Multiple sclerosis

Recent modalities of treatment

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ABSTRACT

Multiple sclerosis (MS) has devastating physical, psychological, and economic consequences. The disease commences in most patients with a relapsing–remitting course, and it is likely that treatment is most effective during this phase before permanent axon damage has occurred. Despite the absence of a cure for MS, the 4 available drug therapies (Interferon (IFN) ß-1a, IFN ß-1b, glatiramer acetate, and mitoxantrone) play a role in the management of MS based on their demonstrated efficacy. In particular, the use of disease-modifying drugs has been shown to reduce the frequency and severity of debilitating relapses and to delay disease progression. Efforts to develop alternative therapies with increased efficacy and patient acceptability are in progress.

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We now realize, with better understanding of the natural history of multiple sclerosis (MS) that the condition leads to disability in the majority of cases. While only 5% will be wheelchair or bed bound 5 years after their first relapse, a full 40% will need assistance with ambulation by their 10th year. Ninety percent of cases follow a relapsing-remitting course (RRMS), with freedom from symptoms and signs between attacks.[1] However, with progress of the condition, there is increased neurological deficits persisting after a given number of attacks; this is termed a "secondary progressive" phase (SPMS).[1] Unlike the usual relapsing-remitting course, 10% of cases of "primary progressive MS" (PPMS), present with the insidious onset of progressive neurological deficits, most typically a spastic paraparesis.[2] Primary progressive MS appears to involve less inflammatory and more neurodegenerative pathology. Lastly, when the disease is stable, in remission, "burnt out," sufferers are unlikely to obtain or perceive benefit from the currently available immunotherapy. The challenge is figuring out, at the diagnosis of MS or a first attack of demyelination (and someday perhaps even preclinically), who is destined to have this benign form of MS and who will have more active or even malignant MS. It is therefore becoming increasingly important to be able to prognosticate the future disease course.[3,4] Parameters associated with good prognosis include: a long interval between the first and the second (MS-defining) attacks; absence of residual neurologic deficit after the first attack; a relatively benign 2- and especially 5-year course of MS; pediatric onset MS, though such individuals have a longer life span remaining to manifest disease activity and disability; absence of cerebrospinal oligoclonal immunoglobulin G (IgG) bands; a normal or low MRI scan disease burden at the time of an MS diagnosis.[5-6] Many physicians are now reluctant to withhold immunotherapy, as clinical indicators do not always correlate with pathological involvement. Serial MRI scan studies have demonstrated 5-10 times more disease activity seen clinically, with relentless accumulation of disease burden and brain atrophy even in early and

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clinically mild MS (and even some cases of "benign" MS). High MRI disease burden appears to correlate with future disability and with neurocognitive deficits.[7] Repeat "surveillance" MRI scan at arbitrary intervals, looking for new T2, fluid attenuated inversion recovery (FLAIR), especially gadolinium-enhancing lesions, are increasingly being used to either reassure the patients or for making the decision to start immunotherapies. However, routine scans are not standardized and their quality is often too poor for meaningful comparisons or therapeutic decisions. There is a critical need to standardize protocols used to diagnose and monitor MS and suspected MS.[8] The new MRI-based McDonald criteria for MS diagnosis will hopefully fill that gap.[8,9]

Treatment of MS. The goals of treatment are to 1. Reduce relapse rates. 2. Prevent fixed disability directly attributable to relapse. 3. Provide symptomatic relief management of fixed neurological deficits. 4. Prevent disability acquired through progression. 5. Treat established progression.

Relapse reducing treatments. In the last decade, 4 new treatments have been Federal Drug Agency (FDA) approved for the treatment of relapsing multiple sclerosis. These are interferon (IFN) beta 1b (Betaseron®), IFN beta 1a (Avonex®), (Rebif®) and glatiramer acetate (Copaxone®). All of these reduced the frequency of clinical attacks of MS and the number of new or enhancing MRI lesions in randomized, double-blinded, placebo-controlled clinical trials involving patients with relapsing MS.[10,11]

Interferons: overview. Interferons are naturally occurring cytokines with a variety of immunomodulating and antiviral activities that may account for their therapeutic utility.[12,13] Two major types have been identified: IFN α and IFN ß (type I) and IFN γ (type II).[14] The beta-interferon products were approved for the treatment of MS.[15] They are not considered interchangeable, mainly because of differences in administration schedules adverse events and clinical efficacy.[14,16] Differences in antigenicity and the formation of neutralizing antibodies have also been suggested.[15,17]

Interferons: efficacy. Interferon ß-1b (Betaseron). Administration subcutaneously every other day reduced the exacerbation rate by approximately one-third compared with placebo.[18] The severity of relapses was also reduced and maintained for a median period of approximately 46 months.[18,19] The Expanded Disability Status Scale (EDSS) scores changed minimally in all treatment groups and there was, no apparent reduction in confirmed disease progression based on this end point. On the basis of available annual MRI data throughout 4 years of treatment, IFN ß-1b 0.25 mg was associated with reduction in lesion area each year. In contrast, increases in lesion area were observed each year in the placebo and IFN ß-1b 0.05-mg groups. A post-hoc analysis of annual MRI scans showed that IFN ß-1b treatment reduced the appearance of new lesions, and the enlargement of existing ones.[20] Subsequent studies, including open-label trials, have shown that IFN ß-1b also reduces the number of gadolinium (Gd)-enhanced MRI lesions (T1-weighted) by almost 90%. These MRI effects of IFN ß-1b occur within weeks of initiation of therapy.[21,22] Follow-up studies have, however, demonstrated considerable individual variability, which suggests that monitoring may be needed in most cases to determine sustained efficacy.[23,24]

Interferon ß-1a (Avonex). Once-weekly intramuscular injections of 6 MIU (30 µg) of Avonex delayed the time to sustained disability progression of ≥1 unit on the EDSS score (n=85 IFN-treated patients, n=87 placebo-treated patients who completed 104 weeks of study; p=0.02).[25] The annual relapse rates, a secondary end point, were 0.61 for the Avonex group and 0.90 for the placebo group (p=0.002, a difference of 32%) for patients who completed 104 weeks of study.[25] Additional post-hoc analyses indicate that Avonex treatment slowed progression of disability and reduced clinical exacerbations.[26,27] In another study, Avonex therapy decreased the number of new T2 lesions and enlarging T2 lesions over 2 years.[28-30] The effects of Avonex on cognitive function were evaluated in a study of 166 patients with RRMS.[31] Based on a comprehensive neuropsychological battery, Avonex therapy had a beneficial effect on information processing and learning/memory.

Interferon ß-1a (Rebif). In a 2-year clinical trial (n=560), both a low (22 µg, 6 MIU) and a high (44 µg, 12 MIU) dose of Rebif administered 3 times weekly reduced the number of clinical relapses.[32] Additional analyses using "area under the disability/time curve" to assess the overall disability experience confirmed the benefits of Rebif therapy.[33] Time to sustained disability progression was prolonged by 18 months in the group receiving the 44-µg dose for 4 years compared with a group that received placebo during the first 2 years of study (p=0.047). Although more long-term data are needed, these results show the potential benefit of Rebif therapy on modifying the natural course of MS during the 4-year study period.[34] The benefit from both doses compared with placebo was noted in MRI analyses of burden of disease (namely by proton density T2 MRI) and in the mean number of active MRI lesions at each scan. There was a dose effect for these end points favoring the high-dose group compared with the low-dose group.[32,35] As with Avonex, the benefits of early intervention with Rebif have been studied. Fewer patients developed clinically definite MS while taking Rebif [52/154

(34%)] than placebo [69/154 (45%); p=0.047].[36] The time to 30% of patients converting to clinically definite MS was delayed by 9 months in the active treatment group (p=0.034). This study also confirmed benefits of Rebif on annual relapse rate compared with placebo (0.33 for the Rebif group, 0.43 for the placebo group; p=0.045). The number of new T2-weighted MRI lesions and the increase of lesion burden were also significantly lower with active treatment.

Glatiramer acetate. Glatiramer acetate is a mixture of synthetic polypeptides containing 4 amino acids: L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. This polypeptide mixture was originally designed to mimic myelin basic protein (MBP). The mechanism of action of glatiramer acetate is distinct from that of IFNs. Therefore, an individual patient may respond differently to glatiramer acetate not only with respect to side effects but also in terms of effects on their MS disease activity. The drug down regulates the inflammatory and autoimmune responses associated with MS.[37,38] The effects of glatiramer acetate may be mediated through selective actions on T cells that suppress proinflammatory cytokines and elevate anti-inflammatory cytokines. Glatiramer, in particular, acetate binds to class II major histocompatibility complex molecules that are involved with antigen presentation to T cells. Glatiramer acetate (20 mg subcutaneously every day) has also been shown to reduce the frequency of relapses by approximately one-third.[39,40] Analyses of changes in disability (EDSS score) showed that more patients in the glatiramer acetate group improved, whereas more patients in the placebo group worsened. An extension of a pivotal 2-year study provided a total blinded treatment period of up to 35 months and confirmed the tolerance and safety profile of glatiramer acetate.[41] At the end of the extension trial, there were significant differences favoring glatiramer acetate over placebo in the mean relapse rate and proportion of patients who remained relapse-free. More recently, extended observations for up to 6 years have confirmed the long-term benefits of glatiramer acetate therapy.[42] In this extension phase of the trial, consisting of 152 of the original 251 patients, the relapse rate was reduced to a mean of 0.42 exacerbations per year and 0.23 for the sixth year of the study (in 83 patients who were originally randomized to glatiramer acetate). The mean EDSS remained stable or improved in 69% of these patients. In the MRI studies, the benefits of glatiramer acetate therapy included decreases in the number of contrast-enhanced lesions and in the percent annual change of lesion volume compared with placebo.[43,44] The results of a randomized, double-blind, placebo-controlled study (n=239) at 29 centers in Europe and Canada showed that patients treated with glatiramer acetate had a significant reduction in total enhancing lesions, with a mean of 25.96 enhancing lesions versus 36.8 for placebo patients (mean difference of -10.8, a 29% reduction; p=0.003).45 In addition, the reduction in relapse rate over 9 months was 33% for the glatiramer acetate-treated group (p=0.012). These results confirm the effects of glatiramer acetate on MRI-measured pathology.[45,46] Patients who switched from placebo to glatiramer acetate showed a significant reduction in mean number of enhancing lesions (12.6 to 5.9; p<0.0001) and mean volume of enhancing lesions (1.8 to 0.8 ml; p<0.0001). The median percent change of T2 lesion load was 17.4% in patients initially randomized to placebo and 13% in patients treated with glatiramer acetate throughout the study (p=0.018). In the open-label extension of a pivotal trial, the risk of finding an enhancing lesion on MRI was 2.5 times greater for patients originally randomized to the placebo group but who switched to glatiramer acetate (for approximately 4 years of active treatment) compared with those who always received glatiramer acetate (for an average of 6.7 years).[47]

Interferon ß in primary progressive MS. Ten to 15% of patients with MS have PPMS, which is characterized by the progressive accumulation of neurologic deficit from disease onset without relapse or remission.[1] Patients with PPMS have atypical clinical, MRI, and pathologic characteristics that create difficulties for patient selection and therapeutic monitoring in treatment trials, resulting in a paucity of trials in this population.[48-50] Immunomodulators, such as IFN β 1a or 1b, have shown some efficacy, particularly in patients with a still inflammatory form of secondary progressive MS.[51-54] Other studies support the feasibility of therapeutic trials in PPMS. A pilot trial of riluzole has also been completed in this group and exploratory studies of interferon β-1b and mitoxantrone and a large, multicenter, phase III trial of glatiramer acetate are under way.[55-59]

When to initiate therapy. Evidence is accumulating that the best time to initiate disease-modifying treatment is early in the course of the disease.[60,61] Data indicates that irreversible axon damage may occur early in the course of RRMS[51] and that available therapies appear to be most effective at preventing new lesion formation but do not repair old lesions. With disease progression, the autoimmune response of MS may become more difficult to suppress due to epitope spreading. It is hypothesized that pathogenic immune cells initially respond to only one antigen but subsequently gain the capacity to respond to many related antigens.[62,63] It may be useful to repeat the brain MRI in 6 months or one year to determine how quickly the disease process is evolving.

Switching therapies. There are few data regarding the benefits of switching therapies for MS. Problems with tolerability, lack of response, or loss of efficacy might be reasons to switch therapies. In-patients receiving an IFN, loss of efficacy may be attributed to the development of neutralizing antibodies (Nabs), although the relationship is controversial. Interferon ß-1a and IFN ß-1b cross-react in both binding and biologic assays, suggesting no benefit in switching to the other form of IFN ß in treatment-refractory patients who have a high Nab titer.[64,65] Data from open-label studies showed that glatiramer acetate was effective and well tolerated in patients who had previously received IFN therapy.[66,67]

Oral disease-modifying agents. Oral disease-modifying agents would offer significant benefits in terms of convenience and acceptability for patients with RRMS. Preclinical studies show that orally administered glatiramer acetate inhibited development of experimental autoimmune encephalomyelitis (EAE).[68] Oral glatiramer acetate has been demonstrated to be safe and well tolerated in initial clinical trials, and further investigations, including a large-scale phase III trial (the CORAL study), show progress in RRMS.[69,70] Oral IFNα is effective in EAE and has also been tested clinically.[71,72] Thirty patients (10 per group) were randomized to receive either 10,000 IU IFN2a, 30,000 IU IFN2a, or placebo ingested on alternate days for 9 months. Interferon therapy did not exhibit a significant effect on enhancing lesions, clinical relapse or adverse events. Despite the lack of benefit on the primary outcome measure, a post-hoc analysis suggested a possible effect of the 10,000-IU dose, because there were 73% ($p<0.05$) fewer enhancements in the 10,000-IU group than in the placebo group at month 5.[70,71]

Combination therapy. Several trials are studying the addition of oral immunosuppressive drugs, intravenous Ig, or glatiramer acetate to IFN ß in patients who continue to display disease activity. The rationale for this approach is based on experience with other diseases, but further testing is required both to ensure its safety and to ensure that the mechanism of action of one drug does not interfere with that of the other drug. A 6-month trial of Avonex administered along with glatiramer acetate suggests that the combination is safe, setting the stage for longer-term trials to assess clinical efficacy.[72,73]

Does intravenous immunoglobulin enhance recovery in MS? A non-randomized, placebo-controlled crossover trial of intravenous immunoglobulin failed to demonstrate improvements in central motor conduction time in 10 RRMS patients.[74] In a randomized, double-blind, placebo-controlled study, intravenous immunoglobulin was not shown to reverse long-standing motor deficits in 67 patients with established weakness.[75]

Antigen-specific immunotherapy. Two phase II trials of specific immunotherapy designed to block T cell response in RRMS using altered peptide ligands (APL) of myelin antigens were reported in 2000. The APL administered in the first trial (CGP77116) was poorly tolerated (continued relapses, systemic hypersensitivity reactions) despite dose reduction, and was terminated when only 8 of the planned 24 patients had been enrolled.[76] Two of the 3 patients with on-study relapses developed high precursor frequencies of T cells reacting to both the APL and MBP, suggesting that treatment may have led to increased disease activity. The second trial was also terminated for safety reasons when hypersensitivity reactions developed in 9% of the 142 enrolled patients.[77] Immunological studies demonstrated that treatment was followed by regulatory Th2 responses to APL and MBP in the study. There was MRI evidence that the low dose of the APL in the study (NBI5788, 5 mg subcutaneously once a week; dose range tested in trial: placebo, 5, 20 and 50 mg) was followed by reduced subclinical disease activity, but the short trial duration prevented any evaluation of meaningful clinical efficacy. Such studies illustrated both the potential for benefit and harm with immunotherapy, and further work is in progress with these treatment approaches. The intravenous administration of different doses of a solubilized complex of human leukocyte antigen-specific DR2 with MBP (AG284) was safe, but produced no clinical or MRI effect or cell tolerance to MBP or MBP in 33 patients with SPMS.[78-80]

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