Cleveland Clinic

Mellen Center Approaches: Managing Breakthrough MS Disease

Framework: All of the presently available disease modifying therapies for multiple sclerosis are partially effective in reducing disease activity. In some patients this will be sufficient to keep their disease process adequately controlled. In others there will be an unacceptable level of ongoing disease activity. This Mellen Center Approach addresses our management of patients who break through our standard treatment protocols; how we define this, how we think about changes in treatment, and our recommendations for action.

When should changing MS therapy be considered?

Changing therapy should be considered when there is evidence of continued MS disease activity despite adherence to a standard MS disease modifying therapy.

How is continued MS disease activity defined?

Continued MS disease activity may manifest as a clinical relapse, new or enlarging lesions on MRI, or gadolinium-enhancing lesions on MRI. These signs of disease activity may occur with or without changes in neurological disability. Often, clinical and radiological disease activity occurs together, but one can be seen without the other.

How common is breakthrough disease?

Based upon the Phase III clinical trial data, about 2/3 of MS patients on interferon or glatiramer acetate therapies will have a relapse within two years of starting therapy. About 1/2 - 2/3 will also have new lesions on brain MRI.

How much disease activity is too much disease activity?

There are no validated definitions of an unacceptable level of disease activity. Measures to consider when evaluating a patient include frequency of relapses, severity of relapses, extent of recovery from relapses, number of new or enhancing lesions, and size of new or enhancing lesions. For most therapies, continued disease activity over the first 1-3 months of treatment does not indicate the need to change therapy. A patient's tolerance of the current therapy may also affect the assessment of disease activity, as poor tolerance may lower the threshold to change therapy. For extensive discussion on the identification of breakthrough disease activity in MS, see Rudick and Polman, Lancet Neurology 2009.

What about a patient who has had no relapses but has new lesions on MRI?

Longitudinal studies evaluating predictors of disability progression suggest that MRI is a more sensitive predictor of future disability than clinical relapses. As a result, clinical relapses do not need to accompany new lesions to consider a patient sub-optimally responding to therapy. At the Mellen Center we are most concerned about patients who have new or enhancing lesion formation while on interferon therapy, as this appears to confer a significant risk of clinical progression.

What contributes to sub-optimal response to an MS therapy?

Several factors contribute to sub-optimal response to MS therapy. These include the partial efficacy of the therapy, incomplete medication adherence, and antibodies that block the biologic effect of the therapy. Other conditions can contribute to the appearance of clinical decline or sub-optimal response, including depression, anxiety, and intercurrent medical conditions such as diabetes, arthritis, obesity, and inactivity. These conditions should be differentiated from patients who are truly breaking through standard DMA.

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How long should a patient be on a therapy before considering changing therapy?

Since interferon and glatiramer acetate are not effective immediately after initiation, at least 6-12 months is typically needed to assess a therapy's efficacy. However, in patients with very active disease, it may not always be appropriate to wait 6-12 months to decide a therapy is ineffective. In some active patients we will consider pulse steroids for the first few months while waiting for the DMA to have effect.

What evaluation should be done before changing therapy?

A brain and sometimes spine MRI is typically performed when considering a change of therapy. In patients with a progressive clinical deterioration, evaluation of other non-MS conditions could be considered, such as B12, thyroid, anemia, and infections, e.g. urinary tract infection. For patients treated with biologic therapies (i.e. interferon, natalizumab), the presence of serum antibodies against the biologic therapy should be considered. Additional studies may be considered as clinically indicated. We consider whether patients have concurrent conditions such as cervical cord impingement syndromes in those who are progressing and image accordingly.

What about a patient with very frequent relapses and no change on MRI?

In patients who appear to have very active clinical disease (i.e. frequent relapses) but stable imaging studies, an alternative explanation for a patient's symptoms should be considered. Some patients describe temperature or activity related variation in symptoms as 'attacks'. Others will have repeated infections causing pseudo relapses. Often, a non-MS condition is precipitating the clinical decline. In this setting, addressing the underlying non-MS condition is more effective than changing therapy.

Does gradually progressive disability represent continued MS disease activity?

In the absence of clinical relapses and new, enlarging, or enhancing lesions on MRI, gradually progressive disability usually does not represent ongoing MS inflammation. In this situation, changing therapy is typically not effective. One exception is young patients with rapidly progressive disability, where changing immune-modifying therapy can sometimes be effective in slowing gradually progressive disability.

What treatment options are there for changing therapy?

There are two common approaches to changing MS disease modifying therapy. The choice of approach depends upon the severity of the disease while on the current therapy, which is measured by frequency and severity of clinical relapses, degree of recovery from relapses, ongoing disease activity on MRI. The expected tolerance to side-effects of each therapy and, of course, patient preference also integrate into the decision.

- Changing to another injectable therapy. No controlled clinical trials have evaluated changing from one injectable therapy to another. However, given the toxicities of infusion therapies, changing class of injectable therapy (i.e. from glatiramer acetate to interferon-ß or from interferon-ß to glatiramer acetate) is sometimes recommended in patients with only mild MS disease activity. In addition, there is rationale for switching patients with anti-interferon-ß antibodies from interferon-ß to glatiramer acetate therapy. Because anti-interferon antibodies cross-react between different interferon-ß preparations, patients with neutralizing antibodies against interferon-ß are unlikely to benefit from changing to another interferon-ß preparation. For patients on weekly interferon-ß (Avonex), some Mellen Center clinicians consider changing to a higher dose and more frequently administered interferon-ß preparation (i.e. Rebif, Betaseron), although no well-controlled studies have evaluated this approach.
- Changing to an infusion therapy. Two infusion therapies are currently FDA-approved: mitoxantrone and natalizumab. Natalizumab is a monoclonal antibody targeting an adhesion molecule. Natalizumab is a common therapy used in patients with break-through disease activity. For additional details on natalizumab therapy, see *Mellen Center Approaches: Natalizumab*. Mitoxantrone is a parenteral chemotherapy and is given as either trimonthly infusions for ~2 years or monthly for several months as an induction therapy. Because of its association with cardiac injury and leukemia, mitoxantrone is rarely used. In addition to these FDA-approved therapies, cyclophosphamide and rituximab both have clinical trial evidence suggesting they may be effective in relapsing forms

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of MS. Rituximab is currently used as a two-infusion treatment, with infusions separated by two weeks. The rituximab treatment course is then repeated every six months. Cyclophosphamide is currently used as monthly infusions.

Another approach to managing break-through disease activity is to add another immune modulating therapy to the current therapy. Although several trials have evaluated adding another therapy to an injectable therapy, most trials have produced disappointing results. Therefore, adding therapies to an injectable is not frequently employed. Some therapies that are sometimes tried when the above two common approaches are not appropriate include methotrexate, azathioprine, mycophenolate mofetil, and intermittent pulse corticosteroids.

Note: The Mellen Center has protocols for natalizumab, rituximab, mitoxantrone, cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, and intravenous immune globulins. These protocols are available upon request.