

Multiple Sclerosis: Troubleshooting Treatment

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Multiple sclerosis (MS) is widely recognized as the most common disabling neurologic disorder of young people, affecting about 350,000 to 500,000 Americans. MS is typically characterized by attacks of neurologic dysfunction targeting any part of the central nervous system (CNS) and producing a myriad of symptomatic complaints. The 4 clinical subtypes of MS are relapsing–remitting, primary progressive, secondary progressive, and progressive–relapsing. Since the time of Charcot and his contemporaries, MS has been clinically characterized as a lifelong multiphasic disorder (multiple attacks in “space and time”) and pathologically indicated by the disruption of myelin, with only relative preservation of the axonal cylinders.¹



Contemporary advances in the understanding of immunology and histopathologic profiling have augmented current knowledge by elucidating a central role of exaggerated trafficking of circulating mononuclear cells (T cells, B cells, and macrophages) across brain and spinal cord endothelium, mediated by the interaction of specific families of adhesion molecules. Specifically, we now understand that circulating mononuclear cells express an adhesion molecule receptor, very late antigen 4 (VLA-4). This cell surface receptor binds to vascular cell adhesion molecule (VCAM), which is expressed on the surface of brain and spinal cord endothelium. Whereas small amounts of VCAM are normally expressed on microvessels, the expression of VCAM is upregulated in MS. Upon physical stabilization of these cells at the blood vessel walls, enzymes (eg, matrix metalloproteinases, or MMPs) are released that can digest basement membrane collagen and fibronectin to facilitate the trafficking of lymphocytes into the CNS.²

During this process, a breach in the integrity of the blood–brain barrier (disruption of endothelial tight junctions) occurs, with consequent CNS inflammation and edema. The entering inflammatory cells orchestrate a series of injury cascades mediated by antibodies, chemokines, cytokines, free radicals, and superoxides. These processes culminate in changes in tissue architecture, including demyelination, axonal transection, oligodendrocyte damage and loss, and gliosis (the principal component of “sclerosis”).

Table. Practice Pearls

This complex and authentic vignette underscores a number of important practice pearls:

- Most patients with a CIS already have disseminated lesions on MRI.
- Do not hesitate to offer IFN or glatiramer acetate therapy at the earliest period when you diagnose a CIS or MS.
- Be assertive in educating patients about what they have and what you are calling it. A working diagnosis is appropriate. When working diagnoses no longer work, explore alternatives to identify a diagnosis that does.
- Evidence-based studies support intervention with IFN treatment (Avonex, Rebif, Betaseron) at the time of CIS.
- Carefully exclude other conditions.
- Inform and educate patients about what occult, sub-clinical lesions signify.
- Other conditions can, and do, develop in patients with MS.
- Do not be afraid to reconsider the diagnosis.
- Consider adherence as a factor in the selection of treatment.
- Consider the risk for the development of neutralizing antibodies in the selection of early treatment. Clinical and radiographic progression of disease is influenced by the presence of neutralizing antibodies. Do not forget this. This phenomenon is evidence-based and now established (although clinicians should avoid testing for the first year of IFN therapy because neutralizing antibodies take about 12 months to develop).
- Do not forget to assess treatment adherence at each office visit.
- Do not confirm breakthrough disease or intensify therapy until treatment adherence has been established.
- Do not have a myopic, short-term view of the treatment objectives. MS is a lifelong disease that requires effective and persistently acting therapy.
- A diagnosis of MS remains a clinical one.
- MRI should not be used in a vacuum.
- New MRI activity in a patient who is clinically stable confirms active disease. Define MRI breakthrough in each individual patient. Do not get stuck on changing monotherapy when MRI activity continues. Consider combination therapy and an assessment of anti-IFN antibodies.
- Do not listen to industry rhetoric. Read the data for yourself.
- Steroids are a good first choice for adjunctive therapy.
- Both I.V. and oral routes of steroid administration are appropriate (no evidence-based data favor 1 over the other, and the pharmacodynamics and pharmacokinetics are actually similar).
- Do not forget to perform regular surveillance laboratory studies.
- Do not forget to discuss expectations of what is to be derived from combination therapy.
- Education beginning at the onset of disease is crucial.
- Neurologic symptoms in the context of an infection do not necessarily mean that the patient has a pseudoexacerbation. The patient may have both an infection and a new attack of MS.
- Establishing reasonable expectations of what is to be derived from therapy is important ... we cannot promise a favorable outcome. Do not pretend to know what will happen. It will only get you into trouble.
- Patients with newly diagnosed MS are at risk for denial and nonadherent behavior.
- Establishing easy access to patient and family education is part of the quality of care.
- Do not promise that “all will be fine,” and do not predict doom and gloom; you cannot predict the future of an individual patient.
- Do not forget to reassure patients that you will not quit if they will not quit.
- Make sure to indicate that if the initial care plan is not effective, changes can be made.
- Natalizumab reduces attacks by about 70%, new brain lesions by about 90%, and progression of disability by about 50%. Patients treated with natalizumab have been shown to experience improvements in validated quality-of-life measures.
- Natalizumab has been associated with JC virus-mediated PML when used in combination with other immune modulators. It can be, and has been, lethal. As such, the drug should not be administered in conjunction with any other long-term immune-modulating therapy.
- Natalizumab is generally used in those patients not deriving enough benefit from current first-line therapy. There are exceptions. Those with very active early disease who might require intensive chemotherapy or combination treatment might just as well and just as safely/dangerously benefit from natalizumab monotherapy.
- Natalizumab-treated patients should be followed very carefully (potentially every 3 months).
- No guideline is available with respect to surveillance imaging or virus testing in natalizumab-treated patients. In our practice, we perform MRI of the brain and JC virus tests at baseline, imaging studies at 6-month intervals, and JC virus testing quarterly.
- Antibodies can develop in natalizumab-treated patients that clearly have been shown to abrogate efficacy. Most antibodies emerge in 12 to 24 weeks; half of these patients revert to negative status and derive full benefit from the treatment.
- Although this article has not addressed the myriad of symptom issues in MS, it has delineated how the clinician must treat each patient who has MS as an individual according to evidence-based practices, with a keen eye for individual pathology. This part of practice is crucial to optimizing quality of life and is most important to our deserving patients.

CIS, clinically isolated syndrome; IFN, interferon; MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy

The FDA has approved 6 disease-modifying therapies for the treatment of relapsing forms of MS. The β -interferons (IFNs) are a class of naturally occurring agents that have a multitude of effects on immune system function, including the ability to reduce adhesion, inhibit MMPs, and promote the expression of regulatory cytokines.² These agents (interferon beta-1a [Avonex, Biogen Idec; Rebif, Serono/Pfizer] and interferon beta-1b [Betaseron, Bayer HealthCare]) have been demonstrated to reduce the risk for attacks of MS, the severity of such attacks, and the development of new lesions on magnetic resonance imaging (MRI). These agents also appear to exert modest effects in reducing the progression of disease.

Glatiramer acetate (Copaxone, Teva Neuroscience) is a random synthetic polymer that has been shown to orchestrate the development of regulatory T lymphocytes, which are hypothesized to be important for “balancing” the mechanisms of immune activation and immune suppression.³ This agent has been shown to reduce both exacerbations of MS and disease activity on MRI.

Mitoxantrone is a chemotherapeutic agent that is approved for the treatment of worsening of the relapsing forms of MS, including relapsing-remitting, secondary progressive, and progressive-relapsing MS. This agent has been shown to reduce both clinical and radiographic aspects of disease activity, but in light of its potential to produce a vacuolar cardiomyopathy that can compromise the cardiac ejection fraction, it can be administered only up to a maximum dose⁴⁻⁶ of 140 mg/m². This agent also appears to be associated with a higher risk for leukemia than that observed in the general population. Given these potentially serious adverse events, mitoxantrone is generally reserved for use as a temporizing treatment in patients exhibiting severe inflammatory activity, in an attempt to induce disease stabilization or remission.

Natalizumab (Tysabri, Elan/Biogen Idec), a selective adhesion molecule inhibitor (an anti-VLA-4 antibody) has been demonstrated to dramatically reduce both cell trafficking and clinical and radiographic evidence of MS disease activity.^{7,8}

The early phase of relapsing MS is associated with exacerbations and inflammatory brain lesions, whereas the progressive phases are characterized by less inflammation and a greater predominance of axonal loss and brain and spinal cord atrophy in conjunction with physical and intellectual deterioration. A major advance in the diagnosis of MS has been the application of MRI to identify disseminated inflammatory demyelinating lesions within the brain and spinal cord. Although a confirmed diagnosis continues to be a clinical exercise based at least partly on the exclusion of other conditions, the vast majority of patients present with highly characteristic syndromes and features of MRI that make the diagnosis straightforward.

At the time of the first attack—or the so-called clinically isolated syndrome (CIS)—the vast majority of

patients already show unmistakable evidence of the neuroradiographic signature of MS (MRI lesions with characteristic profiles and locations).⁹ These observations, coupled with evidence that IFN treatment at the time of CIS significantly reduces future clinical and radiographic evidence of disease activity, have changed the diagnostic rubric from multiple clinical events in “space and time” to a preemptive approach at the time of a single clinical attack when evidence of multiple radiographic attacks cannot be explained by an alternative etiology.¹⁰⁻¹³

Strong class I evidence from clinical trials (eg, the ETOMS [Early Treatment of Multiple Sclerosis] trial, CHAMPS [Controlled High Risk Subjects AVONEX Multiple Sclerosis Prevention Study], and the BENEFIT [Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment] trial) indicates that it is appropriate to render a “working diagnosis” of MS at the time of the first attack and to recommend disease-modifying therapy with IFN at that time.¹⁰⁻¹³ In addition, clinicians have become substantially more sophisticated in managing ongoing disease activity despite treatment, and in applying the multidisciplinary approach to mitigate MS-related symptoms (not the subject of this article).

Case Study: Jennifer

The following vignette illustrates a practical approach to using disease-modifying therapy in MS patients, and how to troubleshoot when disease activity persists. The interventions discussed are not presented as the correct or best options; instead, the case describes a very challenging young patient and the pathway that was navigated in an attempt to control her MS disease activity. Although some decisions may be supported by evidence-based medicine, much of what is done in actual practice is more akin to art than science (Table). This vignette is no exception.

Jennifer is a highly accomplished 16-year-old high school junior and soccer player who had been healthy until August 2002. At that time, she sought medical attention from her pediatrician after she awoke with numbness from her waist to her toes in a circumferential pattern. Sensation to the passage of urine and stool was reduced. She denied weakness or a change in gait except when walking in dim lighting, at which point she noted some instability. The examination showed sensory loss in the trunk and legs with a T10 sensory level. The reflexes were brisk and the toes were down. The only other finding was pallor of the right optic disc.

When specifically queried about past visual problems, Jennifer denied any acute event or change, but she did describe transient blurred vision and color changes in the right eye at soccer practice in the heat (for the last 2 years), which easily resolved with the ingestion of ice cold Gatorade or water (consistent with Uhthoff’s phenomenon). This may have been evidence of occult disease activity affecting the anterior visual system (signifying subclinical optic neuropathy). An MRI of the spinal cord revealed a midthoracic

gadolinium-enhancing plaque with mild edema spanning 2 segments. Lesions were also identified in the deep cerebral white matter, corpus callosum, and periventricular zones. None of these were enhancing (signifying that they were not new, or at least not hyperacute, because enhancement generally lasts only a few weeks to a few months in most inflammatory demyelinating lesions).

A series of laboratory studies failed to reveal an alternative etiology. Treatment with high-dose steroids (by an I.V. or oral route of administration) was discussed. It was decided to treat with oral dexamethasone at a dosage of 80 mg twice daily, taken with breakfast and lunch for 3 days with no taper. Jennifer rapidly recovered over 1 week. A follow-up MRI of the spinal cord 2 weeks later showed complete resolution of enhancement. After extensive discussion, the “working” diagnosis of MS was confirmed, and it was recommended that Jennifer start therapy with IFN-beta. After instruction about injection and intensive education concerning potential side effects and the importance of adherence, she was titrated to a full IFN dose over 4 weeks. She used a long-acting form of naproxen for side effects. Jennifer described only some post-injection “migraine” the morning after her shots. Oral triptan was added, to be taken 1 hour before the injections. This eradicated the headaches.

The results of surveillance laboratory tests (eg, liver function, complete blood cell count, and thyroid-stimulating hormone level) were normal, and repeat brain MRIs at 6 and 12 months were unchanged. She denied any depression. At 14 months after starting treatment, Jennifer presented with a left optic neuritis. She was emphatic about her complete adherence to treatment and described pain and visual loss on the left side. An MRI of the brain showed a gadolinium-enhancing lesion of the left optic nerve on T1 (longitudinal relaxation time) fat-suppressed coronal views. The MRI also showed 6 new deep white matter brain lesions on FLAIR (fluid attenuated inversion recovery) and T2 (transverse relaxation time) sequences, 1 of which was periventricular and associated with enhancement. She was treated with oral steroids once again and recovered to nearly her baseline level of visual function over about a month. An IFN-neutralizing antibody test was performed and found to be positive at 1:40 titer. It was decided to continue therapy and recheck the titer in 3 months to determine its trajectory. The next titer was increased at 1:120. At that time, Jennifer was further educated about the significance of elevated and persistent anti-IFN antibody titers and that such antibodies cross-react with all 3 IFN preparations (scientifically based). It was therefore decided to stop the IFN and instead start daily glatiramer acetate.

Jennifer was maintained on daily subcutaneous treatment without any side effects except for some transient lumps at the injection site. Given the recent activity, and the time necessary for glatiramer acetate to significantly reduce MRI activity, an oral pulse of 80 mg of dexa-

methasone twice daily was recommended, taken with breakfast and lunch 1 day per month for 6 months, at which time the steroids were stopped.

Jennifer did very well until January 2005, at which time she presented with profound fatigue, bladder urgency, urge incontinence, and subtle but definite weakness in the right leg and arm. A urine culture revealed a urinary tract infection, which was treated with antibiotics. This was in fact a pseudoexacerbation; however, we also identified a new enhancing plaque within the spinal cord at C5-7 (infections can in fact trigger new exacerbations, so it is important not to assume that infection is the cause of novel or persistent neurologic symptoms—the patient may have both an infection and an exacerbation).

Jennifer came to the clinic with a copy of the *Archives of Neurology* series on whether neuromyelitis optica (NMO; Devic's disease) is MS. Despite counseling that her brain lesions were classic for MS, she was emphatic that such abnormalities could be associated with NMO (her course was mainly optic neuritis/neuropathy and episodes of partial myelitis, and classic lesions of MS can occasionally occur in patients with NMO). It was not thought that she had NMO (optic neuritis and myelitis are the 2 most common exacerbations in MS, and she had short-segment disease). A negative result of an NMO immunoglobulin G assay confirmed this.

A new brain MRI revealed 3 new lesions, 1 of which was gadolinium-enhancing. After intensive discussion, adjunctive combination therapy was considered. The team discussed using pulse intermittent steroids, azathioprine, methotrexate, mycophenolate (CellCept, Roche), I.V. immunoglobulin, plasma exchange, and natalizumab. Ultimately, it was decided to add 1 g of mycophenolate twice daily to her daily glatiramer acetate. Surveillance laboratory tests and MRIs were performed every 6 months, and Jennifer did well until October 2006, at which time she presented with complaints of cognitive slowing, insidious visual loss, recalcitrant fatigue, difficulty reading, slow bilateral horizontal eye tracking, and bladder hesitancy. An examination showed a bilateral internuclear ophthalmoparesis (INO). Once again, she reported nearly full adherence to glatiramer acetate and mycophenolate.

After intensive discussion with Jennifer and her parents, it was decided to treat with a 5-day course of oral dexamethasone at a dose of 80 mg twice daily taken with breakfast and lunch. The team then sat down to discuss how this patient with MS could have been managed at a dedicated MS center and experienced so much activity despite multiple treatment regimens. We were honest in communicating that the management of an individual patient is not a clinical trial or a statistical activity, but rather an art form. I indicated that I could not promise a favorable outcome or predict the future, but that I would not quit if Jennifer stayed with us. I also counseled her on the advancements in our understanding of MS and new therapeutic options. Based on these

discussions, it was decided that Jennifer's therapy would be transitioned to monthly natalizumab. A protracted discussion ensued with respect to the benefits and potential risks of natalizumab therapy, including progressive multifocal leukoencephalopathy (PML).

To prepare for this change in treatment, we stopped the mycophenolate, continued the glatiramer acetate for 2 months, then stopped this agent and started natalizumab in January 2007. We performed a baseline MRI of the brain for benchmark purposes and polymerase chain reaction testing for JC/BK viral DNA in plasma to exclude the presence of JC virus before starting treatment with this agent (the result was negative). Jennifer did well with the first I.V. natalizumab infusion but experienced an infusion reaction at the time of the second despite the use of an antihistamine and acetaminophen. We discussed the association of infusion reactions and the development of neutralizing antibodies.

Three months after the start of treatment with natalizumab, we tested Jennifer for the presence of anti-natalizumab antibody, and the result was positive. We indicated that antibodies develop in 9% of patients treated with this drug (at between 12 and 24 weeks) but that two-thirds of the patients then revert to a negative status and seem to derive as much benefit as those in whom antibodies do not develop. By April 2007, we rechecked the antibody status and found it to be negative. We saw Jennifer back in the clinic in July. She described an amazing transformation. Her fatigue and depression had vanished, her cognitive capabilities had greatly improved, and her vision had improved in both eyes. Follow-up MRI showed interval stability. Our plan is to perform quarterly JC virus assays and periodic MRIs.

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