Use of Disease Modulating Agents in Multiple Sclerosis

VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Group

It is expected that significant, new information will be forthcoming in this disease area. Thus, the following recommendations are dynamic and will be revised, as new clinical data becomes available. These guidelines are not intended to interfere with clinical judgment. Rather, they are intended to assist practitioners in providing cost effective, consistent, high quality care".

EXECUTIVE SUMMARY

The quality of evidence and strength of recommendation follow the summary statement. See Table 1 for a definition of grading abbreviations.

- Multiple Sclerosis (MS) is a treatable disease. Most concurrent medical conditions do not contraindicate use of these therapies. The frequency of relapses, age or level of disability should not limit consideration and evaluation of a patient for therapy. Discussion of therapy needs to include risks and benefits of pharmacotherapy.
- The standard immune modulating therapies available include the "ABC" drugs, beta interferon 1a (Avonex® and Rebif®) and 1b (Betaseron®) and glatiramer acetate (Copaxone®). Therapy should be initiated and monitored by a neurologist or MS expert. Routine follow-up care should be from these same individuals. (III,B) Patient education and compliance is key to successful therapy with these agents. Use of antipyretics to prevent the flu-like syndrome associated with interferon therapy may increase patient acceptance of this therapy.
- Treatment needs to be continued indefinitely, except in cases where there are unmanageable side effects, lack of clear benefit or new data reveals other reasons for discontinuation. (III,C)
- Several clinical trials support the use of interferon therapy in RR-MS to decrease exacerbation rates and delay progression of disease. (I,A)
- Interferon beta-1b has been studied in SP-MS and shown to delay progression of disability (increase in EDSS score). This finding was from a European study and not corroborated by a North American trial.(I,C)
- Interferon beta-1a has been studied in SP-MS and showed positive results on relapse rate and MRI outcomes. However, confirmed progression of disability was not improved with IFN treatment. (I, C)
- Glatiramer acetate has been shown to be an effective long-term treatment for RR-MS, with efficacy and safety followed for six years.
- The use of mitoxantrone in MS has been FDA approved. However, clinical trials suggest it may be efficacious in SP-MS. (I-C)
- There is not sufficient data to support the use of co-therapy with agents such as interferon beta-1a or 1b, and glatiramer acetate. Trials are currently in progress to address this issue.
- Monitoring of patients receiving these therapies should not be limited to EDSS scales but may also include MRI determination of lesion burden, new lesion appearance and lesion size. (I,B)
- Determination of neutralizing antibodies for interferon beta is not required in all treated patients but should be reserved for patients who display therapeutic failure. However, the cost of testing is high and switching to an alternate therapy may be a rational choice.(I,C)
- There is preliminary evidence to suggest Rebif® achieves a superior effect on relapse rate, time to first relapse and MRI outcomes than Avonex®. This evidence is based on a 24-week trial so the long-term benefits are unknown. (I, A)
- There are differences in dosing and side effect profiles among the ABC agents that allow for patient individualization.
- **Independent of the methods used to obtain cost utility data, the "ABC" therapies for MS have a high cost per benefit gained. (II-1,B)**

Introduction

The management of Multiple Sclerosis (MS) has been significantly improved with the use of disease modulating drugs (DMD). The currently available therapies include newer agents; interferon beta-1a (Avonex® and Rebif®) and beta-1b (Betaseron®) and glatiramer acetate (Copaxone®) in addition to more traditional therapies such as azathioprine, methotrexate and cyclophosphamide. The use of mitoxantrone has been investigated in secondary progressive MS. Controversy surrounds the use of these agents. There is considerable debate on the relative merits of each drug. Additionally, early clinical trials involved differing patient populations, disease characteristics, primary endpoints and dosages. The initial trials were of shorter duration and therefore left long-term safety and efficacy in question. Few trials were conducted in secondary progressive MS, leaving applicability of DMD therapy for these patients undefined. This has resulted in restrictions being placed on therapies for certain patients. In light of new clinical evidence, these restrictions must now be re-examined to ensure appropriate therapy for each individual patient with MS. Several trials are now underway investigating the ABC therapies in head to head comparisons or in combination. These studies should help elucidate the relative efficacy of the agents.

The use of DMD therapy is based on the autoimmune characteristics of MS with activity of the immune system directed against central nervous system antigens. Over the last decade clinical trials have led to a further understanding and definition of the disease. Additionally, these trials have helped to define realistic treatment goals and monitoring parameters for therapy.

This review will address the use of DMD therapy in relapsing- remitting and secondary progressive MS. It will present information from recent trials and extrapolate the results from these trials to the Veteran population.

Background

It is beyond the scope of this review to define the diagnosis of MS. However, the subtypes of MS used in the clinical trials will be discussed as this will aid in interpretation of results. The most common form of MS is relapsing remitting (RR), accounting for 80-85% of patients with a diagnosis of MS. It is characterized by acute attacks with periods of baseline function between. Within 10 years, 30-50% of these patients will develop progressive deterioration of neurologic function marked by less evident acute attacks, secondary progressive (SP). In 10-15% of patients the disease presents with progressive deterioration from the onset, primary progressive disease (PP). [1] The majority of clinical investigations have centered on RR-MS with recent investigations employing SP-MS.

Monitoring of drug efficacy and disease progression has become more clearly defined in recent trials. Initial studies employed changes in disability scales as primary indicators of disease progression or remission. The Krutzke Expanded Disability Status Scale (EDSS) was the cornerstone of these evaluations. Inherent problems with this endpoint included rater variability and weighting of the scale toward motor disturbances and ambulatory deficits. This could account for the relative lack of DMD efficacy in patients with progressive disease who are wheelchair bound. Paty et al; have shown that the use of quantitative MRI techniques with T_2 weighting can more accurately define the location and extent of MS lesions.[2] The use of systematic serial cranial MRIs can give an accurate picture of the dynamic lesion changes seen, while clinical changes often lag behind.

Initially, only ambulatory patients with RR-MS were treated with DMDs, particularly interferon beta, as early trials showed benefits limited to this population. Subsequent trials have now shown that these therapies may benefit a wider patient population than initially defined. Additionally, it has now been shown that therapy early in the disease may prevent cranial lesions from expanding and causing more clinical impairment. In SP-MS, it has been shown that preservation of existing neural function can prevent further progression of the disease. This finding is not associated with changes in the EDSS but is more accurately defined with serial cranial MRI. However, a paucity of data exists in this disease type and the majority of studies show benefit in patients who have relapse in addition to progression of disease. A more in depth discussion of these trials will follow. They suggest that all patients may benefit from some form of DMD

therapy. An important caveat remains. There will be responders and non-responders to DMD therapy. Patients will exhibit varying degrees of response, no single outcome is guaranteed. It is important to note that patient education is critical to the success of therapy.

Interferon (IFN) Beta-1a and 1b

Several trials have shown that therapy with IFN beta can decrease the number of acute attacks and slow disease progression as measured by EDSS scores in patients with RR-MS.[3-5] These trials employed both forms of IFN beta, 1b and 1a. Due to differences in trial design, dosing and primary outcomes, no head to head comparisons of these agents can be made. The number of acute attacks in RR-MS patients was decreased by approximately 30% in these three trials. A significant decrease in disease burden as measured by MRI was also show with the higher doses on IFN used in the trials.[3,4] Data for up to three years after therapy initiation is reported in these trials with no decrease or plateau of effect.

A study conducted by the European Study group described the benefits of IFN beta therapy in patients with SP-MS.[6] In this trial 60% of treated patients were progression free with effects becoming statistically significant after 12 months. The appearance of new gadolinium-enhancing lesions was significantly less in treated patients than in placebo. This benefit remained over the two-year duration of the trial. Total disease burden on MRI was 4-5% decreased in treated versus placebo patients. The positive MRI findings in this trial have been duplicated with a 3-year IFN beta-1a trial.[7] In contrast; a North American trial did not display the same findings. A difference in patient type and number of relapses being experience may have affected patient responsiveness to IFN therapy, thus accounting for more positive results in the European study.

These trials have brought dosing frequency, route and dosage forward as issues to be defined. Both IFN beta-1b and 1a have demonstrated a possible dosage effect.[5,8,9] In these trials, higher dosages correlated with significantly improved response. The use of a weekly intramuscular injection was also shown to significantly decrease exacerbations and volume of new T2 MRI lesions. [9] A positive effect on MRI lesions was found with weekly subcutaneous injections of IFN beta-1a.[10] Further trials are required to define the optimal frequency and route of IFN administration.

The optimal time to initiate therapy is being investigated. Current guidelines from the National MS Society recommend therapy be initiated following a definite diagnosis of MS.[33] However, the results from the CHAMPS trial showed that initiating therapy with IFN beta-1a after the first clinical demyelinating event lessened the chances of developing clinical MS in comparison to placebo treated patients.[34] After 3 years 50% of placebo treated patients had not experienced a second clinical demyelinating event. These results demonstrate that IFN treatment may be unnecessary in a significant proportion of patients because of the unpredictable nature of the disease.

There are currently two preparations of IFN beta-1a available. Considerable debate concerning the optimal product exists. Both products are structurally identical to human IFN beta but differ in the cell line used for production. Avonex® uses a mammalian cell culture and Rebif® a Chinese hamster ovarian cell culture. The products also differ in dosing and FDA approved indications. Table 1 compares the products. The EVIDENCE trial compared these two agents with Rebif demonstrating better results. However, the results available are only for 24 weeks, long term results remain unknown and could prove significant.

The use of IFN beta-1b in SP-MS was evaluated by a cost utility analysis.[11] The rate of relapse and proportion of patients becoming wheelchair dependent over a three year time period were analyzed. The cost/quality adjusted life year (QALY) gained was high; 1,024,667 British pounds or $1,639,467. Brown, et al have conducted a similar evaluation of IFN beta-1b therapy in Canadian patients with RR-MS and found the cost of IFN therapy would approximate $100,000/QALY with the improvements being seen the longer a patient received therapy, not during the initial period.[12] Similar cost utility models were used to compare IFN beta-1a and 1b, and glatiramer acetate. Estimates from this analysis ranged from $790,000 to $1,000,000/QALY.[13]

Table 1 Interferon beta-1a products

Product	FDA indication	Dose	frequency
Avonex®	RR-MS to slow accumulation of disability and reduce relapse rate	6 MIU (30 *u*g) IM	weekly
Rebif®	RR MS	12 MIU (44 *u*g) SC	Three times weekly

Glatiramer Acetate

Glatiramer Acetate is postulated to work by a different mechanism than IFN in therapy of MS. IFN is thought to decrease the inflammatory process by interactions with cytokines, T cells and other inhibitors of inflammation.[14,15] Glatiramer acetate is thought to mimic myelin basic protein and induce suppression of the T cell immune response.

Clinical trials with glatiramer acetate have focused on RR-MS. Positive results on EDSS scores and relapses versus placebo were seen in three Level 1 trials.[16-18] These trials employed 20 mg of glatiramer acetate injected subcutaneously on a daily basis. Beneficial effects on MRI lesions have been demonstrated by a recent trial. [19] In this study, treated patients demonstrated a 35% decrease in total gadolinium enhancing lesions versus placebo. There were also significantly fewer new T_2 lesions versus placebo. The newer trials have suggested the effects of glatiramer acetate may increase over time.

Glatiramer acetate does not display the same side effect profile as IFN therapy. It does not cause flu like syndrome, anemia, leukopenia, depressive symptoms or liver changes. It has no known drug interactions. These differences may make it an alternative product for some patients unable to tolerate IFN therapy or with contraindications.

Mitoxantrone

A phase II clinical trial of this cytotoxic agent showed benefit in RR-MS.[20] This early trial demonstrated positive changes in clinical and MRI endpoints. These results were extended into SP-MS with a European trial. [21] Dosages of 5 and 12mg/m2 were used in this trial. Significant benefits were seen with mitoxantrone therapy versus placebo. The EDSS score was decreased from baseline, relapses were reduced and there was a decrease in T2 and gadolinium enhancing lesions.

Due to its structural similarity with anthracyclines, mitoxantrone is associated with cardiotoxicity. Left ventricular ejection fraction was decreased in 19.2% of treated patients versus 13.8% of the placebo group.[21] Cumulative doses of greater than 140mg/m^2 should be used cautiously with appropriate monitoring. Other adverse effects include, nausea, hair loss and leukopenia. These effects may limit patient acceptance of this therapy.

Discussion

The clinical investigations of DMD therapy for MS have shown this to be a treatable, not a curable disease. The use of DMD therapy has been shown to delay progression and prevent relapses in RR-MS. (refer to Table 2) Early treatment with these agents may provide the best outcomes. Selection of an appropriate agent must be individualized and take into account tolerability, dosing frequency and route, and the degree of patient involvement and compliance. An important caveat to remember is that treatment with DMD will not reverse or lessen any existing neurologic compromise. Once therapy is initiated it should not be discontinued except for unmanageable adverse effects, as benefit gained with therapy may be lost upon discontinuation. The impact on healthcare expenditures should be considered as several cost utility analyses of DMD therapy have shown the cost/QALY to be high in relation to other interventions. Appropriate monitoring of patients receiving DMD therapy is crucial. The use of the EDSS scales should not be the sole

marker of treatment efficacy. Other parameters include decreased hospitalizations, and MRI markers of lesion burden. The measurement of neutralizing antibodies to IFN beta may be necessary in some but not all patients. Development of these antibodies may result in decreased efficacy of the drug. Since development of these antibodies is unlikely in most cases, it is reasonable to make the clinical choice of increasing IFN dose to overcome a dose affect or change therapy to glatiramer acetate or other immunosuppressive therapy to increase the cost effectiveness of therapy. If levels are indicated, they should be repeated at 3-month intervals to determine if therapy with an alternate DMD would be indicated.[22,23] The management of MS patients is an intricate and specialized area. Studies have shown patients with few relapses may already exhibit irreversible axonal damage.[24] Neurologist or MS specialists are the most appropriate physicians to be providing care to these patients. This will insure the optimal care for each patient.

Table 1

Strength of Recommendation
A: There is good evidence to support that the intervention be adopted.
B: There is fair evidence to support that the intervention be adopted.
C: There is insufficient evidence to recommend for or against the intervention, but recommendations may be made on other grounds.
D: There is fair evidence to support that the intervention be excluded.
E: There is good evidence to support that the intervention be excluded.

Quality of Evidence
I: Evidence obtained from at least one properly randomized controlled trial.
II-1: Evidence obtained from well-designed controlled trials without randomization.
II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3: Evidence obtained from multiple time series studies with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III: Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

Table 2: Results of Large Randomized Trials

Relapsing Remitting						
Trial	**Design[a]**	**N**	**Drug**	**Duration**	**Baseline EDSS[b]**	**Results**
Jacobs et al[4]	RDB, PC, MC	301	Interferon beta –1a 30ug IM[c] weekly	2 years	1-3.5	Decrease in sustained progression in EDSS Decrease in exacerbations Decrease in number and volume of gadolinium enhancing MRI lesions
PRISMS Study Group[5]	RDB, PC, MC	560	Interferon beta-1a 22 *u*g, 44 *u*g SQ[d] three times weekly	1 and 2 year analysis	0-5	Relapse rate 27% and 33% risk reduction for 22 *u*g and 44 *u*g respectively Time to first relapse 3 months longer and 5 months longer for 22 *u*g and 44 *u*g respectively Decrease in active lesions and on burden of disease as measured by MRI
The INFB Multiple Sclerosis Study Group[8]	RDB, PC, MC	372	Interferon beta-1b	48 months	0-5	Decrease in annual exacerbation rate continued over 5 years Decrease in exacerbation rate not statistically greater than placebo after year 2 of treatment
Johnson et al[17]	RDB, PC, MC	251	Glatiramer acetate 20 mg daily	2 years	0-5	
OWIMS[10]	RDB, PC,MC		Interferon beta-1a 22 *u*g, 44 *u*g SQ weekly	48 weeks	0-5	MRI endpoints; new and newly active T2 and gadolinium enhancing lesions were decreased by 29% and 53% over placebo for 22 *u*g and 44 *u*g respectively
Johnson et al[25]	RDB, PC, MC	251	Glatiramer acetate 20 mg daily	6 year extension		6 year mean relapse rate of 0.23
Herndon et al[27]				Safety Extension of Jacobs et al[4]		5% incidence of NAB[e] 47% decline in IV[f] steroid courses for exacerbations
INCOMIN Study[28]	R, MC	188	IFN beta-1b 8 MIU SC QOD IFN beta-1a (Avonex®) 6 MIU IM weekly	1 and 2 year results		Relapse free- IFN beta-1b 51%, beta-1a 36%, p=0.03 Free of new T2 lesions- IFN beta-1b 55%, beta-1a 26% p<0.0003
EVIDENCE Trial[32]	RDB, MC		IFN beta-1a Rebif®- 12 MIU three times week Avonex® 6 MIU IM weekly	24 weeks		Response to Rebif® superior for outcomes of relapse rate, time to first relapse, proportion of patients relapse free and steroid use.
Secondary Progressive						
Trial	**Design**	**N**	**Drug**	**Duration**	**Baseline EDSS**	**Results**
SPECTRIMS study[30]	RDB, MC,PC	618	Interferon beta-1a 22 or 44 ug three times weekly	3 yr.		relapse rate both IFN doses vs. placebo 0.50 vs. 0.7 p <0.001 No significant effect on disability progression
European Study Group[6]	RDB, PC, MC	358	Interferon beta-1b		3-6.5	Delayed progression of disease for 9-12 months Decrease in T2 lesion volume and newly active lesions on MRI Decrease in time to becoming wheelchair bound
Hughes et al[26]				Secondary analysis of SPECTRIMS		If patients had relapses in 2 years prior to interferon therapy they were more likely to respond. This is likely due to a more active disease process in these individuals

[a] RDB= randomized double-blind, MC= multicenter, PC= placebo-controlled
[b] EDSS= Kurtzke Expanded Disability Status Scale
[c] IM intramuscular
[d] SQ subcutaneous
[e] NAB neutralizing antibody
[f] IV intravenous

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