

42 *Newer Advances in the Management of Multiple Sclerosis*

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Abstract: Multiple sclerosis (MS) is a multifocal demyelinating disease of central nervous system that inflicts mostly the younger population. It mostly occurs in patients of 20 to 50 years of age. The onset, course and prognosis of MS differ among different individuals. About 2.5 million people worldwide are afflicted by multiple sclerosis. The variable natural history of multiple sclerosis confounds the decision about the timing and type of treatment to choose for a patient. Advances have been made in the diagnosis and treatment of MS. It was estimated that in 2002, only 45% of eligible patients received disease modifying therapy. The figures for the developing country like India are likely to be lower. With the availability of sophisticated MRI techniques and the latest research favoring early institution of Disease Modifying Agents (DMAs), there is a need for recognizing and implementing therapeutics appropriately and timely to prevent excessive burden of disease.

The role of disease modifying agents is discussed and overview of some of the newer modalities of treatment like the use of monoclonal antibodies and stem cells transplantation are presented and combination therapy using immunomodulatory agents are highlighted.

Multiple sclerosis (MS) is a multifocal demyelinating disease of central nervous system that inflicts mostly the younger population. It mostly presents in 20 to 50 years of age. However, it is known to occur from 2nd year to 85th year of life¹. The onset, course and prognosis of MS differ among different individuals. Some patients experience short periods of progression while others shows steady downhill progression. About 2.5 million people worldwide are afflicted by multiple sclerosis.² Multiple sclerosis, depending on the onset and course, may present as Relapsing Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS) and Progressive Relapsing Multiple Sclerosis (PRMS).

Relapsing Remitting MS is the most common initial presentation of multiple sclerosis. More than half of patients with RRMS develop significant disability if left untreated for 10 years.³ Secondary progressive MS (SPMS) develops in most of the patients after 25 years of disease. The variable natural history of multiple sclerosis confounds the decision about the timing and type of treatment to choose for a patient. Advances have been made in the diagnosis and treatment of MS. It was estimated that in 2002, only 45% of eligible patients received disease modifying therapy.² The figures for the developing country like India are likely to be lower. With the availability of sophisticated MRI techniques and the latest research favoring early institution of Disease Modifying Agents (DMAs), there is a need for recognizing and implementing therapeutics appropriately and timely to prevent excessive burden of disease. Most of the data available earlier was from small open label or controlled trials. Over the years, more and more evidence is being gathered about the use of DMAs individually and in combinations.

DIAGNOSIS

Diagnosis of MS is often delayed due to presentation with non-specific complaints and Clinically Isolated Syndromes (CIS). In the earlier years, the diagnosis of MS was based on clinical history

and physical examination. Over the years, paraclinical (including evoked potentials and MRI) and laboratory evidence of disease have been incorporated in the diagnostic criteria. The various criteria like Shoemaker's, Poser and Mc Donald are reviewed by Poser and Brinarl.⁴ Quantification of load of lesions on MRI, including on Gadolinium enhancement (Gd +), is used frequently in assessment of efficacy of a DMA for MS. The total volume of T2W abnormality on MRI represents the burden of disease and correlate with disability to certain extent. MRI techniques of proton Magnetic Resonance Spectroscopy and Magnetization Transfer Ratio help in quantification of axonal loss and distinction of edema from demyelination respectively. These techniques are mostly used as research tools for assessing the efficacy of various modes of therapy. These are not frequently and routinely used in clinical practice as yet. It must be emphasized that the diagnosis of MS is still a clinical one and is supported by investigations, including MRI..

TREATMENT

Treatment of MS can be considered under the following headings:

1. Treatment of acute attack or exacerbation.
2. Disease modifying/preventive strategies.
3. Supportive/symptomatic treatment.
4. Curative remedies including modalities that repair damage to myelin and axons.

This article deals primarily with treatment of acute attacks and disease modifying strategies. There is no curative treatment for MS.

Treatment of Acute Attacks or Exacerbations

The goals of acute treatment are:

1. Reduction of the severity and the duration of attack/relapse.
2. Limiting the permanent damage resulting from the attack, thereby decreasing the burden of disease accrued over time.

Most experts would initiate treatment when the symptoms interfere with normal functioning of the patient. Gadolinium enhancement on MRI may show the new active lesion(s) or the reactivation of older lesion(s). As inflammation appears to damage the myelin and cause exacerbation, the therapy is directed at anti-inflammatory and immunomodulatory strategies. These include:

- Steroids
- Plasmapheresis/plasma exchange
- IV immunoglobulins.

Steroids

Corticosteroids are anti-inflammatory and immunomodulators that alter functions of immune system. **Typically corticosteroids are given for 3 to 14 days with a slow taper afterwards.** High dose methylprednisolone is preferred by most physicians. This has gained acceptance after the observations of faster recovery and reduction of Gd + lesions on MRI in various studies. Low dose steroid treatment, while reducing the symptoms, may increase the risk of subsequent relapse.

Optic neuritis treatment trial is still the landmark trial which provided important information and insight into use of steroids in MS.⁵ Faster recovery and less incidence of relapse was observed in the high dose methylprednisolone group over 2-year period. The dose of methylprednisolone used by various authors has ranged from 500-2000 mg orally or IV for 3-10 days. There is no scientific confirmation of the best type, route and effective dose of steroids in acute attack of MS. There have been reports of reduction of effectiveness of steroids, if used repeatedly.

Plasmapheresis

Patients with severe steroid unresponsive multiple sclerosis relapse may be helped by plasmapheresis. Weinschenker, et al, conducted a randomized placebo-controlled trial on patients of severe MS relapse who did not respond to steroid pulse therapy.⁶ They found plasmapheresis useful in their group of patients. The usefulness of plasmapheresis in steroid unresponsive patients has been linked to different pathological pattern of MS in the subgroup. Actively demyelinating plaques are classified into 4 patterns based on pathology.⁷ Most of the MS lesions are pattern I with cellular cytotoxicity or pattern II with antibody and complement mediated demyelination. The third pattern of lesion is pattern III with oligodendroglipathy. In the 4th pattern, there is primary oligodendrocyte damage with secondary demyelination. Keegan, et al found patients who responded to plasmapheresis had pattern II plaques on histopathology. The patient with non-steroid responsive disease should be offered 4-5 sessions of plasmapheresis within 4 weeks.⁸ This would suggest that the patients with different pathological pattern may benefit from different therapeutic agents.

Intravenous Immunoglobulins

Evidence available does not support the use of intravenous immunoglobulins for acute relapses individually or in combination with methylprednisolone.

In the largest study, known as TARIMS, no significant difference was observed between immunoglobulin and placebo group with regard to primary endpoint of significant change in neurological deficit from baseline to 12 weeks.⁹ A similarly designed smaller study found the comparable results.¹⁰ In another study in patients with optic neuritis,¹¹ no significant differences were observed in the IVIG group and placebo over 6 months of follow-up.

PREVENTIVE DISEASE MODIFYING STRATEGIES

Preventive strategies for MS are as yet principally pharmacological agents for decreasing the frequencies of relapse, delaying the progression of the disease and postponing the conversion of early MS into clinically definite MS. Drugs used under the category are called Disease Modifying Agents (DMAs) and as of now consist of 5 FDA approved drugs and multiple other off label therapeutic agents.

Disease Modifying Agents

Disease Modifying Agents approved by FDA for MS include:

1. The two formulations of interferon-beta 1a (IFN- β 1a)
 - a. Formulation used by intramuscular route (Avonex)
 - b. Subcutaneously administered interferon- β 1a (Rebif)
2. Interferon-beta 1b (IFN- β 1b)(Betaseron)
3. Glatiramer acetate (copaxone)
4. Mitoxantrone (novantrone)
5. Natalizumab (tysabri) has been recently again approved for use but in a limited manner and under a strict protocol. It is available only through a special restricted distribution program called TOUCH program. Under the program only those who are registered with the program are eligible to obtain and use the product.

Besides these agents a number of off label agents are also used singly or in combination with the above mentioned agents.

Table 42.1 showing various agents used for the treatment of MS.

Table 42.1: Immunomodulatory agents for MS

- IFN-β1a
- IFN-β1b
- Glatiramer acetate
- Mitoxantrone
- IVIG
- Natalizumab
- *Immunosuppressants*: Corticosteroids, cyclophosphamide, Azathioprine, Mycophenolate Mofetil, Methotrexate, Cyclosporine A
- Minocycline
- Simvastatin
- Pentoxifylline
- Estriol
- Rituximab
- T-cell vaccination
- Stem cell transplantation
- All trans retinoic acid

Interferons and glatiramer acetate are approved for RRMS. Mitoxantrone is approved for progressive RRMS, SPMS and PRMS. IFN- β1a (Avonex), IFN-β1b (betaseron) and glatiramer acetate (copaxone) are known as A-B-C drugs for MS. The letters A, B and C being derived from the first letter of their trade names.

IFN-β and glatiramer acetate are used as what is called as platform therapy, i.e. as baseline pharmaco-therapeutic agents, and the corticosteroids and the immunosuppressants are used for acute exacerbation and periods of disease instability with increased activity.

Interferon-β

Interferon-β is a class I interferon which helps in MS by various immunomodulatory mechanism.¹²

IFN-β1a (Avonex)

Over the years, various trials for use of IFN in MS have confirmed the benefit of use of interferons. Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) was a double blind randomized placebo-controlled study to determine usefulness of Avonex in delaying development of clinically definite MS in patients presenting with clinically isolated syndrome (CIS).¹³ The probability of developing CDMS was shown to be reduced by 44% in the treatment arm. The analysis revealed that patients at high risk developed CDMS in 50% of placebo while only 20% of IFN group developed the CDMS. In an open label extension of CHAMPS (CHAMPIONS) all patients of CHAMPS trial group were offered Avonex and followed for a total of 5 years.¹⁴ The patients randomized to the placebo group in the original CHAMPS trial were considered the delayed treatment group and those randomized to avonex were considered immediate treatment group. It was noted that the immediate treatment group had less probability of developing CDMS as compared to the delayed treatment group. The mean number of relapses were 0.9 (±1.3) and 1.7 (±2.7) in the immediate treatment and delayed treatment groups respectively.

The trials favor use of intramuscular IFN-β1a in dose of 30 µg every week in patients with RRMS and even in selected Clinical Isolated Syndrome (CIS).

IFN-β1a (Rebif)

Early Treatment of Multiple Sclerosis (ETOMS) study¹⁵ with rebif showed results similar to CHAMPS. In the IFN group, 34% developed CDMS while the percentage in placebo group was 45%. The annual relapse rates were 0.33 and 0.43 in active treatment group and placebo group respectively. Change in the volume of T2 lesion volume on MRI also favored the IFN group.

In the prevention of relapses and disability by interferon- β 1a subcutaneously in multiple sclerosis-2 (PRISMS-2) trial, the percentage of patients who experienced sustained disability at 2 years were 38%, 30% and 27% in placebo, IFN- β -1a (Dose = 22 μ g) and IFN- β -1a (Dose = 44 μ g) respectively.¹⁶

The trials confirm the usefulness of IFN- β 1a subcutaneously in dose of 22-44 μ g thrice weekly. The higher dose is associated with greater adverse effects and possibly more likelihood of developing neutralizing antibodies.

IFN- β 1b (Betaseron)

Paty et al, conducted a placebo controlled study with IFN- β 1b in 327 patients and assessed MRI outcomes in them.¹⁷ At 1, 2 and 3 years, the median percentage change in burden of disease in the treatment arm was significantly more favorable.

In another study,¹⁸ the effect of IFN- β 1b 8 MIU was assessed in 29 patients with relapsing MS. Gd+ lesions were assessed at baseline for 6-7 months before treatment and then for 6 months afterwards. The total mean number of Gd+ lesions per month was 7.27 during pre-treatment and 0.66 during treatment months. Similar results were obtained by other studies. IFN- β 1b (Betaseron) is recommended in the dose of 8MIU subcutaneously thrice weekly in RRMS.

Comparative Efficacy of IFN

Head to head open label studies assessing the comparative efficacies of the different IFN have yielded conflicting results with most indicating equal efficacy and small differences if any. Two trials, *evidence* and *incomin* have shown some differences in the IFN.^{19,20} The evidence study compared the 44 μ g subcutaneously thrice weekly IFN- β -1a (Rebif) and 30 μ g intramuscular IFN- β 1a (avonex). In the EVIDENCE study, 75% of patients on Rebif and 63% of patients on avonex remained relapse-free at 24 weeks. However, this difference decreased to 56% and 48% at 64 weeks of follow-up. MRI results showed 36% relative reduction of mean number of T2 lesion per patient per scan in favor of Rebif group. However, some differences in the baseline MRI features have been pointed out explaining the observed better results with rebif. INCOMIN study also observed superiority of Betaseron over Avonex. This observation also needs to be interpreted with caution as the groups who received Betaseron and Avonex had baseline differences in patient characteristics.

Issue of Development of Neutralizing Antibodies

Neutralizing antibodies are reported to develop in 28-47% of patients with IFN- β 1b,²¹⁻²³ 2-6% of those on IFN- β 1a-Avonex^{3,24} and 13-24% of those on Rebif.^{13,25} Comparative studies have indicated that the Betaseron is the most immunogenic and Avonex the least immunogenic agent. However, the significance of neutralizing antibodies clinically is still mooted. The drugs may be effective despite development of antibodies. Additional long term studies are likely to solve the issue in future. As of now, the immunogenicity of IFN influences the selection of type of IFN. Switching to alternative therapy is an option in patient developing neutralizing antibodies.

Glatiramer Acetate (Copaxone)

This is a synthetic chain of 4 amino acids that mimics myelin basic protein structurally and blocks the immune system from attacking myelin. The drug induces glatiramer acetate specific T cell with a shift towards anti-inflammatory Th-2 cells. Antibodies to GA do not interfere with performance of the drug. It is free of side effects like flu like symptoms, fatigue or depression. Approximately 10% of patients in pre marketing surveillance developed immediate post-injection constellation of symptoms consisting of flushing palpitation, chest pain, dyspnea, constriction of

throat and urticaria. A prospective open label study of MS has reaffirmed the role of GA in preventing or delaying disability in patients with RRMS.²⁶

IFN and Glatiramer Acetate

IFN and GA have different mechanisms of action and at first glance they appear to form a counterproductive combination. There are conflicting results of studies exploring the net effect of the combination on T cell functions.²⁷⁻³⁰ A one year study in which GA was added to IFN, reduction in mean number of Gd enhancing lesions with little difference on EDSS was observed.³¹

Mitoxantrone

This is a cytotoxic drug which has been approved for use in worsening RRMS, SPMS and PRMS. In a phase III trial involving 188 patients with worsening RRMS or SPMS, mitoxantrone was shown to slow the progression of disease on EDSS score and decreased relapse rate.³² Two studies involving small number of patients of RRMS and SPMS showed additional benefit with the combination.^{33,34} In one of these studies, 10 patients with RRMS and SPMS who were on IFN for 6 months, were given monthly mitoxantrone for 1-3 months followed by repeat infusions at 3 monthly interval. Relapse rate and median number of Gd + lesion decreased by 74% and 81% respectively. In the other open label study, patients of worsening RRMS were induced with monthly mitoxantrone and IFN for 6 months. Thereafter, IFN was continued. At the end of 12 months, relapse rate was reduced by 92% and mean EDSS also improved. We have used a regimen of Mitoxantrone and Methylprednisolone in the dose of 12 mg/sqm and 1 gram respectively every three months in 12 subjects with a mean follow-up of at least one year in subjects of RRMS with secondary generalization. Ten subjects are completely relapse free while two had no significant relief.³⁵ *A word of caution that the total dose of this drug should not exceed 200 mg and leucocyte count and echocardiogram must be performed in each and every case before the next dose is administered.*

Monoclonal Antibodies

Various monoclonal antibodies including anti-T12, anti-T11, anti-T4, cM-T412, OKT3, daclizumab, rituximab, IDEC-131 and natalizumab have been studied for use in MS. Most of these were not successful due to unimpressive effectiveness or significant side-effects

Natalizumab

This is recombinant IgG4 κ monoclonal antibody produced in murine myeloma cells. It showed impressive clinical results in phase II and III trials.³⁶ There were reports of progressive multifocal leukoencephalopathy in the patients and it was withdrawn from market.³⁷⁻³⁹ Now it is available only in a restricted manner under TOUCH program.

Immunosuppressant Medications⁴⁰⁻⁵²

MS is a multifactorial and has heterogeneous nature. Logically enough, the concomitant therapies that affect the pathogenesis of MS at different sites, should be more beneficial in management of the disease.

At present, only non-specific anti-inflammatory and antineoplastic agents are used. These agents include corticosteroids, azathioprine, cyclophosphamide, methotrexate and mitoxantrone. Often the deciding factor for use of one agent over the other is treating physician's familiarity and personal preference of one agent over the other. This is largely due to absence of sound scientific evidence of superiority or effectiveness of one agent over the other. This scenario is likely to change with the availability of outcomes of several large scale trials.

IV Immunoglobulin

As yet the evidence in favor of use of IVIG from randomized controlled trials is for RRMS. Even in RRMS, this is mostly used as second line to already established, FDA approved therapies when these are not tolerated due to side-effects or concomitant disease. The evidence in favor of IVIG for RRMS is still marred by smaller study sizes, defective study designs and lack of established optimal dose regimen. The need to give once monthly infusion of 0.2-0.4 g/kg of IVIG and minimal side-effects favor IVIG over the established agents such as interferons. PRIVIG study is underway to compare different doses of IVIG. A randomized double blind placebo-controlled study of early IVIG therapy in CIS was reported recently. IVIG group patients loaded with 2 g/kg loading dose and followed with boosters of 0.4 g/kg once every 6 weeks for 1 year. The cumulative probability of developing clinically definite MS was found to be significantly lower in IVIG group compared to placebo. A meta-analysis evaluated IVIG and concluded that IVIG decreased relapse rate and reduction in trend towards deterioration in treated patients.⁵³

Stem Cell Transplantation

The postulated mechanism of effectiveness of stem cell transplantation is debulking of autoreactive clones followed by restoration of self-tolerance during the immunological recovery. Various single centre and multicenter trials of hematopoietic stem cell transplantation have been reported. European Group for Blood and Marrow Transplantation retrospective study showed 3-year progression free interval in 74% of their 85 patients.⁵⁴ However, the group included different clinical forms of MS and employed immunoablative regimen warranting cautious interpretation of the results. Another Italian GITMO-Neuro Intergroup selected 19 non-primary progressive MS patients showing radiological and clinical deterioration despite conventional treatments and infused autologous peripheral blood stem cells.⁵⁵ At 3-year interval, all patients showed clinical stabilization or improvement with no new MRI active lesions. Significant improvement on quality of life assessment was reported by the author of the group. Patients with rapidly progressive MS with active disease without significant disability are probably the ideal candidates for the therapy. Further randomized controlled trials are required for confirmation of the utility of this modality.

MISCELLANEOUS POTENTIAL FUTURE IMMUNOMODULATORY AGENTS

Pentoxifylline used along with IFN- β 1b (Betaseron) has been shown to reduce serum cytokine levels. Pentoxifylline is a phosphodiesterase inhibitor and suppresses the TNF- α and IFN- γ production. All-trans retinoic acid potentiates T suppressor cells function by IFN- β in patients with MS.

CONCLUSIONS

Recommended evidence-based therapeutic strategies in MS are mentioned in the Table 42.2.

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