IVIg reduces the relapse rate and the number of gadolinium-enhancing lesions, and in this respect, IVIg seems comparable to the established therapies, ie, IFN- β and GA.^{61,62} Owing to the relatively small sample size of these studies, a meta-analysis⁶³ was recently undertaken, and it demonstrated a significant beneficial effect of IVIg on the annual relapse rate (effect size, -0.5 ; $P < .001$) as well as on the proportion of relapse-free patients and change in neurological disability by the EDSS score. In another small-sample study,⁶⁴ quantitative brain MRI analysis showed a statistically significant decrease in the volume of lesions in IVIg-treated patients with RRMS as compared with patients treated with placebo, at follow-up at both 3 and 6 months. Taken together, these studies support the possibility of using IVIg to treat patients with MS who do not respond to standard treatments.

Future Perspectives. The definite role of IVIg and the extent of its efficacy in the management of patients with progression and/or breakthrough disease should be established in large and long-term double-blind studies. Further, given the heterogeneity of treatment response and the high cost of IVIg, it will be important to elucidate factors that can stratify patients into groups who are either inappropriate or appropriate candidates for treatment.

Azathioprine

Azathioprine (AZA) is a nonspecific immunosuppressant that was first proposed in MS treatment 30 years ago.⁶⁵ It interferes with the biosynthesis of nucleic acids, particularly during the S phase of the mitotic cycle. Azathioprine is believed to primarily affect immature immunocytes and to have little or no effect on mature components of antigenic memory.⁶⁶ One in 300 subjects will experience intolerance to AZA, characterized by effects toxic to bone marrow secondary to a homozygous polymorphism for thiopurine methyltransferase deficiency. Eleven percent of subjects are heterozygous and have intermediate levels of thiopurine methyltransferase activity; the remaining 89% of subjects are homozygous for the allele for high activity. Human thiopurine methyltransferase activity can be easily measured in red blood cells.⁶⁷ In cases of repeated viral infection, immunodeficiency should be excluded, and the dose of AZA should be reduced or the therapy should be changed, especially in cases of herpetic infection. The most concerning risk of AZA treatment has been the putative risk of cancer. In fact, no significant risk was observed during the first years of treatment, and an increased risk was suggested only after approximately 10 years of continuous use, especially in patients who also have other risk factors for cancer.⁶⁸

Evidence. In 1991, a meta-analysis⁶⁹ of all of the published randomized, controlled trials of AZA in MS suggested that AZA significantly decreased the relapse rate and marginally significantly reduced the increase in disability after 2 and 3 years of treatment. Not all of these trials had acceptable methodology, and all of them were

performed in the pre-MRI era. At the present time, however, there is an increasing number of articles supporting positive effects of AZA on the number of T2, new T1, and gadolinium-enhancing lesions.⁷⁰⁻⁷² Most studies carried out in recent years have been designed to test AZA in combination with other approved drugs. In terms of safety and tolerability, 10% to 20% of patients may complain of gastrointestinal discomfort at the beginning of treatment, and in some, this may limit the use of AZA.

Future Perspectives. Azathioprine has been proposed as a suitable candidate drug in combination with IFN- β or IVIg. Small pilot trials have demonstrated acceptable safety and possibly efficacy commensurate with already established monotherapies. Larger, adequately blinded, controlled trials are in progress.

Methotrexate

Methotrexate is an inhibitor of dihydrofolate reductase, which results in anti-inflammatory effects by reducing the release of T_H1 cytokines. Traditionally used in substantial doses for malignancies, low weekly dose regimens have been applied to a number of immune-mediated disorders.

Evidence. A randomized, double-blinded, placebo-controlled trial⁷³ of low-dose methotrexate (7.5 mg/wk) was performed in 45 patients with MS (of various types). This small study provided some evidence to suggest a beneficial effect in those with a relapsing disease course but not in those with progressive disease. In a study⁷⁴ conducted to demonstrate the therapeutic benefit in patients with either primary MS or SPMS, patients were randomized to receive either placebo or low-dose methotrexate (7.5 mg/wk). A composite outcome measure using measures of ambulation (EDSS and ambulation index) and upper extremity function (9-hole peg test and box-and-block test) demonstrated benefit in patients treated with methotrexate. The beneficial effect on the composite score was principally driven by change on the 9-hole peg test.

Future Perspectives. A new combination clinical trial initiative (Avonex Combination Therapy study) is under way to assess the merits of using methotrexate with corticosteroids and IFN- β .

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a selective inhibitor of inosine 5'-monophosphate dehydrogenase type II that is a potent immunosuppressant principally used in transplant medicine as an antirejection agent.⁷⁵ This enzyme is responsible for the de novo synthesis of the purine nucleotide guanine within activated T and B lymphocytes and macrophages without affecting purine salvage pathways. Mycophenolate mofetil exhibits the capability to suppress lymphocyte proliferation and the expression of T-cell surface antigens in whole-blood lymphocyte analysis derived from treated allograft recipients.⁷⁵⁻⁷⁸ In activated lymphocytes, metabolites of MMF inter-

rupt cytokine-dependent signals that control the cell cycle, and they block activation of T cells in the mid-G(1) phase. Humoral effects have also been observed, with MMF suppressing anti-blood-type IgG antibodies in patients receiving ABO-mismatched renal transplants.⁷⁹

Evidence. A small, open-label surveillance study⁸⁰ involving 7 patients with MS who were treated with MMF was described in 2001, and it suggested evidence of tolerability and potential efficacy in this small cohort. We have recently extended this observation with our open-label, exploratory surveillance safety experience with MMF in 79 patients with MS.⁸¹

Future Perspectives. The favorable safety profile, novel mechanism of action, and ease of administration make MMF a potentially useful agent to be used as monotherapy or in conjunction with IFN- β or GA. Mycophenolate mofetil has a specific molecular target through which it mediates its therapeutic effect. Characterizing polymorphisms of the inosine monophosphate dehydrogenase gene may provide for the opportunity to identify patient populations that are more or less likely to respond favorably to this agent.

Statins

Several studies⁸²⁻⁸⁵ indicate that cholesterol-lowering 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have immunomodulatory properties that may be beneficial in the treatment of MS. In contrast with currently approved medications used in MS therapy, which are administered parenterally and are associated with adverse and potentially toxic effects, statins are given orally and, in general, are well tolerated. Several years ago, it was observed that statins inhibited CNS glial cells from producing proinflammatory molecules, including tumor necrosis factor α , nitric oxide synthase, and interleukin 1 β .⁸⁶ More recently, it was observed that in vivo treatment with atorvastatin calcium (Lipitor; Pfizer Inc, New York, NY) promoted a protective T_H2 bias and could reverse relapsing and chronic paralysis in experimental autoimmune encephalomyelitis in the MS model, a model of inflammatory demyelination.⁸³ Atorvastatin calcium inhibited the up-regulation of major histocompatibility complex class II and costimulatory molecules on antigen-presenting macrophages and microglial cells. Mevalonic acid, the product of 3-hydroxy-3-methylglutaryl coenzyme A reductase, prevented atorvastatin calcium-induced T_H2 differentiation and reversed the statin-induced effects on macrophages and microglial cells, indicating that the immunomodulatory effects are mediated through inhibition of the mevalonate pathway, which involves isoprenoid intermediates that participate in post-translational modification of key proteins that direct T-cell differentiation and activation.

Evidence. The beneficial immunomodulatory effects observed in experimental autoimmune encephalomyelitis and other autoimmune models have provided the impetus to test statins in MS and other T_H1-mediated inflammatory diseases. An open-label phase II trial⁸⁷ tested sim-

vastatin (80 mg; Zocor; Merck & Co Inc, Whitehouse Station, NJ) in 30 patients with RRMS for 6 months, and a 44% reduction in the number of new gadolinium-enhancing lesions and a 41% reduction in volume of new enhancing lesions were observed. It is not known whether this modest reduction in new lesions represented a true effect of Zocor or regression to the mean, as patients enrolled in this trial were selected for MRI activity.

Future Perspectives. It is clear that larger, placebo-controlled statin trials will be advantageous in evaluating the clinical and immunomodulatory effects of statins in MS. A placebo-controlled 152-patient phase II trial that will test whether 80 mg of Lipitor will reduce MS activity in patients who have experienced their first CNS demyelinating attack, a "clinically isolated syndrome," will begin shortly.

Plasma Exchange

Plasma exchange is an effective, short-term treatment for acute inflammatory demyelinating polyneuropathy. The underlying hypothesis is that humoral factors, including but not necessarily restricted to immunoglobulins, account for the ongoing inflammatory demyelination in steroid-refractory attacks of MS and other CNS inflammatory demyelinating diseases.⁸⁸⁻⁹⁰ By removing these humoral factors, recovery from acute, severe attacks might be facilitated.

Evidence. A single previous sham-controlled clinical trial⁹¹ in patients with attacks of MS gave equivocal results. A randomized, sham-controlled clinical trial⁹² of 22 patients with acute steroid-refractory attacks of MS (n=12) or other idiopathic inflammatory demyelinating diseases (n=10; including acute transverse myelitis, neuromyelitis optica, acute disseminated encephalomyelitis, and focal cerebral demyelinating disease) showed that plasma exchange was effective in producing moderate or greater recovery within 2 weeks. Uncontrolled experience by the same group and subsequent case reports have further documented the benefits of plasma exchange.^{93,94}

Future Perspectives. The biological basis of the improvement is under continued evaluation by correlative studies including the histopathology of lesions (specifically, the presence of immunoglobulin and markers of complement activation in brain tissue).⁹⁵ Passive transfer of the demyelinating activity would confirm the humoral basis of the effect and would provide a bioassay that would enable further isolation and identification of the specific factors that are responsible for the demyelinating activity.

Cyclophosphamide

Cyclophosphamide, first tested in MS in 1966,⁹⁶ is an alkylating agent used to treat malignancy. Cyclophosphamide has pronounced immunologic effects that involve not only the suppression of T_H1-type responses, but also immunomodulation associated with increases in interleukin 4, interleukin 10, and transforming growth factor β . The adverse effects of cyclophosphamide are well known and include toxic effects in the bladder, infertili-

ty, infection, and cancer risk. Toxic effects in the bladder are generally well managed by adequate fluid intake. The maximum recommended total dose is 80 g. Cyclophosphamide can also be used for short periods of time, eg, pulses monthly for 6 months in patients who need better control on injectable therapy. Data from the lupus nephritis literature suggest that the drug is more effective if given with steroids, and another study⁹⁷ demonstrated that pulsed cyclophosphamide given with steroids is superior in decreasing inflammation as compared with steroids given alone to patients who do not respond to IFN.

Evidence. During the past 30 years, cyclophosphamide has been used for the treatment of selected patients with MS. There have been more than 40 articles on the clinical and immunologic effects of cyclophosphamide in MS. Initial trials suggested a clinical benefit in patients with RRMS and relapsing forms of this disease.⁹⁸⁻¹⁰² However, 2 randomized, clinical trials^{103,104} in patients with SPMS did not demonstrate any effect on the progression of neurological disability. Not surprisingly, the results of these studies initially led to conflicting opinions regarding the use of cyclophosphamide in the treatment of MS.

Future Perspectives. A recent large study¹⁰⁵ of 490 patients suggests that response at 6 months following treatment may predict who in the progressive stage of the disease may be helped by such therapy. Our experience corroborates the observation that those patients who exhibit ongoing clinical and radiographic evidence of disease activity are the most likely to benefit from this therapy.

NEW TREATMENT STRATEGIES

Novel Therapeutic Targets

In the past, our treatment efforts have focused on modulating immunological responses to presumed foreign antigens or self-antigens. This strategy has been successful with regard to treating disease relapses and inflammation. However, there is now a broad consensus among MS specialists that neurodegeneration and the failure to repair damaged CNS tissue may play a critical role in accumulating clinical disability. The Nogo-A protein is a member of the reticulon family present in myelin. It has been demonstrated that Nogo-A inhibits neurite regrowth,^{106,107} which may be a relevant mechanism in incomplete recovery from an MS attack. Several therapeutic strategies aimed at improving axonal regeneration have been used to try to block interactions between Nogo-A and its receptors.¹⁰⁸⁻¹¹² Another potential therapeutic target may be glutamate and its receptors. The possible role of glutamate excitotoxicity in MS was recently demonstrated in experimental autoimmune encephalomyelitis.¹¹³ It was also demonstrated that imbalanced glutamate homeostasis may contribute to axonal and oligodendroglial pathological abnormalities in MS.¹¹⁴ A rational future pharmacotherapy to prevent disease progression may be the combination of anti-inflammatory agents with compounds that reduce neurodegeneration.

Combination Therapy

Combination therapy constitutes treatment with 2 or more medications to improve clinical outcomes. In numerous autoimmune diseases, combination therapy is the standard of care, especially for patients who continue to progress while receiving monotherapy. Ideally, medications chosen for combination therapy should (1) produce an additive or synergistic effect, (2) have nonoverlapping toxic effects, and (3) have different modes of action. While there is currently no evidence that any particular combination of approved or experimental agents would improve the clinical outcome in MS, the recognition that enhanced control of the disease process may be better achieved by instituting multicomponent treatment regimens has been recognized by neurologists and scientists. The ability to down-regulate different “switch points” along the injury cascade in MS could potentially uncouple the coordinated interplay of pathogenetic steps that ultimately culminate in inflammatory demyelination, neurodegeneration, and irreversible physical and cognitive disabilities.

EARLY TREATMENT INITIATIVES SUPPORT EARLIEST INTERVENTION

Remarkable changes have occurred in our ability to diagnose and treat MS. The presentation of a clinically isolated syndrome of inflammatory demyelination in conjunction with the presence of characteristic demyelinating lesions disseminated in regions other than that which has produced the clinical syndrome strongly predicts future conversion to clinically definite MS (multiple events in space and time).¹¹⁵ It would appear that such patients already have MS, given that the histopathological profiles of the lesions present at baseline are virtually indistinguishable from those in patients with confirmed MS by traditional diagnostic criteria.^{116,117} Equipped with this new information, we are faced with the prospect of setting a new precedent in the way we approach the diagnosis and treatment of MS.

There have now been 3 Class I early treatment trials for patients with clinically isolated syndromes.^{27,118,119} In these studies, substantial clinical and radiographic benefits were achieved in those randomly assigned to active treatment (IFN- β or IVIg) vs those who received placebo. These observations confirm the suspicion that such patients appear to benefit from MS disease-altering therapy, even before the diagnosis of clinically definite MS is confirmed by conventional approaches. Almost all of these patients have MS at the time of the initial clinical presentation.¹¹⁵ In fact, up to 80% of patients with a clinically isolated syndrome already have radiographic evidence of disease activity (T2 or fluid-attenuated inversion recovery lesions without gadolinium enhancement) predating the onset of the first clinical presentation.¹²⁰⁻¹²²

In the near future, a new standard of care for MS will evolve, particularly one focused aggressively on the earliest possible identification so that immediate treatment intervention can ensue. It appears that the early phase of the disease (characterized by relapses and new MRI lesions) is more responsive to anti-inflammatory agents

as compared with the disease in those patients with longer-standing disease or progressive forms of the illness. The transition from relapsing to progressive disease likely signals important changes in the pathological cascade and in treatment responsiveness.

COMMENT

Understanding the underlying mechanisms that constitute progression in MS represents one of the most formidable challenges in modern neurobiology. Correspondingly, without such insights, it will be equally challenging to rationally design combination therapy regimens to target the various injury cascades that underlie the final pathways that culminate in changes in brain and spinal cord tissue architecture and the consequent changes in neurological capabilities. Elucidating the genetic, pharmacogenetic, and proteomic rudiments of MS will translate into great dividends for patients with MS and for those who have a predilection for the development of this most common disabling neurological disease.

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