Mellen Center Approaches: Highly Active Multiple Sclerosis

What is “highly active MS”? 

The term highly active MS has not been precisely defined but the most important features include frequent relapses with incomplete recovery, and/or high radiological burden of disease, rapid accrual of disability after disease onset, with otherwise typical features of MS.

A universally accepted definition for highly active MS does not exist. We use of the term “highly active MS” for patients with highly active and inflammatory forms of MS. Patients with highly active MS will have frequent relapses and/or a high burden of enhancing brain MRI lesions. A spectrum of severity exists in highly active MS, ranging from patients with disease that is somewhat more active than average to patients with a fulminant course. The treatment algorithm must be adjusted based on the estimated level of risk, but in general patients with highly active MS will benefit from early aggressive anti-inflammatory treatments selected to maximize the likelihood of disease control.

What are the features of highly active MS? 

Several features are taken into consideration when determining if a patient has highly active MS. These include clinical and imaging characteristics:

Clinical
- Frequent relapses
- Severe relapses
- Incomplete recovery from relapses
- Frequent clinical disease activity (relapses) despite MS therapy
- Early accrual of physical or cognitive impairment

Imaging Features
- Heavy burden of MRI T2 lesions
- Presence of multiple enhancing lesions at onset
- High burden of gadolinium enhancing lesions
- Early brain atrophy
- Continued gadolinium enhancing lesions despite MS therapy
- Increasing in T2 lesion burden despite MS therapy

Can we consider someone with MRI activity but no clinical relapses to have highly active MS? 

Continued MRI activity, even despite apparent clinical stability, can be a feature of highly active MS. New lesion formation and accumulation of lesional tissue is associated with a poor prognosis and accrual of disability over time. Multiple recent publications have made it clear that at least in the setting of interferon use, MRI new lesion activity confers a much higher risk of disability progression. Because of this and our increased understanding of the disease biology, we consider patients who have a high burden of new lesions (T2 or enhancing or both) on MRI without new symptoms who are on disease modifying therapy to have highly active MS and treat accordingly.

What if someone says they have many relapses but the MRI is relatively stable? 

Some patients define their relapses differently than neurologists, and may have a different understanding of what constitutes a relapse. Some patients with day to day fluctuation of their MS baseline will call this relapses. Some patients who are temperature sensitive call this a relapse. In addition patients with recurrent infections will have pseudo relapses with increased symptoms due to increased body temperature. It is important therefore to make sure that the relapses which occur are well defined relapses, and also to correlate this history with MRI activity. If there is no new MRI activity this might call into question whether there is truly significant inflammatory disease requiring a change in medication.

continued on next page
Who gets highly active MS?
Any patient with MS may develop a highly active course over time. Currently we have no method to predict which patients will go on to have a high frequency of MRI lesions with subsequent relapses and accrual of disability. Several CSF and MRI biomarkers are being studied currently for this purpose. Some groups may have a higher risk of highly active MS and this risk appears to be higher in African American patients. Some patients with highly active inflammatory MS may mimic a progressive course of the disease due to frequent relapses without clear remissions. The presence of inflammatory lesions makes all these groups candidates for early highly active disease modifying therapy.

What are the goals of therapy for highly active MS?
The goals of therapy are the same as for other relapsing MS patients. Optimally we treat to target, trying to achieve a state with no relapses, no new lesions on MRI scans, and no worsening of disability. This target may not be realistic in this group of patients as the significant baseline activity and MRI burden may put them at risk for future disability progression despite optimal therapy. However trying to achieve a ‘no evidence disease activity’ state (NEDA) remains our target for therapy in this group. A secondary goal is to minimize side effects and risks of therapy, based on comparing risks of treatment vs. risk of the ongoing disease activity. Obviously, in patients with significantly active MS, a higher risk of medication may be reasonable early in the treatment course. We always discuss risk benefit ratios with families and patients and respect their wishes in the choice of therapy.

How does selection of disease modifying treatment vary in highly active MS as compared to regular cases of MS?
In patients with highly active MS treatment efficacy should be tailored to disease activity. Patients who present with a high burden of radiological disease, frequent relapses, and early accrual of disability will benefit most when highly active disease modifying therapy is used early in the disease course. For patients identified as having highly active MS, our most efficacious agents should be used early despite increased risk of adverse events. The standard platform injectable agents are unlikely to be sufficient to control disease activity and take many months to become fully effective.

What medications should be used to treat highly active MS?
Natalizumab is a highly effective medication for MS and is one of the most used medications to treat highly active forms of MS. The use of natalizumab should be considered early in the disease course of highly active MS. JC virus (JCV) serology (including titer) can help determine the safety of the medication and in JCV negative patients it can be considered as a first line agent. JCV negative patients can use the medication indefinitely (with repeat JCV serology every 6 months) with low risk of PML. JCV serology positive patients are at elevated risk of progressive multifocal leukoencephalopathy (PML). Natalizumab may be appropriate in selected JCV positive patients, but one may want to limit the total time of treatment depending on the severity of the disease course and the patient’s risk aversion profile. In JCV positive individuals quantification of the JCV antibody titer may be helpful to more precisely estimate the risk of PML. The use of natalizumab as a first line agent requires a discussion of the potential benefits and risks, particularly in JCV positive patients. The discussion should take into consideration the risk aversion and disease characteristics of each patient.

Can oral agents be used to treat highly active MS?
Use of oral medications such as fingolimod and dimethyl fumarate can be considered for patients with highly active MS. For fingolimod and dimethyl fumarate phase III clinical trials showed a reduction of 50% in the annualized relapse rate which suggests an advantage over injectable agents. This makes these medications options when patients have failed an injectable agent. The use of fingolimod or dimethyl fumarate as first line agents in patients with highly active MS should be considered, especially among JCV seropositive patients.

Can alemtuzumab be used to treat highly active MS?
Alemtuzumab is also a highly effective medication for MS and may be an excellent choice as a therapy for highly active MS in the future. The medication was approved in 2013 in Europe and Canada, but was not approved by the FDA and is not available for

continued on next page
treatment of MS in the United States. Alemtuzumab was studied as daily intravenous infusions for 5 days followed by daily intravenous infusion for 3 days at 12 months. Risks include the presence of thyroid, platelet and renal autoimmunity.

What other therapies can be used to treat highly active MS?

Several other medications have been used to treat highly active MS. The evidence behind some of these more aggressive treatment regimens is less well established and has not been approved by the FDA (with exception of mitoxantrone). Given the high risk of disability accrual these therapies may be an option depending on individual patient characteristics. For example they if a patient fails to respond to natalizumab one of these agents may be tried. These treatments however carry significant risks and should be used with caution and with adequate monitoring. The possibility of using these agents as induction therapy has been attempted. The rationale is to use a more effective and higher risk therapy for a short period of time and then switch to a more standard therapy, while monitoring disease activity.

Rituximab, an anti-CD20 monoclonal antibody, is currently used every six months, with each infusion course comprising two infusions separated by two weeks. B-cell levels can be monitored for possible re-dosing prior to 6 months but delaying the semi-annual infusion course for a return of B-cell levels is associated with more disease activity than following routine, semi-annual infusions. Clinical trials with a humanized anti-CD20 monoclonal antibody, called ocrelizumab, are ongoing.

Intravenous monthly cyclophosphamide has been used to treat highly active forms of MS. Cyclophosphamide is used monthly for 6 months with dosage based on white blood cell count followed by a prolongation strategy (doses at every 6 months) or transition to other medication. An alternative approach involves high dose induction therapy. Risks include hemorrhagic cystitis, amenorrhea, and myelosuppression.

Mitoxantrone is a parenteral chemotherapy and is given as either trimonthly infusion 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.

At the Mellen Center because of these risks we no longer recommend the use of mitoxantrone in the MS population.

Myeloablation with autologous hematopoietic stem cell rescue (“bone marrow transplantation”), although effective does carry a significant risk of mortality ranging from 3 to 10% Bone marrow transplantation may be attempted in cases with high disease activity despite use of our most aggressive treatments.

Note: The Mellen Center has protocols for natalizumab, rituximab, and cyclophosphamide. These protocols are available upon request.

Referral to centers conducting clinical trials is also an option for some of these patients and they may benefit from therapies such as myeloablation and hematopoietic stem cell transplantation.

Are relapses for highly active MS treated differently than standard MS?

In general, relapses in highly active MS are treated the same as in typical MS. In highly active MS full recovery after relapses is even more important as these patients are at high risk for disability. Additionally patients with highly active MS may have a sub-optimal response to steroids. It may be difficult to determine when corticosteroids have failed and clinical judgment should be used to make this determination. In general a significant loss of function which does not appear to be improving after adequate steroid treatment may be considered a potential failure. Options for treating relapses that fail to respond to a standard course of intravenous steroids include:

- Repeat intravenous methylprednisolone with the second course extended to 5-7 days.
- Plasma exchange.
- IV gamma globulin.

What can be done if a patient already has developed significant disability due to highly active MS?

Symptomatic treatment is all the more important in highly active MS as patients tend to accrue disability quickly. A combination of pharmacological treatment and rehabilitation are needed to help maintain function and quality of life. Referral to Physical Medicine and Rehabilitation may be helpful to

continued on next page
coordinate complex cases and help with treatment of spasticity. Mobility limitations may require a physical therapy referral for gait and transfer safety, mobility devices, and to regain strength. Limitations in activities of daily living (ADL) or in upper extremity function should trigger a referral to Occupational Therapy to help mitigate these symptoms. Speech Language Pathology will benefit patients who develop speech difficulty and may be urgently needed for patients who have developed swallowing limitations.

REFERENCES