

Mellen Center Approaches: Choosing First-Line Treatment

Q: Should my patient with newly diagnosed multiple sclerosis be treated?

A: Most patients with multiple sclerosis (MS) should be treated in an effort to prevent disability accumulation. Natural history studies suggest that, without treatment, the median time to moderate disability is 7.69 years and the median time to requiring a cane is 14.97 years.¹ From the earliest stages of MS, axons and myelin are irreversibly damaged at sites of CNS inflammation. The available MS therapies suppress CNS inflammation and thereby decrease relapse frequency and reduce development of new demyelinating lesions. Disease modifying therapy in the early stages of MS may also prevent, or delay, the onset of secondary progressive MS.

On the spectrum of MS disease severity, most patients experience moderate disease, but small subsets demonstrate either very aggressive or very mild MS. Some patients with a mild disease course may not require treatment. Unfortunately, such patients are not easily identifiable at the time of diagnosis. Monitoring off therapy can be considered in patients who have infrequent relapses with full recovery and who have a minimal and stable MRI lesion burden without enhancing lesions or atrophy. Such patients should be vigilantly monitored for signs of disease activity that may suggest the need for treatment.

Other situations in which treatment might reasonably be delayed would include women planning pregnancy in the near future. It is also advisable to defer treatment if the diagnosis of MS is uncertain while additional diagnostic data is collected.

Q: What treatments are valid to use first-line?

A: There are currently ten approved treatments for MS. With the exception of mitoxantrone (Novantrone[®]), there are circumstances in which any of the agents may reasonably be used first-line. Selecting a disease

modifying therapy requires careful consideration of numerous factors including the patient's risk tolerance, the severity of their MS, other comorbidities that might be affected by particular treatments, and medication side effect profiles. Special considerations for each therapy are presented in Table 1. Treatment cost and payer restrictions are often important considerations as well. Clinical scenarios in which each treatment might be used appropriately as a first-line drug are discussed in more detail below. Mitoxantrone has largely fallen out of favor among MS experts due concerns about its toxic effects on the heart and bone marrow.²

Q: What are the pros and cons of using injectable treatments first-line?

A: The injectable treatments are reasonable first-line therapies in most situations. These agents include intramuscular interferon β -1a (Avonex[®]), subcutaneous interferon β -1a (Rebif[®]), interferon β -1b (Betaseron[®]/Extavia[®]), and glatiramer acetate (Copaxone[®]).

The interferons and glatiramer acetate have had regulatory approval for more than fifteen years without evidence of serious long-term complications. Thus, a significant advantage to the injectable treatments is their excellent safety profiles. From a cost perspective, the injectable treatments are cheaper than the newer agents and are often preferred as first-line agents by third party payers.

A major disadvantage is the risk of injection fatigue, which can affect medication compliance. The interferons can also cause flu-like side effects, including headache, chills, and myalgias. These symptoms can often be ameliorated with combinations of anti-inflammatories and acetaminophen. Mild transaminitis or leukopenia can occur with interferon usage, and should be monitored

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for with routine laboratory investigations. The primary side effect of glatiramer acetate is injection site reactions including erythema and swelling. It may rarely cause a self-limited episode characterized by symptoms such as chest pain, palpitations, dyspnea, and anxiety, which is referred to as an immediate post-injection reaction.

Q: Which injectable agent is the best choice?

A: The injectable agents demonstrated similar efficacy in their pivotal trials, for which the annualized relapse rate was the primary outcome. All agents reduced the annualized relapse rate by about one-third compared to placebo.³⁻⁷ Two direct comparison studies have also been performed, one comparing interferon β -1b to glatiramer acetate and the other comparing subcutaneous interferon β -1a to glatiramer acetate. Neither of these demonstrated a significant difference between agents in their primary outcomes.^{8,9} However, one study performed to assess the benefit of combining glatiramer acetate and intramuscular interferon β -1a found that the annualized relapse rate was significantly lower for glatiramer acetate monotherapy compared to intramuscular interferon β -1a monotherapy.¹⁰

As most data suggests equipoise between the injectable therapies, any of them can reasonably be used as a first-line treatment. Of eminent importance is the patient's ability to tolerate and comply with the prescribed medication because poor compliance is associated with disease worsening.^{11,12} Thus, careful consideration of the medications' side effect profiles and injection schedules is recommended before a decision is made.

Q: What oral treatments are valid to use first-line?

A: The oral medications include fingolimod (Gilenya[®]), teriflunomide (Aubagio[®]), and dimethyl fumarate (Tecfidera[®]). All three can reasonably be used for first-line treatment of multiple sclerosis. However, there is less long-term safety data for the oral agents than the injectables.

Each of the oral medications requires special consideration before initiation. Fingolimod has the potential to cause atrioventricular block and hence should be used with caution in patients who

have a history of cardiovascular disease. It should be avoided in patients on beta blockers, calcium channel blockers, citalopram, and other agents that may have an effect on cardiac conduction. Patients on fingolimod also have a small risk of developing macular edema. The risk of macular edema is higher in diabetics, so fingolimod should be used with caution in that population. Finally, fingolimod treated patients are also at higher risk of complications related to herpes viruses. Patients without serological confirmation of exposure to the varicella zoster virus should be vaccinated prior to treatment initiation.

Teriflunomide can be hepatotoxic and should be avoided in patients with liver disease. It has also been designated as pregnancy category X and, therefore, should not be used in women planning a pregnancy in the near future. Further, teriflunomide is transferred in the semen, so it should also be avoided in men with plans to father a child. Washout protocols are available to accelerate drug clearance if circumstances warrant.

Dimethyl fumarate can cause leukopenia in some individuals and should be used with caution in patients who have low white blood cell counts at baseline. Gastrointestinal side effects are common with dimethyl fumarate and can include nausea, diarrhea, and abdominal pain. Patients may frequently experience skin flushing as well, although this can often be ameliorated by taking low-dose aspirin once daily. The incidence of gastrointestinal symptoms and flushing was observed to decrease after one month on therapy.

The patient's risk tolerance with regards to progressive multifocal leukoencephalopathy (PML) should also be taken into consideration when choosing an oral agent. Progressive multifocal leukoencephalopathy was reported in several patients receiving a German formulation of dimethyl fumarate used to treat psoriasis.¹³⁻¹⁵ A case of PML involving a fingolimod treated patient is also being investigated.¹⁶ Although the likelihood of PML in patients treated with dimethyl fumarate or fingolimod seems to be exceptionally low, some patients may prefer to avoid these agents because of this concern.

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Q: Can natalizumab be used first-line?

A: Natalizumab (Tysabri®) is usually reserved as a second-line agent because of its association with PML. However, it can be used first-line, particularly in patients with features suggestive of an aggressive MS course. Such features would include multiple enhancing lesions, poor recovery from relapses, and early atrophy. Natalizumab is an especially appealing option if the patient has not had prior immunosuppression and has not been exposed to the John Cunningham virus (JCV).¹⁷ Such individuals have a low risk of PML and natalizumab could reasonably be considered even for less aggressive MS under these circumstances. Repeat JCV serologies are recommended every six months due to the risk of seroconversion (which appears to be about 1-3% per year).^{18,19} If the patient remains negative for anti-JCV antibodies, natalizumab can be used long-term with a low risk of PML.

Natalizumab can be considered in patients with positive JCV serologies without a history of immunosuppression. Such individuals have a PML risk of approximately 1:1,130 during the first two years of treatment. As the patient approaches two years on natalizumab, there is a substantial increase in PML risk and alternative treatments might need to be considered. Caution is advised when discontinuing natalizumab because of the risk of rebound inflammation.

Q: What disease monitoring needs to be done once a patient is on treatment?

A: Ideally, treatment will induce a disease activity free state, meaning no relapses and no new lesions or enhancing lesions on MRI. Alternative treatment options should be strongly considered in patients with evidence of breakthrough disease, especially after six months on therapy. Thus, close monitoring is necessary to detect signs of disease activity, such

as relapses. Because new lesions are often clinically silent, routine imaging also is recommended.²⁰ We frequently obtain a baseline MRI, followed by repeat imaging 6 and 12 months after treatment initiation. If the patient is stable, MRIs can be repeated annually or at the neurologist's discretion.

At the Mellen Center it is our practice to change disease modifying agents if there is MRI or clinical data to suggest continued disease activity despite an adequate trial of the present agent. We do not however have a precise guideline for when to change therapy and have left this up to clinical judgment.

Q: Is there a best choice if my patient may become pregnant?

A: We typically recommend strict contraception during disease modifying therapy and cessation of treatment in advance of conception. The Food and Drug Administration classifies the MS disease modifying therapies as pregnancy category C, with the exception of glatiramer acetate, which is category B, and teriflunomide, which is category X. Although data collected from pregnancies with exposure to interferons or glatiramer acetate are mostly reassuring,²¹ the safety evidence is limited. As indicated above, teriflunomide is teratogenic and should not be used in women planning pregnancy in the near future, or in men with partners who may become pregnant. If a patient becomes pregnant unexpectedly, disease modifying therapy should be immediately stopped. Pregnancy is protective against MS inflammatory activity, but women are at higher risk of relapse after delivery.²²

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Table 1

Medication	Special Considerations
Interferons (Betaseron®/ Extavia®, Avonex®, Rebif®)	Leukopenia Liver Disease Depression Significant Spasticity
Glatiramer acetate (Copaxone®)	None
Natalizumab (Tysabri®)	Liver Disease History of Immunosuppression JCV Seropositivity
Fingolimod (Gilenya®)	Leukopenia Liver Disease Diabetes VZV Seronegativity Macular Edema Atrioventricular Conduction Block Medications that May Affect Cardiac Conduction History of Melanoma
Teriflunomide (Aubagio®)	Liver Disease Leukopenia Hypertension Short-term Plans for Pregnancy History of Tuberculosis
Dimethyl Fumarate (Tecfidera®)	Leukopenia
Careful consideration should be given before starting treatment if these conditions are present. VZV = varicella zoster virus.	

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