Multiple Sclerosis Agents Review

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Multiple Sclerosis Agents Review

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
dalfampridine (Ampyra™)[1]	Acorda	Improve walking in patients with multiple sclerosis, demonstrated by an increase in walking speed
fingolimod (Gilenya™)[2]	Novartis	Relapsing forms of multiple sclerosis – to delay the accumulation of physical disability and reduce frequency of clinical exacerbations
glatiramer (Copaxone®)[3]	Teva Neurosciences	Relapsing-remitting multiple sclerosis – to reduce frequency of relapses
interferon ß-1a IM (Avonex®)[4]	Biogen Idec	Relapsing forms of multiple sclerosis – to reduce accumulation of disability and reduce frequency of exacerbations
interferon ß-1a SC (Rebif®)[5]	EMD Serono	
interferon ß-1b (Betaseron®)[6]	Bayer Biologic	Relapsing forms of multiple sclerosis – to reduce frequency of exacerbations
interferon ß-1b (Extavia®)[7]	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).[8] Although the etiology is predominantly unknown, MS is characterized pathologically by demyelination and subsequent axonal degeneration.[9] 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.[10,11,12,13,14]

Approximately 400,000 people in the United States have MS.[15] 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.[16]

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:[17,18]

- 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.[19,20] 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.[21] 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 glatiramer acetate may be 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.[22] Fingolimod (Gilenya) was not available at the time of these statements. Dalfampridine (Ampyra) is not a treatment that affects disease progression, but it may improve impairment of walking associated with the disease.

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.[23,24,25] 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.[26] This study and other published data indicate that 30 mcg IFNß-1a is equivalent to approximately 220 to 280 mcg IFNß-1b.[27]

Fingolimod (Gilenya), once converted to the active metabolite, binds to sphingosine 1-phosphate receptors 1, 3, 4, and 5.[28] Lymphocyte egress from lymph nodes is inhibited, reducing their number in the peripheral blood.[29] While the exact mechanism of action for fingolimod is unknown, it may involve the reduction of lymphocyte migration into the CNS.

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).[30,31,32] 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.[33]

Although the mechanism of action of dalfampridine (Ampyra) has not been fully elucidated, dalfampridine has been shown to increase conduction of action potentials in demyelinated axons through inhibition of potassium channels when studied in animals.[34] Dalfampridine is a broad spectrum potassium channel blocker.

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.[35] Yet, several studies demonstrated no differences in biologic effects between the different routes of administration.[36,37,38] 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*
dalfampridine (Ampyra)[39]	3-4	5.2-6.5	nd	nd
fingolimod (Gilenya)[40]	12-16	6-9 days	nd	nd
glatiramer (Copaxone)[41]	nd	nd	nd	nd
IFN ß-1a IM (Avonex)[42]	3-15	10	48	up to four days
IFN ß-1a SC (Rebif)[43]	16	69	12 to 48	up to four days
IFN ß-1b (Betaseron)[44]	1-8	0.13-4.3	40-124	seven days
IFN ß-1b (Extavia)[45]	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[46,47,48,49,50,51,**52**]

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. Dalfampridine (Ampyra) therapy was associated with increased incidence of seizures in clinical trials and is therefore contraindicated in patients with a history of seizure. Dalfampridine is eliminated through the kidneys primarily as unchanged drug and is contraindicated in patients with moderate to severe renal impairment (CrCl < 50 mL/minute). Increased incidence of seizures has been observed in clinical trials. There are no contraindications for the use of fingolimod (Gilenya).

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. Fingolimod may increase liver transaminase levels.

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.

The first dose of fingolimod may cause a decrease in heart rate and/or atrioventricular (AV) conduction. Patients who experienced bradycardia or conduction abnormalities were generally asymptomatic. A baseline ECG should be obtained for patients at higher risk of bradyarrhythmia, and all patients should be observed for six hours following administration of the first dose. Patients with a low heart rate, history of syncope, sick sinus syndrome, second degree or higher conduction block, ischemic heart disease, or congestive heart failure are at increased risk of developing bradycardia or heart blocks. With continued dosing, the heart rate returned to baseline within one month of chronic treatment and conduction abnormalities resolved within the first 24 hours on treatment. If fingolimod therapy is discontinued for more than two weeks, the same precautions as for initial dosing should apply.

Fingolimod may increase the risk of infections due to its effects on lymphocytes; patients with active or chronic infections should not take fingolimod. Macular edema can occur with fingolimod use. An adequate ophthalmologic evaluation should be performed at baseline and three to four months after treatment initiation. If patients report visual disturbances at any time during fingolimod therapy, an ophthalmologic evaluation should be performed. Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema. Patients may experience a decrease in pulmonary function tests; obtain spirometry and diffusion lung capacity for carbon monoxide (DLCO) when clinically indicated for patients receiving fingolimod.

Dalfampridine should not be administered concurrently with other forms of 4-aminopyridine (e.g., compounded formulations of the drug) since the active ingredient is the same.

Risk Evaluation and Mitigation Strategy (REMS) programs

The manufacturer of dalfampridine has a structured healthcare provider and patient education program as required by the FDA. A medication guide must be provided with each prescription of dalfampridine. Yearly letters on dalfampridine are required to remind prescribers of the name change from fampridine to dalfampridine and the risk of drug-associated seizures.

Fingolimod has a prescriber and patient education program. Letters to prescribers will be sent annually for five years describing the risk of bradyarrhythmias and atrioventricular block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk. A patient medication guide will be dispensed with each fingolimod prescription.

Interferon ß-1b (Extavia) must be dispensed with a medication guide in order to satisfy its patient education requirement.

Drug Interactions

Interactions between glatiramer (Copaxone) and other drugs have not been fully evaluated.[53] 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.[54,55] Drug interactions with dalfampridine have not been identified.[56]

Patients taking class Ia or III antiarrhythmics, beta blockers, and calcium channel blockers are at increased risk of developing bradycardia or heart blocks while on fingolimod (Gilenya). Fingolimod exposure with concurrent ketoconazole may increase by 70 percent; higher risk of adverse effects is possible. Live attenuated vaccines during fingolimod treatment and for two months following discontinuation should be avoided.

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
dalfampridine (Ampyra)[57]	7 (4)	nr	nr	n/a	nr	nr	back: 5 (2)
fingolimod (Gilenya)[58]	3 (1)	8 (7)	nr	n/a	14 (5)	3 (<1)	back: 12 (7)
glatiramer (Copaxone)[59]	41 (38)	reported	nr	66 (19)	nr	≤1	28 (25)
IFNß-1a IM (Avonex)[60]	24 (18)	18-20 (13-14)	49 (29)	3-28 (6)	reported	reported	23 (21)
IFNß-1a SC (Rebif)[61]	reported	17-25 (25-28)	56-59 (51)	89-92 (39)	10-27 (4)	28-36 (14)	10-25 (10-20)
IFNß-1b (Betaseron)[62]	53 (48)	34 (34)	57 (37)	78 (26)	4-12 (1-4)	18 (6)	42 (35)
IFNß-1b (Extavia)[63]	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 or all inclusive. Incidences for the placebo group are indicated in parentheses.
nr = not reported
n/a = not applicable

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.[64] 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.[65] 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.

Urinary tract infections were reported more frequently with dalfampridine (12 percent) in clinical trials compared to placebo (eight percent).[66]

Special Populations

Pediatrics

Dalfampridine (Ampyra), fingolimod (Gilenya), glatiramer (Copaxone), IFNß-1a IM (Avonex), IFNß-1a SC (Rebif), and IFNß-1b (Betaseron, Extavia) are not indicated for use in pediatric patients.[67,68,69,70,71,72]

Pregnancy

Glatiramer (Copaxone) is Pregnancy Category B.[73] Dalfampridine (Ampyra), fingolimod (Gilenya), IFNß-1a IM (Avonex), IFNß-1a SC (Rebif), and IFNß-1b (Betaseron, Extavia) are Pregnancy Category C.[74,75,76,**77**]

Hepatic impairment

Blood levels of fingolimod, but not its active metabolite fingolimod-phosphate, are doubled in patients with severe hepatic impairment, but no dosing adjustments are advised.[78]

Renal impairment

The risk of seizures in patients with mild renal impairment and dalfampridine is unknown, but plasma levels of dalfampridine may approach those seen at a dose that may be associated with

increased seizure risk.[79] In patients with moderate to severe renal impairment (CrCl ≤ 50 mL/min), use of dalfampridine is contraindicated.

Blood levels of fingolimod may be increased in patients with severe renal impairment, but no dosing adjustments are advised.

Dosages

Drug	Dosage	Comments	Availability
dalfampridine (Ampyra)[80]	10 mg by mouth twice daily about 12 hours apart	--	10 mg extended release tablets
fingolimod (Gilenya)[81]	0.5 mg once daily	--	0.5 mg capsules
glatiramer (Copaxone)[82]	20 mg SC once daily	Refrigerate; may be stored at room temperature for up to one week	prefilled syringes - 20 mg
IFNß-1a (Avonex)[83]	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)[84]	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 – 22, 44 mcg
IFNß-1b (Betaseron)[85]	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)[86]	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

For dalfampridine, a Patient Service Hub has also been created as an initial contact between

the patient and prescriber. The role of the Service Hub is to triage all patients receiving dalfampridine to a limited network of Specialty Pharmacies. The specialty pharmacy will dispense the medication and provide the patient with counseling and a medication guide. The specialty pharmacy will also be required to reinforce the recommended dosage of 10 mg twice daily. The pharmacist will contact the prescriber to verify any total daily doses exceeding 20 mg.

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved 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.

dalfampridine (Ampyra) versus placebo

A phase III study assessed efficacy and safety of dalfampridine in patients with ambulatory deficits due to multiple sclerosis.[87] In a randomized, multicenter, double-blind, controlled trial, 301 patients with any type of multiple sclerosis were assigned to 14 weeks of treatment with dalfampridine 10 mg or placebo twice daily. Patients who had a history of seizures or onset of an MS exacerbation within 60 days were excluded from the trial. A consistent improvement on timed 25-foot walk was used to define response, with proportion of timed walk responders in each treatment group as the primary outcome. The proportion of timed walk responders was higher in the dalfampridine group (35 percent) than in the placebo group (eight percent; $p<0.0001$). Improvement in walking speed in dalfampridine-treated patients was 25.2 percent and 4.7 percent in the placebo group. A 20 percent or greater improvement in walking speed is frequently considered clinically meaningful.[88,89,90]

fingolimod (Gilenya) versus placebo

A randomized, double-blind, placebo-controlled, multicenter, 24-month clinical trial evaluated 1,272 patients with relapsing-remitting MS.[91] Patients with median age of 37 years had a score of zero to 5.5 on the Expanded Disability Status Scale (EDSS), had one or more relapses the prior year, or had two or more relapses in the prior two years, and had not received any interferon-beta or glatiramer for at least the previous three months, and had not received natalizumab for at least the previous six months. Patients were randomized to fingolimod 0.5 mg or 1.25 mg daily or placebo. The primary endpoint of annualized relapse rate was 0.18, 0.16, and 0.4 for the fingolimod 0.5 mg, fingolimod 1.25 mg, and placebo groups, respectively ($p<0.001$ for either dose versus placebo). Both doses of fingolimod significantly reduced the

secondary endpoint of time to disability progression, confirmed after three months, over the 24-month study period (hazard ratio [HR] 0.7 for the 0.5 mg dose and 0.68 for the 1.25 mg dose, p=0.02 versus placebo for both). The cumulative probability of disability progression confirmed after three months was 17.7 percent, 16.6 percent, and 24.1 percent with the fingolimod 0.5 mg, fingolimod 1.25 mg, and placebo, respectively. At 24 months, both doses of fingolimod resulted in statistically significant reductions (p<0.001 for all comparisons) in magnetic resonance imaging (MRI)-related endpoints. Adverse events included bradycardia and atrioventricular block at drug initiation, as well as elevated liver enzymes, macular edema, and mild hypertension.

fingolimod (Gilenya) versus interferon ß-1a (Avonex)

A 12-month, randomized, double-blind, double-dummy, multicenter study compared fingolimod 0.5 mg or 1.25 mg daily and interferon ß-1a 30 mcg IM weekly.[92] A total of 1,292 patients had RRMS with a recent history of at least one relapse, median age of 36 years, and a score of zero to 5.5 on the EDSS. The primary endpoint of annualized relapse rate was significantly lower in the fingolimod groups compared to interferon: 0.16 (95% CI, 0.12 to 0.21) in the 0.5 mg group, 0.2 (95% CI, 0.16 to 0.26) in the 1.25 mg group, and 0.33 (95% CI, 0.26 to 0.42, p<0.001 for both comparisons) in the interferon group. MRI results supported the primary findings as measured by the mean number of new and newly enlarged T2 lesions at one year (1.6 for fingolimod groups versus 2.6 for interferon ß-1a, p=0.002). There was no significant difference in the time to three-month confirmed disability progression between fingolimod groups and interferon ß-1a patients at one year. Two fatal infections occurred in the group that received the 1.25-mg dose of fingolimod: disseminated primary varicella zoster and herpes simplex encephalitis. Other adverse events in the fingolimod group were nonfatal herpes virus infections, bradycardia/atrioventricular block, hypertension, macular edema, skin cancer, and elevated liver enzymes.

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.[93] 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.[94] 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.[95] 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.[96] 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.[97] 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, 301 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.[98] The annual relapse rates were virtually equal in the two arms of the randomized study (IFNβ-1a: 0.70; IFNβ-1b: 0.71), as were the time to first relapse and the time to sustained progression. 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.[99] 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.[100] 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.[101] 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 IFNß-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.[102] 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.[103] 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.[104,105,106]

To evaluate the incidence and the prevalence of NAb in each of the three IFNß products, sera were tested from 125 patients with RRMS.[107] 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.[108] 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.[109] 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.[110]

Summary

According to the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines, it is appropriate to consider IFNß therapy 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 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.

Data suggest antibodies (NAb) against IFNß reduce that bioavailability and clinical efficacy of the drug leading to an increase in relapse rates. In the EVIDENCE trial, the incidence of NAb development appeared to be less with IFNß-1a than with IFNß-1b and less when given IM in comparison to SC. Some studies suggest that NAb, once present, might disappear over time with continued treatment.

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.

Fingolimod (Gilenya) has shown significant efficacy compared to placebo by reducing relapse rates, MRI measures, and lowering risk of disability progression. Compared to IFNß-1a (Avonex), it has shown significant efficacy in regards to relapse rate and MRI activity, but the risk of disease progression did not differ significantly between the treatment groups. These results, in addition to the novel route of administration in MS, are encouraging; however, fingolimod is not without adverse events that require significant monitoring. The long-term safety and efficacy of fingolimod are unknown.

Dalfampridine (Ampyra) is an add-on therapy to disease modifying therapy for MS. It is unclear if the benefits of dalfampridine are clinically significant.

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