Multiple Sclerosis Agents Review

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Multiple Sclerosis Agents Review

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
glatiramer (Copaxone®)[1]	Teva Neurosciences	Relapsing-remitting multiple sclerosis – to reduce frequency of relapses
interferon ß-1a IM (Avonex®)[2]	Biogen Idec	Relapsing forms of multiple sclerosis – to reduce accumulation of disability and reduce frequency of exacerbations
interferon ß-1a SC (Rebif®)[3]	EMD Serono	
interferon ß-1b (Betaseron®)[4]	Bayer Biologic	Relapsing forms of multiple sclerosis – to reduce frequency of exacerbations
interferon ß-1b (Extavia®)[5]	Novartis	Relapsing forms of multiple sclerosis – to reduce frequency of exacerbations

Overview

Multiple sclerosis (MS) is a complex human autoimmune-type inflammatory disease of the central nervous system (CNS).[6] Although the etiology is predominantly unknown, MS is characterized pathologically by demyelination and subsequent axonal degeneration.[7] The nerve degeneration associated with MS can result in a wide variety of symptoms including sensory disturbances (numbness, paresthesias, burning, and pain) in the limbs, optic nerve dysfunction, ataxia, fatigue, bladder, bowel, and sexual dysfunction. Severe cases may result in partial or complete paralysis. While cognitive impairment occurs in approximately 50 percent of people with MS, only 10 percent experience serious intellectual deterioration.[8,9,10,11,12]

Approximately 400,000 people in the United States have MS.[13] This disease occurs most commonly in whites, with rare cases in African-Americans and Asian-Americans. Like other presumed autoimmune diseases, MS is more common in females and often first manifests clinical symptoms during young adulthood. The prevalence of MS varies widely with location; the highest prevalence reported at higher latitudes in northern regions of Europe and North America.

At onset of the disease, MS can be clinically categorized as either relapsing-remitting MS (observed in 85–90 percent of patients) or primary progressive MS (observed in 10 percent of patients). Relapses or "attacks" typically present subacutely, with symptoms developing over hours to several days, persisting for several days or weeks, and then gradually dissipating. The attacks are likely caused by the migration of activated, myelin-reactive T-cells into the CNS, causing acute inflammation with associated edema. The ability of high-dose corticosteroids to quickly relieve MS symptoms suggests that the acute edema and its subsequent resolution underlie the clinical relapse and remission, respectively.[14]

The clinical course of MS, therefore, falls into one of the following categories, with the potential to progress from less severe to more serious types:[15,16]

- Relapsing-remitting MS (RRMS): Clearly defined, self-limited attacks of neurologic dysfunction, followed by periods of remission without disease progression. Most patients experience a recovery of function that is often, but not always, complete.

- Primary progressive MS (PPMS): Nearly continuous worsening of disease that is not interrupted by distinct relapses; some of these individuals have occasional plateaus and temporary minor improvements.

- Secondary progressive MS (SPMS): Relapsing-remitting disease course at onset, followed by progression with or without occasional relapses, minor remissions, and plateaus; most patients eventually convert to progressive MS.

- Progressive-relapsing MS (PRMS): Progressive disease from onset, with clear, acute relapses that may or may not resolve with full recovery; unlike RRMS, the periods between relapses are characterized by continuing disease progression.

Interferon beta (IFNß) and glatiramer (Copaxone) are immunoregulatory agents that have been shown to reduce the relapse rate and possibly slow disease progression. Treatment with these medications has been shown to reduce the frequency and severity of relapses in persons with RRMS by approximately one-third, improvement in brain lesion activity on magnetic resonance imaging (MRI), and possibly modify disease progression.[17,18]

According to the 2002 Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines, based on several consistent Class I studies, IFNβ has been demonstrated to reduce the attack rate, whether measured clinically or by MRI, in patients with MS or with clinically isolated syndromes who are at high risk for developing MS.[19] It is appropriate to consider IFNß for treatment in any patient who is at high risk for developing clinically definite MS, or who already has either RRMS or SPMS and is still experiencing relapses. The effectiveness of IFNß in patients with SPMS but without relapses is uncertain. These guidelines also state that glatiramer acetate based on Class 1 evidence has been demonstrated to reduce the attack rate, whether measured clinically or by MRI, in patients with RRMS and is appropriate to be considered for treatment in any patient who has RRMS. Although it may be that glatiramer acetate also helpful in patients with progressive disease, there is no convincing evidence to support this hypothesis. The indication for glatiramer acetate was recently revised to include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.[20]

Pharmacology

As suggested by their name, the immunomodulators mechanism of action impact the immunologic pathophysiology of MS. IFNß binds to cell surface-specific receptors, initiating a cascade of signaling pathways that end with the secretion of antiviral, antiproliferative, and immunomodulatory gene products.[21,22,23] While IFNß has no direct effects in the CNS, it rapidly (within two weeks) blocks blood-brain barrier leakage and resolves gadolinium (Gd)-enhanced MRI activity.

Two subspecies of IFNß are indicated for use in MS: IFNß-1a (Avonex, Rebif) and IFNß-1b (Betaseron, Extavia). While both subspecies have similar biological effects, the extent of activity varies between the two. The two IFNß-1a products are equipotent. A recent study utilized *in vitro* stimulation of peripheral blood with each of the three IFNß products resulting in a dose-dependent increase in antiviral protein that was roughly equivalent for each agent on an

International Unit (IU) basis.[24] This study and other published data indicate that 30 mcg IFNß-1a is equivalent to approximately 220 to 280 mcg IFNß-1b.[25]

Glatiramer (Copaxone), a synthetic molecule, is thought to inhibit the activation of myelin basic protein-reactive T-cells and may also induce antigen-specific suppressor T-cells (T-cells with activity characterized by anti-inflammatory effects).[26,27,28] Glatiramer produces a less rapid resolution of Gd-enhanced MRI activity, but glatiramer acetate-specific T-cells are believed to have access to the CNS, where they exert anti-inflammatory and possibly neuroprotective effects.[29]

Pharmacokinetics

It is suggested that intramuscular (IM) administration of IFNß-1a causes a greater area under the concentration-time curve for IFNß activity in the serum compared to subcutaneous (SC) administration.[30] Yet, several studies demonstrated no differences in biologic effects between the different routes of administration.[31,32,33] The majority of evidence suggests that the route of IFNß administration is of no clinical importance.

Drug	Tmax (hrs)	Half-life (hrs)	Peak Activity* (hrs)	Duration of Activity*
glatiramer (Copaxone)[34]	nd	nd	nd	nd
IFN ß-1a IM (Avonex)[35]	3-15	10	48	up to four days
IFN ß-1a SC (Rebif)[36]	16	69	12 to 48	up to four days
IFN ß-1b (Betaseron)[37]	1-8	0.13-4.3	40-124	seven days
IFN ß-1b (Extavia)[38]	1-8	0.13-4.3	40-124	seven days

*Activity was measured by the levels of biological response markers (e.g., 2', 5'-OAS activity, neopterin and beta 2-microglobulin), which are induced by IFN ß-1a.

nd= no data

Contraindications/Warnings[39,40,41,42,43]

Glatiramer (Copaxone) is contraindicated in patients with a hypersensitivity to glatiramer acetate or mannitol. IFNß-1a (Avonex, Rebif) and IFNß-1b (Betaseron, Extavia) are contraindicated in patients with hypersensitivity to natural or recombinant interferon beta or any component of the formulation. Except for the IFNß-1a IM (Avonex) prefilled syringes, IFNß-1a (Avonex, Rebif) and IFNß-1b (Betaseron**,** Extavia) are contraindicated in patients with hypersensitivity to albumin. Prefilled syringes of IFNß-1a IM do not contain albumin.

IFNß products should be used with caution in patients with depression. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients

receiving these compounds.

The manufacturers of IFNß-1a have added a warning to their drug's prescribing information that these drugs can cause severe liver damage. The manufacturers and the FDA did note that the reported events have occurred in the presence of other drugs that have also been associated with hepatic injury. A similar, but less cautionary warning has also been added to the prescribing information of IFNß-1b. Monitoring of liver function at regular intervals is recommended for patients receiving these drugs.

Injection site necrosis has been reported in four percent of patients in controlled clinical trials for IFNß-1b. Injection site necrosis typically occurred within the first four months of therapy, although post-marketing reports have documented injection site necrosis occurring over one year after initiation of therapy. It generally affects the subcutaneous layer of fat around the injection site. Reports indicated that some patients experienced healing during continuation of therapy and others did not. The manufacturers recommend to hold therapy if the patient experiences multiple lesions, and then to resume therapy once the lesions have healed.

Drug Interactions

Interactions between glatiramer (Copaxone) and other drugs have not been fully evaluated.[44] No formal drug interaction studies have been conducted with IFNß-1a (Avonex, Rebif) or IFNß-1b (Betaseron, Extavia). Caution and/or additional monitoring of liver enzymes is required when using IFNß-1a with potentially hepatotoxic drugs.[45,46]

Adverse Effects

The most frequent adverse effects in patients receiving immunomodulators requiring clinical intervention were flu-like symptoms and depression. Adverse effects occurring in more than 25 percent of patients at a rate higher than placebo are listed.

Drug	Asthenia	Depression	Flu-like symptoms	Injection site reaction	Increased liver enzymes	Leukopenia	Pain
glatiramer (Copaxone)[47]	41 (38)	Reported	19 (17)	66 (19)	nr	≤1	28 (25)
IFNß-1a IM (Avonex)[48]	24 (18)	18-20 (13-14)	49 (29)	3-28 (6)	Reported	Reported	23 (21)
IFNß-1a SC (Rebif)[49]	Reported	17-25 (25-28)	56-59 (51)	89-92 (39)	10-27 (4)	28-36 (14)	10-25 (10-20)
IFNß-1b (Betaseron)[50]	53 (48)	34 (34)	57 (37)	78 (26)	4-12 (1-4)	18 (6)	42 (35)
IFNß-1b (Extavia)[51]	53 (48)	nr	57 (37)	78 (26)	4-12 (1-4)	18 (6)	42 (35)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses.

nr = not reported

In premarketing studies, approximately 16 percent of patients receiving glatiramer (Copaxone) versus four percent of patients receiving placebo experienced a transient, immediate post-injection reaction that included flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria.[52] Other adverse events associated with glatiramer included infection (30 percent versus 28 percent for placebo), skin rash (19 percent versus 11 percent for placebo), dyspnea (14 percent versus four percent for placebo), and nausea (15 percent versus 11 percent for placebo).

In a study of the dropout rate in patients with RRMS under long-term treatment with the three available IFNß preparations, 122 patients were divided into four treatment groups: IFNß-1b 24 MIU SC (Betaseron) weekly; IFNß-1a 6 MIU IM (Avonex) weekly; IFNß-1a 18 MIU SC (Rebif) weekly; and ten patients switching from IFNß-1b to IFNß-1a IM.[53] During the five-year observation period, 39.9 percent of enrolled patients dropped out: 48 percent in the IFN ß-1b group withdrew at a median of 758 days, 26 percent in the IFNß-1a IM group withdrew at a median of 356 days, 38 percent in the IFN ß-1b SC group at a median of 421 days, and 40 percent in those who switched from IFN ß-1b to IFNß-1a IM at a median of 259 days. The differences among the groups were not significant on survival analysis. Patients receiving higher

dose treatment (IFNß-1b and IFNß-1b SC groups) dropped out mainly due to clinical adverse events; conversely, patients receiving lower dose therapy (IFNß-1a IM group) dropped out mainly due to ineffectiveness. Patients who switched to a lower dose treatment (fourth group) had a dropout rate similar to that of the initial treatment groups. The remaining two-thirds of patients were still on treatment without problems up to five years of follow-up. In this study, compliance appeared to be related to the dose of the drug.

Special Populations

Pediatrics

Glatiramer (Copaxone), IFNß-1a IM (Avonex), IFNß-1a SC (Rebif), and IFNß-1b (Betaseron, Extavia) are not indicated for use in pediatric patients.[54,55,56,57]

Pregnancy

Glatiramer (Copaxone) is Pregnancy Category B.[58] IFNß-1a IM (Avonex), IFNß-1a SC (Rebif), and IFNß-1b (Betaseron, Extavia) are Pregnancy Category C.[59,60]

Dosages

Drug	Dosage	Comments	Availability
glatiramer (Copaxone)[61]	20 mg SC once daily	Refrigerate; may be stored at room temperature for up to one week	prefilled syringes - 20 mg
IFNß-1a (Avonex)[62]	30 mcg IM once weekly	Refrigerate; may be stored at room temperature for up to 30 days	powder for injection vial with diluent – 30 mcg
		Refrigerate; may be stored at room temperature for up to seven days	prefilled syringes – 30 mcg
IFNß-1a (Rebif)[63]	4.4 or 8.8 mcg SC three times weekly, titrated over four weeks up to 22 or 44 mcg SC three times weekly	Refrigerate; may be stored at or below room temperature for up to 30 days away from heat and light.	prefilled syringes – 8.8, 22, 44 mcg
IFNß-1b (Betaseron)[64]	0.0625 mg SC every other day; increased over a six-week period to 0.25 mg SC every other day	Store at room temperature prior to reconstitution; stable refrigerated for three hours after reconstitution	powder for injection vial with diluent – 0.3 mg
IFNß-1b (Extavia)[65]	0.0625 mg SC every other day; increased over a six-week period to 0.25 mg SC every other day	Store at room temperature prior to reconstitution; stable refrigerated for three hours after reconstitution	powder for injection vial with diluent – 0.3 mg

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, other criteria included studies with clearly stated, predetermined outcome measure(s) of known or probable clinical importance, used data analysis techniques consistent with the study question, and included follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation.

Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Many of the trials with agents in this class were performed in an open-label manner; introduction of bias must be considered when evaluating study findings.

glatiramer (Copaxone) versus placebo

In a double-blind study, 251 patients with RRMS were randomized to receive glatiramer 20 mg or placebo SC daily for up to three years.[66] Over a two-year period, glatiramer significantly reduced the primary end point of clinical attack rate by 29 percent (p=0.007) compared to placebo. There was no significant difference between groups in EDSS.

In a nine-month study, 249 patients with RRMS were randomized to receive glatiramer 20 mg or placebo SC daily.[67] Compared with placebo, patients receiving glatiramer had a 35 percent reduction (p=0.001) in the total number of enhancing lesions, the primary endpoint of the trial. The treatment effect occurred six months after initiation of treatment. Patients receiving glatiramer also had a 33 percent (p=0.012) reduction in clinical attack rate and an 8.3 percent (p=0.0011) reduction in the median change in T2 burden of disease compared to placebo. There was no significant difference between the groups in EDSS change.

IFNß-1a IM (Avonex) versus IFNß-1a SC (Rebif)

The EVIDENCE (Evidence of Interferon Dose-Response: European North American Comparative Efficacy) trial was a randomized, controlled 64-week trial of IFNß-1a 44 mcg SC three times weekly or IFNß-1a 30 mcg IM once weekly in 677 patients with RRMS.[68] Patients were aware of their treatment assignment; blinded clinical evaluators performed neurologic and MRI evaluations. At 24 weeks, the proportion of relapse-free patients (primary endpoint) was 75 percent in the SC arm and 63 percent in the IM arm (p<0.001). At 48 weeks, the proportion of relapse-free patients was 62 percent in the SC group and 52 percent in the IM group (p=0.006). Fewer active MRI lesions (principal MRI endpoint) were observed in the SC arm at 24 weeks (p<0.001). The 48-week MRI results were similar to those at 24 weeks, with nearly 40 percent fewer active MRI lesions in the SC group (p<0.001). There was no significant difference in drug discontinuations, the rate of adverse events, or severity of adverse events; the majority of adverse events were rated mild by investigators. Hepatic and hematological adverse events and laboratory abnormalities were more common with the SC regimen. Flu-like symptoms were more common with the IM dosage.

In an extension of the EVIDENCE study, patients were all given IFNß-1a 44 mcg SC three times weekly and were followed up for an average additional 32 weeks.[69] At the transition visit, 223 (73 percent) of 306 patients originally receiving 30 mcg IM weekly converted to 44 mcg SC three times weekly, and 272 (91 percent) of 299 receiving 44 mcg SC three times weekly continued the same therapy. The post-transition annualized relapse rate decreased from 0.64 to 0.32 for patients switching to the SC dosage (p<0.001), and from 0.46 to 0.34 for patients continuing the three times weekly SC dosage (p=0.03). The change was greater in those switching to the SC dosage (p=0.047). Patients converting to the three-time weekly SC regimen had fewer active lesions on T2-weighted MRI compared to before the transition (p=0.02), whereas those continuing the higher dose had no significant change in T2 active lesions. Patients who converted to high-dose/high-frequency IFNß-1a therapy had increased rates of

adverse events and treatment terminations consistent with the initiation of high-dose SC IFN therapy.

IFNß-1a IM (Avonex) versus IFNß-1b (Betaseron)

The Independent Comparison of Interferon (INCOMIN) trial was a single-blinded, randomized comparison of IFNß-1a IM and IFNß-1b in 188 patients with RRMS.[70] IFNß-1a was given at a dose of 30 mcg IM once weekly, and IFNß-1b was administered at a dose of 250 mcg SC every other day. Over the two-year study period, 36 percent of patients randomized to IFNß-1a IM were relapse-free compared to 51 percent of patients receiving IFNß-1b (p=0.03). More patients remained free from new T2 lesions, which indicate inflammatory damage on MRI, in the IFNß-1b group (55 versus 26 percent, p<0.0003). Delay of confirmed disease progression was significantly higher in the IFNß-1b group. Discontinuation of therapy due to disease progression was more prevalent in the IFNß-1a IM group. Significantly more patients withdrew from therapy with IFNß-1b due to adverse events or laboratory abnormalities. It should be noted that while MRI was assessed blindly, the physician evaluating clinical outcomes was unblinded.

IFNß-1a SC (Rebif) versus IFNß-1b (Betaseron)

In an open-label study, 224 patients with RRMS were randomized to receive IFNß-1a 22 mcg SC once weekly or IFNß-1b 250 mcg SC every other day for two years.[71] By per protocol analysis, there was no significant difference between treatment groups in number of T2 lesions identified by MRI. Also, no significant difference existed in proportions of relapse free patients, 40.8 percent in the IFNß-1a SC group and 45.2 percent in the IFNß-1b group. Subsequent intent-to-treat analysis indicated a statistically insignificant difference in the proportion of relapse-free patients, 35 and 41 percent in the IFNß-1a SC and IFNß-1b groups respectively.[72] The IFNß-1a dosing interval in the study was less frequent than the FDA-approved dosing regimen.

IFNß-1a IM (Avonex) versus IFNß-1a SC (Rebif) versus IFNß-1b (Betaseron)

In a parallel group, single-blind study, 90 patients with RRMS were randomized to receive IFNß-1a 30 mcg IM once weekly, IFNß-1a 44 mcg SC three times weekly, or IFNß-1b 250 mcg SC every other day for 24 months.[73] The EDSS scores remained stable in patients in the IFNß-1a IM group and decreased in the groups receiving IFNß-1a SC (p<0.05 versus baseline) and IFNß-1b (p<0.001). In the patients treated with IFNß-1a IM, the mean two-year relapse rate decreased from 2.0 to 1.2 episodes (p<0.001 compared to baseline). In the patients treated with IFNß-1a SC, the mean relapse rate decreased from 2.4 to 0.6, while the rate in those treated with IFNß-1b decreased from 2.2 to 0.7 (p<0.001 for both changes from baseline). After two years, 20 percent of patients receiving IFNß-1a IM remained relapse-free. In comparison, 57 percent of patients receiving IFNß-1a SC and 43 of those receiving IFNß-1b remained relapse-free (p<0.05 for both comparisons to IFNß-1a IM).

IFNß-1a SC (Rebif) versus glatiramer acetate (Copaxone)

In the multicenter, parallel, open-label REGARD (REbif versus Glatiramer Acetate in Relapsing MS Disease) trial, 764 patients with RRMS were randomized to receive IFNß-1a SC 44 mcg three times weekly (n=386) or glatiramer acetate SC 20 mg daily (n=378) for 96 weeks.[74] Patients had a history of at least one relapse within the previous 12 months. The primary outcome of time to first relapse was similar in both groups (hazard ratio 0.94, 95%, CI 0.74 to 1.21; p=0.64). Relapse rates were lower than expected: 258 patients (126 in the interferon beta-

1a group and 132 in the glatiramer acetate group) had one or more relapses. A secondary analysis using 460 patients (230 from each group) from the study was completed to compare T2-weighted and gadolinium-enhanced lesion number and volume. There were no significant differences noted in the outcomes for the number and change in volume of T2 lesions or change in the volume of gadolinium-enhanced lesions. However, the IFNß-1a group had significantly fewer gadolinium-enhancing lesions (0.24 versus 0.41 lesions per patients per scan; 95% CI, -0.4 to 0.1; p=0.0002) versus the glatiramer acetate group. Both therapies were well tolerated.

IFNß-1b SC (Betaseron) versus glatiramer acetate (Copaxone)

The BEYOND trial compared the efficacy, safety, and tolerability of IFNß-1b 250 mcg or 500 mcg with glatiramer acetate 20 mg for treating RRMS.[75] A total of 2,244 patients were enrolled in a prospective, multicenter, randomized trial. Patients were randomly assigned to receive IFNß-1b or glatiramer acetate subcutaneously every day. The primary outcome was relapse risk, defined as new or recurrent neurological symptoms separated by at least 30 days from the preceding event and that lasted at least 24 hours. Clinical outcomes were assessed quarterly for two to 3.5 years. No differences were determined in relapse risk, as well as for secondary endpoints such as EDSS progression, T1-hypointense lesion volume, or normalized brain volume among treatment groups. Flu-like symptoms were more common in patients treated with IFNß-1b (p<0.0001), whereas injection site reactions were more common in patients treated with glatiramer acetate (p=0.0005). The source of funding for this study was Bayer HealthCare Pharmaceuticals.

Neutralizing antibodies: IFNß-1a IM (Avonex) versus IFNß-1a SC (Rebif) versus IFNß-1b (Betaseron)

One difference among the three IFNß products is the associated production of neutralizing antibodies (NAb). Data suggest that the presence of NAb against IFNß reduces the bioavailability and clinical efficacy of the drug leading to an increase in relapse rates.[76] These findings also indicate that patients develop NAb independent of age, sex, disease duration, and progression index at start of treatment. Some studies suggest that NAb, once present, might disappear over time even though treatment continues.[77,78,79]

To evaluate the incidence and the prevalence of NAb in each of the three IFNß products, sera were tested from 125 patients with RRMS.[80] Patients were treated with IFNß-1b 250 mcg SC every other day, IFNß-1a 30 mcg IM once weekly, or IFNß-1a 22 mcg SC three times weekly. Patients with two or more consecutive positive samples were considered to be persistently NAb-positive (NAb+). Over 18 months of treatment, the risk of developing persistent NAb was 31 percent for IFNß-1b, 15 percent for IFNß-1a SC, and 2 percent for IFNß-1a IM (p=0.001 for IFNß-1b versus IFNß-1a IM; p=0.19 for IFNß-1b versus IFNß-1a SC; p=0.04 for IFNß-1a SC versus IFNß-1a IM). In all patients with at least one NAb+ sample, the risk of becoming persistent NAb+ was 38 percent for IFNß-1b, 18 percent for IFNß-1a SC, and 7 percent for IFNß-1a IM (p=0.0007 for IFNß-1b versus IFNß-1a IM; p=0.10 for IFNß-1b versus IFNß-1a SC; p=0.07 for IFNß-1a SC versus IFNß-1a IM). At month 18, the prevalence of persistent NAb+ patients was 31.6 percent for IFNß-1b, 18.7 percent for IFNß-1a SC, and four percent for IFNß-1a IM.

In the EVIDENCE trial, NAb developed in 25 percent of the patients who received IFNß-1a SC compared with two percent of the patients given IFNß-1a IM.[81] The incidence of NAb development appears to be less with IFNß-1a than with IFNß-1b and less when given IM in comparison to SC.

Meta-analyses

A population-based retrospective chart review of the liver tests of 844 Canadian patients with MS and prescribed an IFNß product was performed between 1995 and 2001.[82] Overall, 37 percent of patients developed new elevations of alanine aminotransferase (ALT). All IFNß products caused elevated aminotransferase levels compared with pretreatment levels ($p<0.005$) and were higher than reported in clinical trials. In this review, the relative effect on aminotransferases was approximated as IFNß-1b SC = IFNß-1a SC > IFNß-1a IM. This is consistent with the ALT elevations reported in the EVIDENCE trial in which IFNß-1b SC had a significantly higher incidence of ALT elevation than IFNß-1a IM (12 and 5 percent, respectively; $p=0.02$). All elevations were reversible either spontaneously or with dose reduction.[83]

Summary

According to the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines, based on reports of improvement in patients with RRMS with Class I studies, initiation of IFNß treatment is appropriate to prevent further relapses and progression. Also utilizing Class I studies, these guidelines favor glatiramer (Copaxone) treatment to help reduce the number of attacks for patients with RRMS. Note that due to various comorbidities and the risks involved with using these agents, the prescriber must still use discretion when selecting the most appropriate treatment for patients with RRMS based on disease severity and progression.

There is sufficient evidence to indicate that either the dose or the frequency of IFNß administration, or both, significantly influences the short-term outcome in patients with RRMS. The route of administration of IFNß is not of clinical importance with regard to efficacy, but does have an impact on the side-effect profile. Questions remain as to comparable and optimal dosages and frequencies for the various interferons.

Although there are no double-blind studies directly comparing glatiramer (Copaxone) and IFNß, these agents appear to be similarly effective for the control of exacerbations in MS.

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