

PEER REVIEWED

Multiple Sclerosis Agents

A review of interferon-beta and glatiramer acetate

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Multiple sclerosis (MS) is a chronic neurological disease characterized by idiopathic inflammation of the central nervous system (CNS). Inflammation is theorized to result from lymphocyte and macrophage infiltration, which causes demyelination and axonal injury and presents as neurological signs generally disseminated in both location and time.^{1,2} The development of MS is theorized to be genetically determined and may be triggered by an environmental factor. The clinical signs of MS can be classified based on presentation into several categories which include relapsing-remitting MS (RRMS) characterized by acute attacks followed by complete or partial recovery; primary progressive MS (PPMS) is disease progression from onset; secondary progressive MS (SPMS) occurs when an initial RRMS course progresses with or without occasional relapses, remissions, and disease stabilization; and progressive relapsing MS (PRMS) is progression from the onset of disease with acute relapses followed by full or partial recovery to the level of prior disability.²

The McDonald Criteria³ recommends that a diagnosis of MS be based on objective demonstration of lesion dissemination in both time and space. These recommendations support the need for both clinical and imaging (e.g., MRI) evaluations with MS diagnosis specifically defined based on the number and location of neurological symptoms, as well as the time interval between occurrences. These criteria have been used to determine the initiation of disease-modifying treatments that include interferon-beta-1a and -1b and glatiramer acetate. These agents are used to prevent and delay long-term disability which generally occurs gradually over several years.⁴

PHARMACOLOGY/ PHARMACOKINETICS

Type I interferon-beta (INFB) has been theorized to impact the disease course of MS through the induction of a signaling pathway cascade leading to the production of interferon-stimulated gene products with immunomodulatory, antiviral and antiproliferative properties.⁵ Interferon-beta-1b (INFB-1b) is available as the brand name product Betaseron[®], and is a non-glycosylated recombinant bacterial cell interferon that differs from human INFB by a single substitution in the amino acid sequence.^{6,7} The interferon-beta-1a (INFB-1a) products, Avonex[®] and Rebif[®], are glycosylated recombinant agents, each with an amino acid sequence identical to that of human INFB.⁵ Avonex[®] and Rebif[®] differ only in specific manufacturing processes and preservative selection.^{8,9} Serum drug concentrations of INFB are neg-

Summary

Indications. Interferon-beta-1a, interferon-beta-1b and glatiramer acetate are indicated for the management of relapsing-remitting multiple sclerosis exacerbations. Interferon-beta-1b also has the indication for the treatment of secondary progressive multiple sclerosis.

Monitoring parameters. Interferon-beta therapy requires regular monitoring of complete blood count with white cell differential and platelets. Liver function testing is recommended periodically during interferon-beta initiation and use; in addition, thyroid function testing should be performed every six months for patients with a history of thyroid dysfunction or as clinically indicated. Routine laboratory monitoring is not currently recommended for glatiramer acetate administration.

Dose. The recommended dose for Avonex[®] (interferon-beta-1a) is 30 mcg injected intramuscularly once weekly and the dose for the other marketed interferon-beta-1a product (Rebif[®]) is 44 mcg subcutaneously three times weekly. Interferon-beta-1b (Betaseron[®]) is dosed 250 mcg subcutaneously every other day. The dose for glatiramer acetate (Copaxone[®]) is 20 mg subcutaneously once weekly.

Pregnancy Category. Interferon-beta is classified as pregnancy category C and glatiramer acetate is category B.

Pediatrics. The safety and efficacy of interferon-beta and glatiramer acetate have not been established in patients below the age of 18.

Geriatrics. Patients over the age of 65 have not been evaluated in sufficient enough numbers for the determination of treatment difference with interferon-beta or glatiramer acetate compared to the general population.

Dosage Formulations. Avonex[®] (interferon-beta-1a) is available as a 30 mcg single-use, pre-filled syringe and a 30 mcg lyophilized powder vial. Rebif[®] (interferon-beta-1a) is available as both a 22 mcg and 44 mcg pre-filled syringe. Betaseron[®] (interferon-beta-1b) is packaged as a 0.3 mg lyophilized, single-use vial. Finally, glatiramer acetate is available as a 20 mg single-use, pre-filled syringe.

TABLE 1. AVAILABLE DOSAGE STRENGTHS AND DOSE EQUIVALENCE APPROXIMATIONS^{7-9,12}

Drug	Product Packaging	Equivalent Dosing
Avonex [®] (interferon beta-1a) by Biogen, Inc.	30 mcg lyophilized powder vial 30 mcg pre-filled syringe	30 mcg weekly (intramuscular)
Betaseron [®] (interferon beta-1b) by Berlex Lab	0.3 mg lyophilized powder single use vials	250 mcg every other day (subcutaneous)
Copaxone [®] (glatiramer acetate) by Aventis Pharm.	20 mg single-use pre-filled syringe	20 mg/week (subcutaneous)
Rebif [®] (interferon beta-1a) by Serono, Inc.	22 mcg pre-filled syringe 44 mcg pre-filled syringe	44 mcg three times weekly (subcutaneous)

ligible after intramuscular or subcutaneous administration; therefore, biologic response markers have been used to determine the equipotent doses of available interferon products. A correlation has been observed between increased dosing of these agents and corresponding elevations in these biological markers.¹⁰ In respect to the amount of INFB found in each preparation, there is a considerable difference, e.g., 8 million international units (MIU) of Betaseron[®] contains 250 mcg of INFB-1b protein, 6 MIU of Rebif[®] and Avonex[®] contain 22 mcg and 30 mcg of INFB-1a protein, respectively.¹¹

Glatiramer acetate (GA) is a conglomeration of acetate salts of synthetic polypeptides consisting of four naturally occurring amino acids (L-glutamic acid, L-alanine, L-tyrosine, and L-lysine) resembling the amino acid sequence of myelin basic protein. This agent acts as a synthetic molecule for antigen presenting cells and may alter the activity of myelin specific T-cells.^{5,12} The onset of action of GA may be delayed, as supported by *in vitro* data which indicate that treatment over time causes glatiramer-specific T cells to proliferate and secrete anti-inflammatory cytokines typical of TH2 regulatory or suppressor T cells.⁵

CONTRAINDICATIONS AND PRECAUTIONS^{7-9,12}

Interferon therapy is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta or formulation components. Use of lyophilized vials of Avonex[®] and single-use Rebif[®] syringes is contraindicated in patients with hypersensitivity to human albumin. Use of GA is contraindicated in patients with hypersensitivity to the active ingredient or mannitol. Rare anaphylactic events have been reported with both INFB and GA use.

INFB should be used with caution in patients with pre-existing depression or mood disorder. The manufacturer of Avonex[®] (INFB-1a) provides warnings for use in patients with seizure or cardiac disorders. Rebif[®] (INFB-1a) should also be used with caution in patients with pre-existing seizure disorder. INFB requires monitoring of blood counts, liver function tests and thyroid function during administration. INFB also has been shown to have abortifacient potential.

CLINICAL TRIALS

This review will summarize pivotal trials that evaluate the efficacy of INFB and GA therapy with a focus on the clinical practice

issues relating to the benefits of early intervention, comparison of product efficacy (including optimal dosing frequency), and utility of these agents in the management of SPMS.

Intervention after first neurological event

The objectives of the CHAMPS¹³ and ETOMS¹⁴ trials were to assess the effects of INFB therapy on the risk of conversion to clinically definite MS (CDMS) in patients with a first neurological event and MRI evidence of subclinical demyelination. The CHAMPS trial included patients (n=383) who had experienced a unifocal onset 2 weeks prior to enrollment, while ETOMS trial subjects (n=309) could have had either unifocal or multifocal symptom presentation 3 months prior to study entry. Both trials were placebo controlled with patients randomized to INFB-1a, specifically Avonex[®] [30 mcg intramuscularly (IM) once weekly] in the CHAMPS trial and Rebif[®] [22 mcg subcutaneously (SC) once weekly] in the ETOMS trial. The primary endpoint of each trial was the development of CDMS defined as a new visual or neurological event (lasting >48 hours; CNS location effects different from previous occurrence) confirmed by neurological examination. Secondary endpoints included MRI changes in both trials and changes in the Kurtzke expanded disability scale (EDSS) or the Scripp's neurological rating scale (SNRS) in the ETOMS trial.

The CHAMPS trial was terminated after 22 months due to statistically improved efficacy of INFB-1a compared to placebo as related to the primary endpoint of CDMS (p=0.029).¹³ The results of the CHAMPS trial showed the probability of CDMS development was statistically lower in the INFB-1a group compared to placebo, based on a rate ratio of 0.56 (95% CI, 0.38-0.81; p=0.002). When subjects were stratified by type of event and number of MRI lesions, the results also indicated a lower probability of CDMS in the INFB-1a group (adjusted rate ratio=0.49, 95% CI, 0.33-0.73, p<0.001; similar effect among subgroups). Increases in the volume of brain lesions based on T₂-weighted MRI scans were statistically lower in the INFB-1a group compared to placebo at 6 months (p<0.001), 12 months (p=0.004) and 18 months (p<0.001). Lesion presence may have been underestimated due to MRI data exclusion at 6, 12 and 18 months of those patients who discontinued treatment as a result of CDMS development.

The duration of the ETOMS trial was 2 years with 278 of 309 randomized patients participating until trial completion.¹⁴

TABLE 2. CLINICAL TRIAL ENDPOINTS: INFB INITIATION AFTER FIRST NEUROLOGICAL EVENT^{13,14}

STUDY	CHAMPS	ETOMS
CDMS Conversion	Cumulative probability (3 yr follow/up)	
	AV=35% PL=50%	RR=0.56; 95%CI, 0.38-0.81, p=0.002
MRI Changes	Number of patients per group	
	RB=52/154 (34%) PL=69/154 (45%)	p=0.047
EDSS or SNRS	T2 lesion volume: +8.8% (PL) vs. -13% (RB), p=0.002	
	Unchanged both groups	

*mean % change
Key: AV=Avonex®, PL=placebo, RR=risk ratio, RB=Rebif®, GEL=gadolinium-enhancing lesions

Thirty-four percent of the INFB-1a patients converted to CDMS compared to 45% of placebo patients; odds ratio (OR) for conversion was 0.61 (95% CI, 0.37-0.99, p=0.047). Time to second relapse occurrence was 569 days in the INFB-1a group compared to 252 days in the placebo group based on observations of 30% of study participants (30th centile; last quantile reached by both groups). Annualized relapse rates between the groups were 0.33 (INFB-1a) vs. 0.43 (placebo), incidence density ratio=0.77 [0.059-1.00], p=0.054. Functional deterioration based on EDSS and SNRS scores was unchanged for both groups and was attributed to the early stage of disease presentation. MRI results showed significantly fewer median T2 lesions in the INFB-1a group compared to placebo, p<0.001. The absolute change in lesion volume was improved in the INFB-1a group (-13 mean % change) compared to placebo (+8.8 mean % change); p=0.002. Lesion activity may have been underestimated in the placebo group due to open-label treatment allocation subsequent to CDMS development in select patients.

Despite the benefits seen in the reduction of CDMS development in the short term, long-term benefits of early interferon therapy could not be supported by the CHAMPS¹³ and ETOMS¹⁴ trials. Previous pathology and MRI evaluations indicate that axonal damage may occur early in the course of MS.²⁰⁻²⁴ Information is available that indicates MRI evaluation is beneficial because of the unpredictability of lesion number and volume at the time of initial and subsequent demyelinating events for the development of CDMS over 10 years.²⁵ MRI results may assist in risk factor assessment for CDMS development and guide therapy. Currently, the Executive Committee of the Medical Advisory Board of the National Multiple Sclerosis Society supports the initiation of therapy with an immunomodulator “as soon as possible following a definite diagnosis of MS with a relapsing course, and may be considered for selected patients with a first attack who are at high risk for MS.”²²⁵

Therapy selection

Two clinical trials^{11,15} directly compared available INFB products. These trials were not double-blinded due to the difficulties in ethically treating patients and maintaining blinding standards

while administering products with various injection schedules. The INCOMIN¹⁵ trial was a two year study comparing INFB-1b 250 mcg SC every other day to INFB-1a 30 mcg IM once weekly in patients with RRMS, EDSS between 1-3.5; ≥ 2 relapses in the prior two years, but with no relapses or treatment with corticosteroids 30 days prior to study initiation (n=188). The EVIDENCE¹¹ trial included patients with RRMS, who were interferon naïve and had EDSS scores between 0-5.5, and experienced ≥ 2 exacerbations in the prior two years (n=677). This trial compared SC Rebif[®] 44 mcg administered three times weekly (TIW group) to 30 mcg IM Avonex[®] once weekly (OW group). The primary outcome measurement for each study was the proportion of relapse-free patients after 24 weeks in the EVIDENCE trial and 24 months in the INCOMIN trial. Relapses were defined as the development of new neurological symptoms or worsening of a prior symptom lasting at least 24 hours in the absence of fever after at least 30 days of disease stability.

The number of patients required to achieve a statistical power of 80% in the INCOMIN trial was 236.¹⁵ Due to the commercial introduction of a third INFB product and the potential for its use by participating centers, enrollment was discontinued after 20 months and resulted in the randomization of 188 patients who were evaluated by intention-to-treat analysis. A larger proportion of INFB-1b patients remained relapse-free (49/96) compared to the INFB-1a group (33/92), p=0.03. The relative risk (RR) of relapse in the INFB-1b group compared to INFB-1a was 0.76 and the number needed to treat (NNT) was seven. More patients discontinued therapy in the INFB-1a group compared to INFB-1b because of disease activity or progression (p=0.21); however, more patients in the INFB-1b group required discontinuation as a result of adverse effects or laboratory abnormalities, p=0.015. Less patients in the INFB-1b groups had progression of sustained and confirmed disability compared to the comparator group; RR=0.44 (0.25-0.80), p=0.005 and NNT=6. MRI results were available for 149 patients, and significantly more patients in the INFB-1b cohort had the absence of new proton density/T2 lesions compared to INFB-1a, p<0.0003. Results indicated the potential for increased effec-

TABLE 3. CLINICAL TRIAL ENDPOINTS: COMPARATIVE INFB TRIALS^{15,11}

STUDY	INCOMIN	EVIDENCE
Proportion relapse free (24 mos.)	<ul style="list-style-type: none"> • INFB-1b: 49/96 (51%) • INFB-1a: 33/92 (36%) 	<ul style="list-style-type: none"> • RR=0.76, 95% CI, 0.59-0.99 • NNT=7
Sustained/ confirmed disability/progression	<ul style="list-style-type: none"> • INFB-1b: 28/92 (30%) • INFB-1a: 13/96 (13%) 	<ul style="list-style-type: none"> • RR=0.44, 95% CI, 0.25-0.80 • NNT=6
Discontinuation reason (# patients)	<ul style="list-style-type: none"> • INFB-1b: DP(3), ADR(5) • INFB-1a: DP(10), ADR(1) 	<ul style="list-style-type: none"> • TIW: ADR(16), efficacy(3) • OW: ADR(14), efficacy(1)
MRI disease burden	<ul style="list-style-type: none"> • INFB-1b: decrease 2.8% • INFB-1a: increase 11.7% (p<0.0001) 	<p>Proportion(%) CU (week 24):</p> <ul style="list-style-type: none"> • TIW: 48 • OW: 33, p<0.001 <p>Proportion(%) T2 (week 48):</p> <ul style="list-style-type: none"> • TIW: 63 • OW: 45, p<0.001

Key: DP=disease progression or persistence; ADR=adverse drug reaction; TIW=INFB-1a (Rebif®) 44 mcg tiw; OW=INFB-1a (Avonex®) 30 mcg once weekly; OR= odds ratio (TIW relapse-free/ OW relapse-free); CU=combined unique lesion (T2 and T1 Gd-enhancing)

tiveness of both INFB products over time, as demonstrated by only a marginal relative difference in the number of relapse-free patients between the two groups after 6 months, followed by 19% higher relative difference in favor of INFB-1b after one year and 47% higher difference after 2 years.

Patients who were randomized to either once (OW) or three time weekly (TIW) INFB-1a in the EVIDENCE trial were included in the primary analysis based on an intention-to-treat cohort, with encouragement of protocol procedure continuation (including MRI) for those patients who discontinued therapy.¹¹ The primary endpoint of relapse-free patients was evaluated using logistic regression with an odds ratio (OR) defined as the odds of being relapse free with TIW divided by the odds for OW. After 24 weeks, 75% (254/339) of TIW patients and 63% (214/338) of OW patients remained relapse free; OR of 1.9 (95% CI, 1.3-2.6, p=0.0005). After 48 weeks, 62% (209/339) of TIW and 52% (177/338) of OW patients remained relapse free, OR=1.5 (95% CI, 1.1 to 2.1; p=0.009). The time to relapse was also prolonged further by the TIW group compared to OW, hazard ratio (HR)=0.70 (95% CI, 0.55 to 0.88, p=0.003). Disability progression was defined by one point or greater progression in EDSS confirmed at 3 or 6 months. In the TIW group, 43 patients had confirmed disability progression at two consecutive clinic visits separated by three months, HR=0.87 (95% CI, 0.58 to 1.31, p=0.51). Patients randomized to TIW had fewer combined active (T2 and T1 Gd-enhancing) lesions per MRI scan, compared to OW at week 24, p<0.001. Gd was not used during the week 48 MRI evaluations; however, the results of T2-lesion assessment were favorable for the TIW group, p<0.001.

An open-label trial conducted by Khan, et al¹⁶ compared the efficacy of INFB-1a 30 mcg IM once weekly (n=40), INFB-1b 250 mcg SC on alternating days (n=41), GA 20 mg SC daily (n=42) and untreated patients (n=33). The study included patients with RRMS with EDSS ≥ 4 who had at least one exacerbation in the previous two years. It was required that patients had not received previous treatment with the study agents and had stable disease with no use of corticosteroids for four weeks prior to study entry. Patients chose their therapy after neurologist consultation, and during the course of the study 10 patients switched therapy (six from non-treatment, and two from each INFB group). The primary efficacy endpoint was a comparison of relapse rate between groups, with relapse defined as the appearance of new or worsening neurological symptoms lasting at least 48 hours. Two cohorts were used for statistical evaluation; the intention-to-treat (I) group classified by initial enrollment agent and the final drug (F) cohort based on final agent used at the end of 12 months. After 12 months, the mean number of relapses were 0.97 (untreated), 0.85 (INFB-1a), 0.61 (INFB-1b) and 0.62 (GA) in each group based on “I” analysis. Only patients in the INFB-1b and GA groups had a significant reduction in relapse rate compared to those untreated, p=0.002 and p=0.003, respectively. When “F” analysis was used, the mean number of relapses was 0.96 (untreated), 0.86 (INFB-1a), 0.61 (INFB-1b) and 0.65 (GA). Changes observed in the secondary endpoint of EDSS were increases of 0.21 and 0.11 points in the untreated and INFB-1a groups, respectively and decreases of 0.18 points in the INFB-1b group and 0.31 points in the GA group. Reductions were significant for both the INFB-1b (p=0.01) and GA (p=0.001) groups compared to untreated patients.

The results of INFB and GA comparative product trials^{11,15,16} suggest that more frequent dosing of INFB (such as INFB-1b and INFB-1a dosing of every other day and three times weekly, respectively) may be of greater benefit than a once weekly regimen. Additionally, GA, which is dosed once weekly and has fewer adverse effects compared to interferon therapy, was shown to have better results in an open-label trial comparing this agent to once weekly doses of INFB-1a. To date, there has not been a clinical trial comparing three times weekly dosing of INFB-1a with GA or INFB-1b.

Secondary progressive MS

Three randomized, double-blind trials have evaluated the use of INFB in patients with SPMS. The study populations of the European Study Group of INFB-1b in SPMS¹⁷, SPECTRIMS¹⁸ and IMPACT¹⁹ trials included patients with SPMS defined as clinical deterioration sustained over six to 12 months after an initial RRMS course. Patients were required to have EDSS of approximately 3.0 to 6.5. In the European Study¹⁷, patients were randomized to placebo (n=358) or INFB-1b titrated from 4 million units (MIU) during the first two weeks to 8 MIU every other day thereafter. The primary endpoint of this trial was the time to neurological deterioration from baseline assessment to a scheduled, quarterly visit when an increase in ≥ 1 point was observed in the EDSS. Patients with baseline EDSS of 6.0-6.5 were considered to have progression with a lower 0.5 point increase. All measures were confirmed during a subsequent clinic visit three months later. The nonparametric analysis of covariance was used to evaluate the results due to the non-linearity of the EDSS score. Patients in the INFB-1b group had a longer time to deterioration compared to placebo, $p=0.0008$. Confirmed progression was found in 49.7% of placebo patients compared to 38.9% INFB-1b patients, $p=0.0048$. Logistic regression showed that placebo patients had a 1.6 time higher probability of disease progression, OR=0.63, 95%CI, 0.46-0.85. Time observed until becoming wheelchair bound (EDSS ≥ 7) was also delayed in the treatment group, OR=0.66, 95%CI, 0.47-0.93. In the placebo group, 24.6% of patients obtained an EDSS higher than 7 compared to 16.7% in the INFB-1b group, $p=0.0277$. INFB-1b treatment resulted in a mean decrease of 5% in the mean MRI T2 lesion volume, compared to an 8% increase in the placebo group, $p<0.0001$.

The SPECTRIMS¹⁸ trial evaluated the efficacy of two different doses of INFB-1a in SPMS patients over three years. Subjects were randomized to 22 mcg (n=172) or 44 mcg (n=161) INFB-1a three times weekly or placebo (n=173). The primary endpoint of this trial was time to clinically confirmed disability progression as similarly defined in the European Study. There was no significant difference in time to sustained disability progression between the placebo and either INFB-1a group. When patients were stratified based on sex, males had a 0.49 (44 mcg) and 0.43 (22 mcg) per year exacerbation rate during INFB-1a administration compared to 0.66 for placebo ($p=0.007$ for 44 mcg vs. placebo and $p=0.0025$ for 22 mcg vs. placebo). Women had yearly exacerbation rates of 0.51 (44 mcg), 0.53 (22 mcg), and 0.75 (placebo); $p=0.009$ (44 mcg vs. placebo) and $p=0.012$ (22 mcg vs. placebo). Multiple study outcomes were evaluated using a composite log rank score of assessments of time to progression, exacerbation rate, MRI lesion burden, MRI T2 activity, and Integrated Disability Status Score or IDSS (area-under-an-EDSS-time-curve adjusted for baseline). The composite score showed a treatment benefit for each dose ($p<0.001$) and a treatment-by-sex interaction ($p=0.014$) for this outcome.

The IMPACT¹⁹ trial assessed the efficacy of 60 mcg INFB-1a IM once weekly (n=217) versus placebo (n=219) in patients with SPMS with or without recent relapses, disease progression over the prior year, MRI lesions consistent with MS, and EDSS of 3.5-6.5. In this trial, disease progression was evaluated based

on both the EDSS and the National MS Society's Clinical Outcomes Assessment Task Force recommended alternative, the MS Functional Composite (MSFC). The MSFC is based on quantitative tests of ambulation, unlike the EDSS which depends on standard neurological examinations. Disease progression was observed in both groups based on MSFC, with a 40.4% reduction in median worsening reported in the INFB-1a group. There was no significant difference in benefits when patients were stratified based on recent relapses, EDSS score range, and baseline MRI lesion volume. When EDSS was used, the difference between groups in relation to disease progression were not statistically significant. Based on the intention-to-treat cohort, 139 (63%) placebo and 160 (74%) INFB-1a patients were relapse-free during the trial, $p=0.023$.

SPMS clinical trial results have inconclusively determined the benefits of immune therapy in this MS patient population. It is unclear as to the effect of therapy on disability accumulation; however, there has been limited benefit observed in relation to relapse rate in the groups evaluated in these specific trials. These results may be based on the previous history of relapses in the years immediately prior to study entry.²⁶

ADVERSE DRUG REACTIONS^{7-9,12}

Due to the variability of clinical trial design and sample populations, a direct comparison of adverse drug reaction rates between agents may not be reflective of those observed in clinical practice. Patients should be advised that if depression or thoughts of suicide occur while taking INFB therapy, a physician should address these feelings immediately, as they could be related to treatment. INFB therapy is associated with the occurrence of flu-like syndrome characterized by fever, chills, fatigue and muscle ache. Acetaminophen administration may help to control such symptoms. GA appears to be better tolerated than INFB with lower incidences of flu-like syndrome; however, self-limited, systemic reactions do occur during administration. Systemic reactions described with GA include chest tightness, facial flushing, palpitations, dyspnea, and anxiety, which typically last several minutes. Those products administered subcutaneously [INFB-1a (Rebif[®]), INFB-1b, and GA] have also been associated with injection site pain and reactions.

DRUG INTERACTIONS¹⁻⁴

To date, there have been no formal evaluations of the potential for drug interactions with any INFB formulation or GA. Many clinical trials have included patients who had received agents in accordance with current clinical management of MS, including corticosteroids, with no significant correlation to adverse effects observed. Some study subjects in Avonex[®] (INFB-1a) clinical trials have received concomitant anti-depressant and/or oral contraceptive agents with no significant adverse events associated. Due to the potential for neutropenia and lymphopenia with interferon administration, patients receiving concurrent myelosuppressive agents should be properly monitored. Additionally, combination therapy of INFB and GA has not been formally studied.

SUMMARY/RECOMMENDATIONS

In summary, clinical trial data support the belief that early treatment of MS may lower relapse rate and suppress inflammatory MRI changes. Long-term effects on disability accumulation and tissue damage remain to be determined. Therapeutic intervention using immunomodulators should occur based on the assessment of the individual patient. The decision to initiate treatment should be based on discussions with the patient concerning the benefits and possible limitations of therapy, as well as the adverse effects associated with these agents and the frequency of drug administration. Patient response tends to be individualized as a result of genetics, disease severity and compliance. The therapeutic approach to the management of SPMS patients is unclear. Currently, INFB-1b has an FDA indication for this subpopulation; however, this is based on a single study and it is still unclear what the potential benefits of the other agents are when used as treatment options. The therapeutic endpoint in relation to the benefits of drug therapy in this population is also undetermined, due to the emotional aspects of this disease as well as the unpredictability of its course.

Pharmacy can play an important role in the management of MS patients. One important function is to aid in coordination of treatment based on health insurance coverage. In addition to patient education on the administration and safety of GA and INFB, there is opportunity for education and support in relation to the management of MS-related symptoms. These symptoms include bladder dysfunction, bowel dysfunction, pain, fatigue, spasticity and depression. There is also an increase in the number of Internet sites specializing in patient education and support, which may lead to increased questions for a pharmacist. With greater access to support services, there is greater demand for health care professionals to function as treatment evaluators and information sources. ●

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