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Pharmacological Treatment of Early Multiple Sclerosis

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Abstract

Currently, six medications are approved by the US FDA for the treatment of relapsing forms of multiple sclerosis (MS). In contrast, no pharmacological agent has proved to be effective in patients with secondary-progressive MS without relapses, or in patients with primary-progressive MS. One of the principal issues concerning an optimal pharmacotherapy for relapsing forms of MS is the optimal time of treatment initiation. There is now an almost universal consensus among MS experts that many patients will benefit from early therapy. However, several formidable challenges exist in identifying individuals who will benefit versus those who will do well without intervention. How do we define early MS and what clinical and paraclinical markers may be useful in defining the timing and nature of therapy? Do patients with a benign form of MS require therapy or are they exposed unnecessarily to adverse effects of our currently available medications? How do we identify disease progression and treatment failures? This review discusses these issues and outlines the evidence for application of 'early' treatment in patients with relapsing forms of MS.

1. Early Forms of Multiple Sclerosis (MS)

In the past, documentation of clinically definite multiple sclerosis (CDMS),[1] defined as two clinical events separated in time and space, was an absolute requirement prior to starting treatment. In contrast, it is now acceptable to treat patients with a so-called clinically isolated syndrome (CIS), given the results of early treatment trials in CIS subjects with two or more T2 lesions on magnetic resonance imaging (MRI).[2-4] Indeed, 80% of patients with a CIS who go on to have CDMS already have radiographic evidence of multiple sclerosis (MS) at the time of their initial presentation,[5-12] indicating that the first documented clinical event may not represent 'early MS' at all. In addition, ascertainment of the first clinical event is not always easy for the examining physician. Not infrequently, patients describe antecedent symptoms that might suggest a disease onset earlier than the actual CIS, but that were not adequately documented. Because neurologists do not have the ability to predict when an individual will have their first or second clinical symptom of MS, waiting for new clinical or radiographic manifestations of disease activity in 'at-risk' individuals may allow demyelination and neuronal injury to proceed unchecked.

There is accumulating evidence that subclinical inflammation, demyelination and neurodegeneration may be present for months, or even years, before a patient experiences clinical symptoms. Several studies have demonstrated that occult MRI lesions consistent with MS may be present in as many as 18% of healthy monozygotic twins of patients with this disorder.[13-16] Oligoclonal bands in cerebrospinal fluid were detected in 12 of 17 (71%) identical twins without MS and antedated clinical manifestations of disease.[17] Ultimately, the ascertainment of the first clinical event is, in many cases, a highly complex and often elusive process for the examining physician. Not infrequently, patients describe medically undocumented antecedent (and sometime highly remote) symptoms that might suggest a disease onset earlier than the actual CIS.

If a patient with a CIS can clearly be identified, the question arises as to whether there is a biological difference between the interval separating the first and the second attack, versus that separating the second and subsequent attacks. Intuitively, the answer would probably be no. Clinically, it is often not possible to reliably detect evidence (generally in the form of signs) to confirm the early compromise of healthy brain and spinal cord tissue. Therefore, neurologists currently rely on neuroimaging techniques to monitor disease progression and treatment responses. The extensive white matter and grey matter injury of the CNS, even in the case of early MS, is now well documented.[18-20]

The loss of *N*-acetylaspartate (NAA) may be a particularly important, sensitive and early marker for loss of neuronal function and/or integrity.[21] Proton MRI spectroscopy (1H-MRS) studies in patients with a CIS showed a substantial reduction in NAA concentrations of the whole brain, and increased amounts of myo-inositol and creatine in normal-appearing white matter.[22,23] Another MRI disease surrogate marker, brain atrophy, deteriorates at faster rates in patients with early relapsing-remitting MS (RRMS) than in advanced RRMS or secondary-progressive MS (SPMS).[24,25] Interestingly, progressive brain atrophy is one of the best predictors of cognitive and physical disability from the earliest disease stages.[26] Numerous MRI studies have provided evidence for irreversible tissue damage in some patients with a CIS.[22,23,27-29] Specifically, a reduced magnetisation transfer ratio (MTR), a measure that helps characterize the integrity of myelin architecture, was detected to be already abnormal in the normal-appearing brain tissue of patients with CNS demyelinating disease at the time of the initial presentation.[27,28] The extent of these abnormalities was shown to be an independent predictor of subsequent disease evolution.[27,28] Another imaging technique, diffusion tensor imaging, was utilized to detect an increased mean diffusivity (signifying a loss of organ tissue barriers to water diffusion and thereby reduced tissue architecture) and a decreased fractional anisotropy (a measure of water diffusion along geometrically ordered tract systems such as the corticospinal tract or the cerebellar peduncles) in the normal-appearing white matter of these patients.[30] Both of these surrogate markers have been used to demonstrate the breadth and extent of altered tissue architecture in early MS.[31]

A second key question is whether the degree of tissue damage differs quantitatively between patients with very early forms of MS and later stages of the disease. The intuitive answer, given the clinical progression of neurological disability, would be an unequivocal yes. Indeed, substantial evidence now suggests that the extent and rate of axonal and neuronal injury is milder in CIS than in RRMS patients. One study that followed 55 patients with a CIS for 3 years prospectively showed that after the first year, patients who evolved to have CDMS[32] developed significantly more brain atrophy than did those without disease evolution.[20,33] After 3 years, 53% of the patients had met criteria for MS and patients with MS still displayed more ventricular enlargement.[20] Similarly, the average lesion and brain MTR values have been found to be lower in patients with RRMS than in those with a CIS. Taken together, these findings are consistent with a higher degree of brain tissue disorganisation in patients with confirmed forms of MS than in those with a CIS. Interestingly, there was no difference with regard to similar outcome measures in cross-sectional studies between patients with RRMS and those with SPMS.[27,34] A recent 1-year follow-up study of patients with a CIS showed that over this relatively short period, the average lesion MTR and normal-appearing brain tissue MTR worsened significantly.[35] Other studies showed that MTR and diffusion abnormalities were demonstrated in the cerebral grey matter of patients with RRMS, whereas no similar abnormalities were detected in patients at presentation with a CIS.[30,36-39] Progressive grey matter damage was also recently demonstrated in an 18-month follow-up study in which diffusion MRI scans were obtained every 3 months in patients with RRMS.[40] A decrease of NAA, choline and glutamate has been documented by MRS in the cortical grey matter of patients with early RRMS, but not in patients with a CIS.[41-43] Abnormalities in cervical cord MTR, which is frequently seen in patients with MS, have not been detected in patients with a CIS.[44-47]

Thus, while CNS tissue damage is already detectable in patients with a CIS, axonal and neuronal compromise advances with clinical disease progression. One major goal of early pharmacotherapy might therefore be focused on the potential capability to slow the transformation from a truly milder histopathology to one that involves a more severe lesion profile with elements of irreversible tissue damage.

2. Benign Forms of MS

Whether or not MS is a benign disease in some patients is of critical importance in the debate on when to initiate treatment. The existence of a truly benign phenotype should possibly preclude affected individuals from all forms of potentially harmful, expensive and life-altering interventions. Given that patients with MS were thought to have a normal or near-normal life expectancy,[48] MS was long considered a benign disorder. This perception has changed with newer studies on MS-associated mortality,[49] and with the recognition that MS as a lifelong illness is characterized clinically by an ongoing accumulation of neurological disability in the majority of affected individuals.[50] Specifically, natural history studies demonstrate that 20–25 years after diagnosis, approximately 90% of patients with MS will have substantial disability on physical examination.[51,52] One of the major recent scientific debates has been the impact of disease activity on subsequent disability accumulation. In patients with RRMS, Confavreux et al.[53] showed that there was no association between disease exacerbations and progression; however, other investigators demonstrated that individuals who have more frequent early attacks are more likely to eventually develop compromising physical limitations,[51,52] and that incomplete recovery from previous relapses leads to a continuous deterioration of neurological function.[54]

The nature and severity of MS disease progression is highly variable and unpredictable. Genetic and environmental factors may influence the natural course of the disease. It was recently demonstrated that patients in Olmsted County, Minnesota, USA, who had minimal or no disability (Expanded Disability Status Scale [EDSS][55] score ≤2) at >10 years from disease onset have a 90% chance of remaining fully ambulatory (EDSS score ≤3.0) 10 years later.[56,57] This particular patient group with 'benign MS' constituted 17% of patients with all clinical MS phenotypes or 33.3% of patients with RRMS in that population-based cohort. Currently, no biomarkers are available to identify patients with MS who are at risk of an aggressive disease course versus patients with a relatively benign prognosis.

It is not universally accepted that the EDSS is indeed a valid outcome measure to define the disease course of patients with benign MS. Also, the question arises as to how long benign MS will remain benign. In a recent study, 20-year EDSS scores were obtained from patients selected from a clinic database with an EDSS score ≤3 at 10 years from onset.[58] Approximately one-half (52.1%) of these patients continued to experience a benign disease course. However, 21% progressed to an EDSS score ≥6.[58] Furthermore, conversion to SPMS occurred in another 23% of patients.[58] In conclusion, this study supports the notion that an EDSS score of ≤3 10 years from onset, which is a time frame sufficiently long for patients to 'declare themselves' as being benign or non-benign, does not adequately represented benign MS. Similar results were presented by the New York State Multiple Sclerosis Consortium at the 58th Annual Meeting of the American Academy of Neurology in San Diego in 2006.[59] Thus, EDSS alone may not effectively represent the constellation of features that would be necessarily identified to truly render a patient within the 'benign' category. For example, no study has systematically evaluated longitudinal features of physical, intellectual, emotional and patient-reported factors that together would more reliably measure the true impact of MS and disability on patients, their families and communities. In addition, paraclinical parameters may become useful in defining a particular disease course. Evidence is mounting that many patients with MS are accumulating tissue damage on conventional MRI[60] and MTR,[61] despite the fact that they are clinically stable for long periods of time.

3. Determining Disease Progression and the Risk–Benefit Ratio of Early MS Therapy

None of the agents that are currently approved or in use to treat patients with MS has convincingly been shown to be reparative or restorative. Thus, the prevention of irreversible neuronal and axonal loss

is currently considered the primary focus of pharmacotherapy. It is also important to remember that all medications currently approved for the treatment of MS are associated with adverse effects, some of which are serious.[62-65] As mentioned in section 2, one study estimated that up to 17% of all patients with MS may have a benign disease course.[56] These patients may derive limited benefit from pharmacotherapy while being exposed to unwanted adverse effects. Conversely, delay of treatment may deprive 83% of patients with relapsing forms of MS and potentially many more from proven benefits associated with these agents.

The presence and extent of certain abnormalities on cerebral MRI scans in patients with a CIS may predict subsequent disease activity. Specifically, International Panel on the Diagnosis of Multiple Sclerosis criteria were designed to help rapidly and accurately identify the conversion from CIS to CDMS.[32] A study that followed patients with a CIS over a 3-year period found these criteria to have a sensitivity, specificity and accuracy of 83%.[66] Other investigators were able to confirm these results.[67] In a trial that tested interferon (IFN)-β-1a (Rebif®)[1] in patients with very early MS, MRI criteria were designed to determine whether dissemination of lesions in space predicted a subsequent evolution to CDMS.[68] When a new T2 lesion was allowed to substitute as evidence for clinical dissemination in time, one study showed that 82% of CIS patients had developed CDMS after 3 years.[67] Applying the same diagnostic criteria, yet another study determined that 80% of CIS patients converted to CDMS after 3 years.[69] There is now ample evidence that the presence of T2 lesions on brain MRI scans at the initial clinical presentation increases the risk of developing MS within the subsequent 5–14 years.[66-69] Specifically, the study with the longest follow-up of 14.1 years, on average, demonstrated that CDMS developed in 88% of CIS patients with an abnormal MRI at presentation, whereas only 19% of those with normal MRI scans had another clinical event.[70] It is worth mentioning that the presence of T2 lesions on a baseline MRI scan not only predicts an increased risk of conversion to MS but also, and perhaps not surprisingly, predicts progression of neurological disability. In the study that longitudinally followed CIS patients over 14.1 years, none of the CIS patients with normal MRI scans at baseline reached an EDSS score of ≥3.[70] Similarly, advancement of clinical disability to an EDSS score of ≥6 was significantly more likely in patients with the greatest burden of disease on MRI scans at baseline.[70] The anatomical location of CNS lesions on brain MRI scans may also be an important prognostic indicator. One group of investigators found that the likelihood of reaching an EDSS score of 3 was best predicted by the presence of at least two infratentorial lesions.[71]

A relatively new method to measure the retinal nerve fibre layer (RNFL) is optical coherence tomography (OCT).[72] The RNFL is the innermost layer of the retina and contains ganglion cell axons that comprise the optic nerve. Thus, the RNFL represents a CNS structure that consists of isolated axons without myelin. There is currently considerable optimism that OCT, which is a fast, non-invasive procedure, will provide real-time insight into the state of axonal and neuronal integrity in MS patients. Indeed, a recent study showed that the RNFL thickness in patients with MS was thinner than in controls, independent of a history of optic neuritis.[73] Interestingly, there was a positive correlation between RNFL atrophy and greater disability.[73] How OCT might compare with alternative measures of regional atrophy remains to be determined. Further studies will be required to test whether OCT is a useful prognostic indicator of MS disease progression.

4. Randomized Controlled Trials in Patients with Early MS

Over the past 14 years, medical treatment of RRMS has advanced with the approval of pharmacological agents that alter the natural course of disease. These agents include IFN-β-1b (Betaseron®), IFN-β-1a (Avonex® and Rebif®), glatiramer acetate

1 The use of trade names is for product identification purposes only and does not imply endorsement.

(Copaxone®), mitoxantrone (Novantrone®) and natalizumab (Tysabri®). It took several more years after the approval of the first medication in RRMS to obtain approval for pharmacotherapy of patients with a CIS.

Currently, all three IFN-β preparations have been shown to successfully delay the occurrence of a second event in patients with a CIS and thus the conversion to CDMS.[1] These three trials are discussed in the following sections.

4.1 Interferon-β-1a in Patients with a Clinically Isolated Syndrome (CIS)

In 2000, a randomized, placebo-controlled, multicentre trial enrolled patients who had a first acute clinical demyelinating event involving the optic nerve (unilateral optic neuritis), spinal cord (incomplete transverse myelitis), brainstem or cerebellum,[2] and who had lesions on brain MRI suggestive of prior subclinical demyelination.[2] The trial design of the CHAMPS (Controlled High-risk Subjects Avonex® Multiple Sclerosis Prevention Study) was truly innovative. At the time, diagnostic criteria required the occurrence of at least two neurological events consistent with CNS demyelination that were separated both anatomically and temporally, in order to establish a diagnosis of CDMS.[1] Newer, more sensitive, MRI-based criteria were not yet introduced.[32] Patients were randomly assigned to receive either weekly intramuscular IFN-β-1a (Avonex®) or placebo. The CHAMPS trial showed (i) the cumulative probability of the development of clinically definite MS, as defined by Poser et al.,[1] was significantly lower in the IFN-β-1a treatment group; and (ii) patients treated with IFN-β-1a had a relative reduction in the volume of brain lesions, fewer new or enlarging lesions, and fewer gadolinium-enhancing lesions on MRI scans of the brain. Thus, it was demonstrated for the first time that pharmacological intervention, specifically with IFN-β-1a, can delay the second clinical attack and conversion to CDMS in patients with a CIS with MRI evidence of subclinical demyelinating disease. Because approved therapies for patients with RRMS were available when CHAMPS was conducted, it was considered unethical by the investigators to keep patients in their assigned treatment groups once CDMS was diagnosed. Therefore, CHAMPS did not provide any direct data on the long-term effect of IFN-β-1a on the rate of clinical exacerbations or the progression of neurological disability. Although originally planned for 3 years, CHAMPS was terminated early based on the results of interim data analyses. Specifically, the analyses demonstrated that treatment with IFN-β-1a was significantly better than treatment with placebo and met the stopping guidelines, which included a p-value of 0.029.[2]

The CHAMPS trial was subsequently extended to 5 years (the CHAMPIONS [Controlled High Risk Avonex® Multiple Sclerosis Prevention Study in Ongoing Neurologic Surveillance] study).[74] In this trial, all participating patients were offered intramuscular IFN-β-1a 30 μg once weekly for up to 5 years (from CHAMPS randomization). IFN-β-1a treatment was not a requirement.[74] Patients who had originally been randomized to placebo were considered the delayed treatment (DT) group.[74] In contrast, patients who had originally been randomized to receive IFN-β-1a in the CHAMPS trial were the designated immediate treatment (IT) group. Again, the primary outcome measure was the rate of development of CDMS.[1] Additional outcomes included the annualized relapse rate, disability level at 5 years as measured by the EDSS, and various MRI measures. The median time to initiation of IFN-β-1a therapy in the DT group was 29 months.[74] The probability of developing CDMS was significantly lower in the IT group than in the DT group after 5 years (36% ± 9% vs 49% ± 10%). Multivariate analysis indicated that the only variables independently associated with an increased risk of developing CDMS were (i) randomization to the DT group; and (ii) younger age at onset of neurological symptoms.[74] Although the early treatment group still maintained a significant advantage over the delayed treatment in the number of patients developing a second clinical attack, no differences were observed in the number of T2 MRI lesions, T1-gadolinium lesions and EDSS score between the IT and DT

groups.[74] In addition, there was no significant difference in the relapse rate between the DT and IT groups from years 3–5.[74] Therefore, there remains an opportunity to carefully follow questionable, at-risk CIS patients to reach a diagnosis of definite MS without the risk of irreparable changes in clinical or MRI measures of inflammation.

The ETOMS (Early Treatment of Multiple Sclerosis) study was also designed to determine whether another IFN-β-1a preparation (Rebif®) would delay the onset of CDMS in individuals who had experienced a clinically isolated symptom.[3] Cerebral disease activity determined by MRI scans constituted a secondary outcome measure. The 308 study participants were randomly assigned to receive either low-dose subcutaneous IFN-β-1a 22 μg or placebo weekly for 2 years. There were some differences between ETOMS and CHAMPS with regard to study design and conduct. Patients, by definition, could not convert to CDMS within the first month of treatment in CHAMPS, but they could in ETOMS.[3] Based on the assumption that the effect of IFN-β-1a therapy may take some weeks to become fully manifest, the design of ETOMS was biased against active therapy.[3] Similarly to the CHAMPS trial, this treatment regimen significantly reduced the rate of conversion to clinically definite MS (34% in the treatment group vs 45% in the placebo group). Furthermore, the accumulation of new MRI-detected lesions in the brain was reduced. There was no detectable effect of IFN-β-1a treatment on clinical disability.[3] Interestingly, 20% of patients in the placebo arm and 15% of patients in the IFN-β-1a group had confirmed progression of one point on the EDSS.[3] This observation was quite surprising, given the short duration of the study. It confirms the notion that even in the very early stages of MS some irreversible nervous damage may take place.

4.2 Interferon-β-1b in Patients with a CIS

In a recently concluded phase III, randomized, double-blind, placebo-controlled, multicentre trial, the BENEFIT (BEtaferon® in Newly Emerging Multiple Sclerosis For Initial Treatment) trial, patients with a CIS who had at least two clinically silent lesions on brain MRI scans were randomized to receive either subcutaneous IFN-β-1b 250 μg every other day or placebo.[4] The study design of the BENEFIT trial was similar to ETOMS and slightly different from CHAMPS in that the BENEFIT study enrolled patients with both a monofocal and multifocal initial manifestation.[4] In contrast, inclusion criteria in CHAMPS did not foresee enrolment of patients with a multifocal disease presentation.[2] The primary endpoint was a diagnosis of CDMS.[1,4] Patients were initially followed for 24 months.[4] In this period, 45% of placebo patients had converted to CDMS,[1] and 85% of placebo patients fulfilled the newer and more sensitive diagnostic criteria for MS, as defined by McDonald and colleagues[4,32] The administration of IFN-β-1b significantly delayed the time to diagnosis of CDMS and McDonald-defined MS.[4] Treatment was well tolerated. Specifically, the percentage of patients who withdrew from this trial before reaching the endpoint of CDMS was remarkably low and indistinguishable between the placebo and treatment groups.[4]

Following the initial 24-month trial period, patients became eligible to enter a follow-up phase with open-label IFN-β-1b therapy. In a prospectively planned analysis 3 years after the original randomization, the effects of early IFN-β-1b treatment were compared with those of delayed treatment initiation.[75] The primary outcomes were (i) time to diagnosis of CDMS;[1] (ii) time to confirmed disease progression measured by EDSS composite;[55] and (iii) score on a patient-reported functional assessment scale (FAMS-TOI).[76] Of all patients originally randomized, 89% entered the follow-up phase and 84% completed the additional 12-month follow-up period. At study endpoint, 37% of patients in the early group developed CDMS[32] compared with 51% of patients in the delayed treatment group. Thus, early treatment initiation with IFN-β-1b decreased the risk of developing CDMS by 41% (absolute risk reduction 14%) compared with delayed treatment. Sixteen percent of patients in the early group and 24% in the delayed group displayed confirmed progression of neurological

disability on the EDSS scale. Early treatment therefore reduced the risk for disability progression by 40% compared with delayed treatment (absolute risk reduction 8%). There was no difference between both treatment groups with regard to the FAMS-TOI score (p = 0.31).

4.3 Evidence from Other Clinical Trials to Support Early Treatment of Patients with MS

IFN-β-1a (Rebif®) was the last IFN-β preparation to be approved in the US. In a phase III, randomized, double-blind, placebo-controlled, multicentre trial, it had previously been shown that this agent significantly decreases the number of clinical exacerbations and the percentage of T2 active MRI scans, and delays sustained disease progression (PRISMS [Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis]-2 trial).[77] A total of 560 patients were enrolled. Specifically, it was demonstrated that the relapse rate was significantly lower at 1 and 2 years with two doses (IFN-β-1a 22 μg three times a week and IFN-β-1a 44 μg three times a week) than with placebo.[77] The PRISMS-2 trial gave evidence of a dose-related IFN-β response, in that the time to first relapse was prolonged by 3 and 5 months in the 22 μg and 44 μg groups, respectively.[77] In addition, the proportion of relapse-free patients was significantly higher in the IFN-β-1a treatment group, and progression in disability was delayed over the treatment period.[77]

An extension study, PRISMS-4, followed patients from PRISMS-2 for an additional 2 years.[78] In this trial, patients who had originally been randomized to placebo in PRISMS-2 were re-randomized to either low-dose IFN-β-1a (22 μg three times a week) or high-dose IFN-β-1a (44 μg three times a week).[78] Interestingly, patients who received the highest dose of IFN-β-1a for the longest time benefited most with regard to clinical disability and MRI measures of disease activity.[78] These results are often cited as the best evidence to date in support of early initiation of treatment with IFN-β-1a in established RRMS.

5. Conclusion

The authors feel that based on the following arguments, the majority of patients with early forms of relapsing MS will benefit from early treatment.

1. MS is not a benign disease in the majority of patients. Most affected individuals will eventually develop significant disability.
2. Tissue damage in the CNS occurs in patients with very early forms of MS, including in patients with a CIS.
3. Patients with a CIS who display surrogate disease markers suggestive of MS on cerebral MRI scans are at substantially higher risk of developing subsequent clinical exacerbations than patients without detectable CNS lesions.
4. With current technology it is impossible to identify patients with RRMS who will have a benign disease course versus patients who will develop significant disability.
5. Compromise of CNS tissue continues to progress over time.
6. All currently approved medicines for MS have been shown to benefit only patients with relapsing forms of the disease. For the later, progressive stages of MS, there is no intervention that has been proven to provide a clinical benefit.
7. A delay in pharmacotherapy results in an increase of disease surrogate markers on MRI scans, as well as in progression of neurological disability.

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