Cleveland Clinic

Mellen Center Approaches: Treatment of progressive MS

What do we mean by "progressive MS" i.e. Which patients are we talking about?

- Primary progressive MS (PPMS) (progressive from onset without relapses)
- Secondary progressive MS (SPMS) (progression that develops after an initial relapsing-remitting course)
- Progressive relapsing MS (PRMS) (progression from onset with superimposed relapses).

There is now a general appreciation that progressive MS may represent a form where destructive and degenerative processes dominate, and inflammatory disease activity may be less prominent. Therefore, it seems plausible that the efficacy of anti-inflammatory drugs may decline as disease duration increases and may explain why immunomodulatory therapies have been less successful in purely progressive subtypes. In an individual patient, the relative contributions of inflammation and degeneration may be difficult to discern and, thus, the response to treatment difficult to predict.

Are there any guiding principles when considering treatment?

1. When a patient with known relapsing MS develops a progressive course, we will routinely obtain updated spinal cord imaging and laboratory studies (such as vitamin B12, copper, HTLV-1 etc.) to evaluate for alternative causes of what often is a progressive myelopathy.
2. Patients with progressive MS tend to be older and tend to have more medical comorbidities than patients with relapsing-remitting MS. The presence of medical comorbidities (especially cigarette smoking and obesity with BMI >30) may accelerate the progression of MS, and management of these risk factors often requires the active involvement of an informed primary care physician.
3. One reasonable differentiation when deciding on treatment is whether a patient is "progressive with relapses" vs. "progressive without relapses". The primary efficacy of immunosuppressive or immunomodulatory therapies is in prevention of new CNS inflammation and relapses. Because PPMS is diagnosed only in the absence of relapses, patients with PPMS are less likely to benefit from immunomodulatory therapies.
4. We strongly recommend exercise routines and stretching. There are numerous studies that support the benefit of such programs in patients with MS.
5. We often have physical therapy reassess gait in the progressive population as there may be changes in assistive devices or methods of walking that will improve safety and function.

What are appropriate goals for treatment of progressive MS?

Attempts at modifying the course of progressive MS are driven by the patient's desire to slow or stop progression and the physician's desire to help. It is important to recognize, however, that evidence supporting the efficacy of DMTs for progressive MS is less convincing compared to RRMS. An appropriate goal for therapies in progressive MS is to stabilize or slow the clinical decline of the primary affected system (i.e. maintain gait at the current level of assist or maintain the ability to perform ADLs with the upper extremities). Patient education to establish these goals at the initiation of treatment is helpful.

How do we monitor patients with progressive MS?

The utility of serial MRI scans diminishes in progressive MS, as subclinical inflammatory activity is uncommon. We generally reserve MRI scans for investigating symptoms that are not consistent with the patient's known disease course, or when initiating

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a new treatment which requires MRI imaging. Functional testing such as the timed 25-foot walk (a reliable measure of ambulation) and 9-hole peg test (a reliable measure of upper extremity dexterity) are easily performed and when followed over time give an indication of the patient's course. We measure them at least yearly in patients with progressive MS.

What are the treatment modalities that we employ?

There are two general categories of treatment: symptomatic treatments and disease modifying therapies.

Symptomatic treatments are particularly important in patients with progressive MS. This includes pharmacotherapy for spasticity, bladder dysfunction, fatigue, neuropathic pain, and mood. An integral part of symptomatic therapy at our center is physical therapy and occupational therapy to help patients compensate for existing limitations. A regular stretching regimen instructed by an experienced therapist can be effective in limiting the symptoms of spasticity. We also routinely utilize health psychology and social work resources to help patients deal with the life complications and stress that accompany progressive disability. A comprehensive rehabilitation evaluation by our spasticity management team (physiatrist, nurse, and therapist) is often employed.

Is there a way to select patients with progressive MS who may respond to immune modulating therapy for MS?

Those with recent relapses, those with recent gadolinium enhancing lesions on MRI, younger patients, and those with shorter disease duration may be more likely to benefit based on subgroup analyses of major clinical trials of immunomodulatory drugs in progressive MS.

REFERENCE: Kappos L et al. 2004

What is the role of the "ABCR" drugs in progressive MS?

Across four major studies testing interferon beta in SPMS, significant beneficial effects were observed for relapses and MRI markers of inflammation, but the effects on disability progression were mixed and of small magnitude. Intramuscular weekly interferon beta-1a had a significant beneficial effect on upper extremity function (measured by 9-hole peg test) in SPMS but no benefit on EDSS. Interferon beta may limit the destructive pathology of SPMS based on a small study showing a reduced accumulation of T1 "black holes" on MRI in treated patients. One small study of glatiramer acetate (GA) in SPMS showed a non-significant trend to slow disability on the EDSS, and a study of GA in PPMS was stopped due to futility.

In patients transitioning from RRMS to SPMS and on an ABCR drug, we generally continue the injectable medication unless there are side effects (spasticity, weakness, injection site or flu-like reactions, financial burden) which outweigh the utility of the medication.

We do prescribe ABCR drugs in newly-diagnosed progressive MS when their expected benefit is perceived to outweigh their inconvenience, potential side effects, and potential toxicities in individual patients. This decision is largely based on the presence or absence of factors discussed above.

REFERENCES:

Li et al., 2001; Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS (SPECTRIMS) Study Group, 2001; Goodkin & The North American Study Group on Interferon beta-1b in Secondary Progressive MS, 2000; European Study Group on interferon beta-1b in secondary progressive MS, 1998; Miller et al., 1999; Cohen JA et al 2002; Bornstein et al., 1991; Barkhof et al., 2001; Brex et al., 2001.

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What are the other therapies that you commonly utilize in progressive MS?

1. **IV pulse methylprednisolone:** We prescribe IV methylprednisolone in a high-dose pulse fashion (500-1000mg daily for 3-5 days with or without oral prednisone taper, repeated on average every 8 weeks) based on its effect of slowing disease progression in two (small) randomized studies. Our experience is that this regimen is generally well-tolerated and is reported by a subset of patients to significantly improve their motor function for 4-8 weeks following each infusion. A common strategy at our center is to prescribe either an initial single course (as a trial of tolerability) or an initial 6-month set of three courses (as a trial of efficacy).

   Periodic monitoring of bone mineral density, gastric ulcer prophylaxis, electrolyte and blood glucose monitoring may require attention while on therapy.
2. **Low-dose oral methotrexate:** There is evidence that low-dose (7.5-20mg) once weekly oral methotrexate slows disease progression in progressive MS when measured using the MS Functional Composite. This regimen is convenient and generally well-tolerated, though we advise daily folic acid supplementation and periodic monitoring for hepatic toxicity.

REFERENCES:

Cazzato et al. 1995; Goodkin DE et al. 1998

Is there a role for combination therapy?

There is very modest evidence for increased efficacy of interferon beta when combined with either pulse IV methylprednisolone or azathioprine, and the effect is primarily seen on relapses not progression. There are limited circumstances where we will employ combination therapy in progressive MS.

REFERENCES:

Fernandez O et al. 2002; Cohen JA et al. 2009

Are there other therapies that you occasionally utilize?

1. **Imuran (azathioprine):** We will occasionally prescribe azathioprine based on suggestion from meta-analyses that it may slow progression of MS when used as monotherapy.
2. **CellCept (mycophenolate mofetil):** We will occasionally prescribe mycophenolate mofetil based on suggestion from large single center experiences that it may slow progression of MS when used as monotherapy.
3. **IV Immunoglobulin:** One large-scale study showed modest delay of disability progression with monthly IVIG infusions in patients with PPMS, however in our experience the magnitude of this effect is small.
4. **Plasma exchange:** Based on mixed efficacy data, cost, and limited access we almost never use plasma exchange as a maintenance therapy to prevent disability progression in MS.

REFERENCES:

Goodkin DE et al. 1995; Yudkin PL et al. 1991; Frohman E et al 2004, Pohlau et al. 2007.

Is there a role for potent immunomodulatory or immunosuppressive therapies in patients with progressive MS?

Potent immunosuppressive therapies (mitoxantrone, cyclophosphamide, rituximab) and immunomodulatory therapies (natalizumab, daclizumab, alemtuzumab) are unlikely to be effective in purely progressive disease based on currently available evidence. However, we recognize that there is a subgroup of patients who have had a recent and rapid decline in function in whom it is difficult to clinically discern the difference between progression and multiple consecutive relapses without recovery. In this group of patients, more potent therapies may be indicated.

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