

Disease Modification in Multiple Sclerosis

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Introduction

Multiple Sclerosis is the most common acquired disorder of myelin in humans. We now know that MS is not only a demyelinating and inflammatory disease, but also, a neuro-degenerative disease. Though it seems autoimmune in nature, environmental factors may play a role in genetically susceptible individuals.¹

Simplified Pathology of NIS

In MS, T cells are inappropriately activated to recognize myelin and myelin-forming cells (oligodendrocytes) as foreign which results in starting of an autoimmune process. This inappropriate immune response can cause the production of cytokines that continue to activate T cells and cause additional damage to the myelin. The first stage in the cascade leading to MS is the inflammatory reaction. White cells penetrate the protective blood-brain barrier (BBB) by traveling from the blood stream into the CNS and settling around the tiny blood vessels. As these white cells (predominantly T cells) enter the CNS, they produce inflammatory proteins called cytokines. The presence of these inflammatory cells and inflammatory proteins lead to edema. This "focal" or localized inflammation around small blood vessels is one of the hallmarks of MS. This causes swelling and damage to the surrounding tissue.³

Inflammation can lead to damage to the surrounding tissue, and can cause demyelination. Once the inflammation has subsided, the nervous system can recover either completely or incompletely. The extent of the problems caused by this process depends on the location and number of places where demyelination occurs, and the severity and the duration of the inflammation. If the demyelination occurs in the same place for an extended period, the repair process may not be able to "keep up," and permanent damage to the axons may take place. When demyelination covers a large area, it can leave a scar in the CNS. The scar is known as a "plaque". Plaques are most common in the periventricular region, brainstem, cerebellum, and spinal cord. If demyelination is severe enough, the nerve fiber may be transected in a process called axonal loss. The greatest degree of axonal damage may be found in areas of active demyelination and inflammation. Axonal loss occurs early in the course of the disease. Over 11,000 transected axons may be found within 1 mm³ of active brain lesions. Experts believe that permanent disability in MS could be the result of both ongoing demyelination and axonal injury.⁵⁻⁷

Rationale of Early Diagnosis and Treatment

MS natural history data indicate that approximately

50% of cases, patients with relapsing-remitting MS (RR-MS) convert to secondary progressive MS (SP-MS) within about 10 years. Based on data from the placebo groups in clinical trials, approximately one third to one half of patients with RR-MS worsen by >1.0 EDSS point within 2 to 3 years. Other studies have shown that about 15% to 44% of patients need an assistive device for walking within 5 years.

All these findings support the initiation of therapy at diagnosis, especially because pathogenesis of MS shows that once inflammatory demyelination results in either axonal transection and loss, the ability of the CNS to recover is severely limited.^s

A recent study of 71 patients with suspected MS at initial visit (baseline) who were followed for 14 years with serial MRIs showed that; 88% of patients whose baseline MRI results were abnormal developed MS; 98% of patients with MRI abnormalities at baseline had either clinical ("visible") or radiologic ("invisible", seen on MRI scans) evidence of MS; 89% of patients with 1 to 3 asymptomatic (clinically silent) lesions at baseline developed MS. In untreated MS, by year 2, up to 6% of brain volume can be lost.^{9,10}

Like any other chronic illness, Multiple Sclerosis, at its presentation, has different severities and the rate of its progression. It is, though, hard to predict which part of the bell shaped curve your patient will fall into. Some experts now suggest that there is probably no such entity as "Benign MS". As stated above, recent research has also made it clear that axonal loss can occur very early in the disease process. Overall disability, therefore, can be prevented by early intervention

In a call to action, the consensus statement of the National MS society of United States released in October 1998, stressed the need to begin therapy immediately after confirmation of the diagnosis in all the patients with MS. Patient and physicians can not take a wait and see approach to the treatment, because "the clinical data confirm sooner the therapy is initiated and possibly longer it is continued. the better the outcome.

Treatment

Overall goal of the treatment is to treat the 'whole disease'. This is accomplished by reducing the inflammation and relapse rate which in turn will reduce the chances of brain atrophy, cognitive dysfunction and disability.

There are two clear aspects in the overall management and treatment of Multiple Sclerosis. Apart from treating the

acute illness or 'clinical attack', there are now options for prevention of such attacks.

As, treating the 'attack' does not change the overall progression of the disease, the goal of new therapies is to prevent such relapses and eventually physical disability and cognitive dysfunction. Cognitive impairment occurs in up to half of the patients with Multiple Sclerosis. This is not well recognized and can sometimes be confused with depression, stress or personality disorder. Symptoms include, slowed thinking, short-term memory loss/forgetfulness, personality changes, difficulty with visual representation and spatial relationships (visuospatial disturbances), language problems, difficulty with problem solving and performing multiple tasks.'

In Summary, the main goals of NIS treatment are to:

Decrease the frequency of acute attacks

Prevent the accumulation of sustained physical disability

Reduce inflammation

Slow the progression of brain atrophy

Improve patients' quality of living.

• Therapy should have a positive impact on cognitive function.

• Therapy should be well tolerated with predictable and manageable side effects. ¹²

Treatment Options

Treatment options include disease modification, like treatment with Immunomodulatory and Immunosuppressants, and symptomatic treatment which can benefit in acute exacerbations and chronic symptoms, like spasticity and pain.

Disease Modifying Agents

Disease Modifying Therapies Include:

interferon3- I a

interferon3- I b

glatiramer acetate

in itoxantrone

Immunotherapy

azathioprine

leustatin

cyclophosphamide

Methotrexate

Most of these therapies show improvement in EDSS (Extended disability score). (EDSS of zero is normal and 10 is death due to MS).

Most of these medications have also shown improvement in number of relapses and improvement in both

T2 weighted images and gadolinium enhanced images. It is now believed that even there are changes in MRI in sub-clinical phase of MS. In clinical phase too, the lesions can appear even between the attacks. It seems that during relapsing remitting phase there is more activity on MRI than during secondary progression which typically shows more loss in brain volume. The activity on MRI probably points towards the active inflammatory phase and that is why more therapies are targeted during this phase. Once the secondary progressive phase ensues, this becomes a more degenerative process. ^{13,14}

Immunomodulators

1) Interferons

These are recombinant proteins. There is now unequivocal evidence to prove that interferon beta have significant role in preventing further progression of the disease. Clear mechanism of action of interferons is not known. All reduce the attack frequency and severity in RRMS/SPMS. There is a minimal, if any, effect on deterioration in walking but helps those on the cusp of RR to SP, or patients with SPMS who continue with attacks. There is suggestion that progression from RR to SP is delayed by treatment. MRI disease burden is decreased and safety is well proven. ¹⁵

There are, though, some unresolved issues about interferon treatment. These include:

Which is the optimal time to initiate treatment?

What is the optimal dosage, frequency and rate may still be an issue for some?

When to stop treatment?

When to add combo therapy?

Occurrence and relevance of neutralizing antibodies.

1. Interferon Beta I b

Interferon Beta I b is indicated for reduction of the frequency of clinical exacerbations in ambulatory patients with RR-MS. This is bacterial form of the protein. This was the first interferon that showed, in double blinded placebo controlled trial, to decrease the frequency of relapses by 34% compared to placebo. It also showed significant decrease in MRI burden of the lesions. In clinical trials. SC-injected Interferon Beta I b was associated with high rates of injection site reactions (85%) and severe reactions, as necrosis, have been reported. Interferon Beta I b reduces attack frequency by 30% over 5 years. Frequency of major attacks is reduced by 50% in Secondary Progressive MS and superimposed attacks in secondary progressive MS are reduced by 30%. ¹⁶ It is shown that it also decreases disability progression in RR but not SP. Interferon Beta I b studies have shown reduction in disease burden by 70-80% on MRI. Dosage is 8MU SubQ QOD. ¹⁷

2. Interferon Beta 1a

This is a human form of glycosylated protein. Interferon Beta 1a is given weekly or three times a week. More recent studies have proven that higher doses of interferons are more effective.

Interferon Beta 1a decreases attack frequency by 32% over 2 years. It has shown to decrease conversion to definite MS by 44% at 3 years and decreases accumulated disability in RR.

MRI shows 52% reduction in lesions over 2 years (91% reduction silent lesions). Dosage is 6MU IM weekly. Interferon Beta 1a showed 40% reduction in cognitive worsening in treated patients. Double blinded, placebo controlled studies also proved significant reduction in relapses for Interferon Beta 1a. The most common side effects are flu-like symptoms, muscle ache (myalgia), fever, and chills. Other side effects that were common but the incidence of which was not statistically different from placebo, were headache (Interferon Beta 1a: 67%, placebo: 57%), pain (Interferon Beta 1a: 24%, placebo: 20%) and asthenia (Interferon Beta 1a: 21%, placebo: 13%). Interferon Beta 1a should be used with caution in patients with depression, seizure disorders with cardiac disease. Routine periodic blood chemistry and hematology tests are recommended during treatment with Interferon Beta 1a.^{3,24}

1) Glatiramer Acetate

This is a random polymer of amino acids. It induces suppression of T cells that affect myelin. It reduces relapse rate by 29%. It is given daily by subcutaneous injections and is also a first line therapy for RR-MS. It is a non-interferon. Dosage is 20mg SubQ daily. It has shown 32% reduction in attacks over two years and 35% reduction in demyelinating lesions on MRI. It may attack killer T-cells and simulate MBP.^{9,220} Glatiramer Acetate is relatively better tolerated than interferons and has a better side effect profile, though all injection site reactions have been reported.⁵⁻⁸

III) Mitoxantrone

This has been approved by FDA for treatment of chronic progressive Multiple Sclerosis in 2000 and is the only FDA approved product for SP MS. It is a chemotherapeutic agent used for acute non-lymphocytic leukemia and prostate cancer. Dosage is 12 mg/m² every 3 months. It decreases relapse rate by 67% and disability by 61%. There is also significant reduction in new MRI lesions (85% compared to placebo). It is highly effective in SP and worsening forms of MS. Some centers are using "induction treatment" by monthly doses for 6 months. Side effects include nausea, amenorrhea, alopecia and pharyngitis. Cardiotoxicity is seen above 160mg/m²-stop at 140mg/m². It is recommended to evaluate LVEF with MUGA initially and after 100mg/m².

III) Other Modalities

Several other treatments have been tried with modest success. Immunosuppressive agents like cyclosporin, methotrexate, 2-chlorodeoxyadenosine, cyclophosphamide and azathioprine have all been used to some extent with mixed results. As MS is a chronic illness, prolonged immunosuppression may lead to dangerous complications. Short term treatment might be more effective in short run.

Monthly corticosteroids, total lymphoid irradiation, IV IG and plasmapheresis have been used in desperate situations where other treatments fail. IVIG and plasmapheresis have shown some benefit in few studies.⁹

Combination Therapies

Combination therapies are also being used specialized centers for Multiple Sclerosis. These include:

IMA (immuno modulators) + mitoxantrone

IMA+ cyclophosphamide

IMA+ IVIG

IMA+ methotrexate

IMA+ azathioprine

IMA + plasma exchange

Unproven Therapies

Snake Venom

Electrical stimulation of spinal cord

Thymectomy

Hyperbaric oxygen

Removal of silver or mercury dental fillings

Conclusion

Though, like many other chronic illnesses, there is no effective cure of multiple sclerosis, there are now definite treatments available. These treatments prevent further disease progression and stabilize the disease process. These should be initiated as soon as the diagnosis of multiple sclerosis is confirmed and should be continued until better and more effective therapies are available.

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