



Multiple Sclerosis Agents Therapeutic Class Review (TCR)

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
alemtuzumab (Lemtrada®) ¹	Genzyme	Relapsing forms of multiple sclerosis; because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of multiple sclerosis
dalfampridine (Ampyra®) ²	Acorda	Improve walking in patients with multiple sclerosis, demonstrated by an increase in walking speed
dimethyl fumarate (Tecfidera®) ³	Biogen	Relapsing forms of multiple sclerosis
fingolimod (Gilenya®) ⁴	Novartis	Relapsing forms of multiple sclerosis – to delay the accumulation of physical disability and reduce frequency of clinical exacerbations
glatiramer acetate (Copaxone®, Glatopa™*) ^{5,6}	Teva Neurosciences (Copaxone), Sandoz (Glatopa)	Relapsing forms of multiple sclerosis
interferon β-1a IM (Avonex®) ⁷	Biogen	Relapsing forms of multiple sclerosis – to delay accumulation of disability and to decrease frequency of clinical exacerbations
interferon β-1a SC (Rebif®) ⁸	EMD Serono	
interferon β-1a SC (pegylated) (Plegridy®) ⁹	Biogen	Relapsing forms of multiple sclerosis
interferon β-1b (Betaseron®) ¹⁰	Bayer Biologic	Relapsing forms of multiple sclerosis – to reduce frequency of exacerbations
interferon β-1b (Extavia®) ¹¹	Novartis	Relapsing forms of multiple sclerosis – to reduce frequency of exacerbations
teriflunomide (Aubagio®) ¹²	Genzyme	Relapsing forms of multiple sclerosis

*Glatopa is a therapeutically interchangeable generic for 20 mg glatiramer (Copaxone).

OVERVIEW

Multiple sclerosis (MS) is a complex human autoimmune-type inflammatory disease of the central nervous system (CNS).¹³ Although the etiology is predominantly unknown, MS is characterized pathologically by demyelination and subsequent axonal degeneration.¹⁴ 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% of people with MS, only 10% experience serious intellectual deterioration.^{15,16,17,18,19}

More than 2.3 million people worldwide have MS.²⁰ Multiple sclerosis 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 clinical symptoms often first manifest during young adulthood. The prevalence of MS varies widely with location; the highest prevalence is reported at higher latitudes in northern regions of Europe and North America.

At onset of the disease, MS can be categorized as either relapsing-remitting MS (observed in 85% to 90% of patients) or primary progressive MS (observed in 10% 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 use 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.²¹

The clinical course of MS, therefore, falls into 1 of the following categories, with the potential to progress from less severe to more serious types:^{22,23}

- **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 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.

Interferons are a family of naturally occurring proteins produced by cells in response to viral infection and attack. Three major groups have been identified: interferon alpha, beta, and gamma. Interferon alpha and beta are grouped as Type I and interferon gamma is Type II. Interferon beta (IFN β) and glatiramer are immunoregulatory agents that have been shown to reduce the relapse rate and possibly slow disease progression in multiple sclerosis. Treatment with these medications has been shown to reduce the frequency and severity of relapses in persons with RRMS by approximately one-third, improve brain lesion activity on magnetic resonance imaging (MRI), and possibly modify disease progression.²⁴

According to the 2002 Subcommittee of the American Academy of Neurology (AAN) and the MS Council for Clinical Practice Guidelines, which were reaffirmed in 2003 and 2008, based on several consistent Class I studies, IFN β 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.²⁵ It is appropriate to consider IFN β 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 IFN β 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 includes patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.²⁶ Alemtuzumab (Lemtrada), dimethyl fumarate (Tecfidera), fingolimod (Gilenya), and teriflunomide (Aubagio), were not available at the time

of these statements, but have since demonstrated efficacy in clinical trials. Dalfampridine (Ampyra) is not a treatment that affects disease progression, but it may improve impairment of walking associated with the disease, which is a clinical measure of impairment in MS patients.²⁷

Neutralizing antibodies (NABs) may occur with IFN β and may also disappear even with continued treatment. A report of the Therapeutics and Technology Assessment Subcommittee of the AAN assessed the clinical effect of these NABs on efficacy of IFN β agents and found that NABs are probably associated with a reduction in clinical and radiographic effectiveness of these agents.²⁸ They further found that the rate of NAb production is probably less with IFN β -1a treatment than with IFN β -1b treatment, but the extent of the difference was difficult to determine. In addition, the intramuscular formulation of IFN β -1a appeared less immunogenic than the subcutaneous formulations of either IFN β -1a or IFN β -1b. However, there was insufficient evidence regarding the utility of NAb testing to recommend in whom testing should occur and how the results should be applied.

PHARMACOLOGY^{29,30,31,32,33,34,35,36}

As suggested by their name, the immunomodulators' mechanism of action impacts the immunologic pathophysiology of MS. IFN β binds to cell surface-specific receptors, initiating a cascade of signaling pathways that end with the secretion of antiviral, antiproliferative, and immunomodulatory gene products. While IFN β has no direct effects in the CNS, it rapidly (within 2 weeks) blocks blood-brain barrier leakage and resolves gadolinium (Gd)-enhanced MRI activity.

Two subspecies of IFN β are indicated for use in MS: IFN β -1a (Avonex, Plegridy, Rebif) and IFN β -1b (Betaseron, Extavia). While both subspecies have similar biological effects, the extent of activity varies between the 2. Plegridy is a pegylated formulation of IFN β -1a. Two IFN β -1a products (Avonex, Rebif) are equipotent and the potency of the pegylated formulation (Plegridy) has not been compared to the other formulations. A study utilized *in vitro* stimulation of peripheral blood with each of the 2 IFN β products (Betaseron, Extavia) resulting in a dose-dependent increase in antiviral protein that was roughly equivalent for each agent on an International Unit (IU) basis.³⁷ This study and other published data indicate that 30 mcg IFN β -1a is equivalent to approximately 220 to 280 mcg IFN β -1b.³⁸

Fingolimod (Gilenya), once converted to the active metabolite, binds to sphingosine 1-phosphate receptors 1, 3, 4, and 5. This inhibits lymphocyte egress from lymph nodes, reducing their number in the peripheral blood.³⁹ While the exact mechanism of action for fingolimod is unknown, it may involve the reduction of lymphocyte migration into the CNS.

Glatiramer (Copaxone, **Glatopa**), 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).^{40,41,42} 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.⁴³

Teriflunomide (Aubagio), the active metabolite of leflunomide, is an immunomodulator with anti-inflammatory properties that inhibits dihydro-orotate dehydrogenase, an enzyme involved in de novo pyrimidine synthesis. Although the mechanism of action of teriflunomide is not completely known, it may involve a reduction in the number of activated lymphocytes in the CNS.

Dimethyl fumarate (Tecfidera) and its metabolite monomethyl fumarate have been shown to activate the Nuclear factor-like (Nrf2) pathway in animal and human studies which may be the mechanism by which it achieves its therapeutic effect, but the exact mechanism is unknown. The Nrf2 pathway is involved in the cellular response to oxidative stress.

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. Dalfampridine is a broad-spectrum potassium channel blocker.

Alemtuzumab (Lemtrada) is a CD52 directed cytolytic monoclonal antibody. Although the exact mechanism of action of alemtuzumab for multiple sclerosis is unknown, it is presumed to involve binding to CD52, a cell surface antigen present on T and B lymphocytes. Following cell surface binding to T and B lymphocytes, alemtuzumab results in antibody-dependant cellular cytolysis and complement mediated lysis.

PHARMACOKINETICS^{44,45,46,47,48,49,50,51,52,53,54,55}

It is suggested that intramuscular (IM) administration of IFN β -1a causes a greater area under the concentration-time curve for IFN β activity in the serum compared to subcutaneous (SC) administration.⁵⁶ Yet, several studies demonstrated no differences in biologic effects between the different routes of administration.^{57,58,59} The majority of evidence suggests that the route of IFN β administration is of no clinical importance.

Drug	Tmax (hrs)	Half-life (hrs)	Peak Activity* (hrs)	Duration of Activity*
alemtuzumab injection (Lemtrada)	nd	2 weeks	nd	nd
dalfampridine oral (Ampyra)	3-4	5.2-6.5	nd	nd
dimethyl fumarate oral (Tecfidera)	2-2.5	1	nd	1 day
fingolimod oral (Gilenya)	12-16	6-9 days	nd	nd
glatiramer SC injection (Copaxone, Glatopa)	nd	nd	nd	nd
IFN β -1a IM injection (Avonex)	6-36	8-54	48	at least 4 days
IFN β -1a SC injection (Rebif)	16	69	12-48	up to 4 days
IFN β -1a SC (pegylated) injection (Plegridy)	1-1.5 days	78	nd	nd
IFN β -1b SC injection (Betaseron)	1-8	0.13-4.3	40-124	7 days
IFN β -1b SC injection (Extavia)	1-8	0.13-4.3	40-124	7 days
teriflunomide oral (Aubagio)	nd	18-19 days	nd	nd

*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 β -1a.

nd = no data

CONTRAINDICATIONS/WARNINGS^{60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70,71,72,73}

Glatiramer (Copaxone, **Glatopa**) is contraindicated in patients with a hypersensitivity to glatiramer acetate or mannitol. IFN β -1a (Avonex, Plegridy, Rebif) and IFN β -1b (Betaseron, Extavia) are contraindicated in patients with hypersensitivity to natural or recombinant interferon beta or any component of the formulation. Except for IFN β -1a SC (Plegridy) and IFN β -1a IM (Avonex) prefilled syringes, IFN β -1a (Avonex, Rebif), and IFN β -1b (Betaseron, Extavia) are contraindicated in patients with hypersensitivity to albumin. Pegylated IFN β -1a SC (Plegridy) and prefilled syringes of IFN β -1a IM (Avonex) do not contain albumin. Dalfampridine (Ampyra) therapy is contraindicated in patients with a history of seizures and in patients with moderate to severe renal impairment (CrCL < 50 mL/minute) as dalfampridine is eliminated through the kidneys as unchanged drug. Dalfampridine is also contraindicated in patients with a history of hypersensitivity to dalfampridine or 4-aminopyridine. Teriflunomide (Aubagio) is contraindicated in patients with severe hepatic impairment. A similar risk of severe liver injury including fatal liver failure and dysfunction would be expected with teriflunomide as leflunomide. Teriflunomide is contraindicated with current leflunomide therapy. Teriflunomide is contraindicated in women who are pregnant or women of child bearing potential not using reliable contraception. Teriflunomide may cause fetal harm when administered to pregnant women due to teratogenic and embryo-lethal effects. Alemtuzumab (Lemtrada) is contraindicated in patients who are infected with human immunodeficiency virus (HIV) because it causes prolonged reductions of CD4+ lymphocyte.

The FDA evaluated a report of a patient who died after the first dose of fingolimod (Gilenya) plus clinical trial and post-market data including reports of patients who died of cardiovascular events or unknown causes.⁷⁴ Although fingolimod was not definitively related to any of the deaths, the FDA remains concerned about the cardiovascular effects of fingolimod after the first dose. Due to the risk of death from cardiac complications, fingolimod is contraindicated in patients who have experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure during the previous 6 months. It is also contraindicated in patients who have a history or the presence of Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless the patient has a functioning pacemaker or who have a baseline QTc interval \geq 500 ms or are receiving treatment with a Class Ia or Class III anti-arrhythmic drug.

Cases of progressive multifocal leukoencephalopathy (PML) have been reported with dimethyl fumarate (Tecfidera) and fingolimod (Gilenya). PML is a rare and serious brain infection caused by the John Cunningham (JC) virus. The JC virus is a common virus that is harmless in most people but can cause PML in some patients who have weakened immune systems.^{75,76}

IFN β 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.

IFN β -1a IM (Avonex), pegylated IFN β -1a SC (Plegridy), and IFN β -1b (Betaseron) have also been associated with rare reports of anaphylaxis. Additionally, decreased peripheral blood cell counts, including rare pancytopenia and thrombocytopenia, have been reported during IFN β -1a IM and pegylated IFN β -1a SC use. Pegylated IFN β -1a SC (Plegridy) therapy has also been associated with an increased incidence of congestive heart failure and seizures. Autoimmune disorders of multiple target organs, including idiopathic thrombocytopenia, hyper and hypothyroidism, and autoimmune hepatitis, have also been reported with use of pegylated IFN β -1a SC (Plegridy).

The manufacturers of IFN β -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 weaker, warning has also been added to the prescribing information of IFN β -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 4% of patients in controlled clinical trials for IFN β -1b. Injection site necrosis typically occurred within the first 4 months of therapy, although post-marketing reports have documented injection site necrosis occurring over 1 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. Injection site reactions, including injection site necrosis, have also been reported with pegylated IFN β -1a SC (Plegridy) treatment.

All IFN β products (Avonex, Rebif, Plegridy, Betaseron, and Extavia) carry a warning for thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Any IFN β should be discontinued should signs or symptoms of TMA occur.

The first dose of fingolimod can cause a decrease in heart rate and/or atrioventricular (AV) conduction. After the first dose, the heart rate decrease starts within an hour. The maximal decline in heart rate generally occurs within 6 hours and recovers, although not to baseline levels, by 8 to 10 hours post dose. There is then a second period of heart rate decrease within 24 hours after the first dose. In some patients, the heart rate decrease during the second period is more pronounced than the decrease observed in the first 6 hours. Patients who experience bradycardia are generally asymptomatic, but some patients experience hypotension, orthostasis, fatigue, palpitations, and chest pain that usually resolve within the first 24 hours of treatment.

With the first dose, patients are to be observed for signs and symptoms of bradycardia and heart block for 6 hours, with an ECG at the beginning and end of the observation period and hourly checks of pulse and blood pressure obtained. Patients who develop a heart rate of less than 45 bpm, or a new onset second degree or higher AV block, should be monitored until resolution of the finding, whereas patients with the lowest post-dose heart rate at the end of the observation period should be monitored until the heart rate increases. Patients experiencing symptomatic bradycardia should begin continuous ECG monitoring until the symptoms have resolved. If pharmacological intervention is required to treat bradycardia, continuous ECG monitoring should continue overnight in a medical facility, and first-dose monitoring procedures should be repeated for the second dose. Patients at higher risk of symptomatic bradycardia or heart block because of a coexisting medical condition, including 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 or who are on certain concomitant medications, including beta-blockers and calcium channel blockers, should be observed overnight with continuous ECG monitoring. In addition, patients with prolonged QTc interval at baseline or during the observation period, or taking drugs with known risk of torsades de pointes, should be observed overnight with continuous ECG monitoring. If a patient requires pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated after the second dose of fingolimod. If fingolimod therapy is discontinued for more than 2 weeks, the same precautions as for initial dosing apply.

Fingolimod may increase the risk of infections, including herpetic and cryptococcal infections, due to its dose-dependent effects on lymphocytes; lymphocyte suppression may continue for 2 months after discontinuation. In addition, obtain complete blood counts at baseline and monitor periodically during therapy. Patients with active or chronic infections should not take fingolimod. Patients should be evaluated for antibodies to varicella zoster virus (VZV) prior to initiation; if vaccination for VZV is needed, it should occur 1 month prior to initiation of fingolimod.

An adequate ophthalmologic evaluation should be performed at baseline and 3 to 4 months after treatment initiation as fingolimod can cause macular edema. An ophthalmic evaluation should be performed if the patient reports visual disturbances during therapy. Patients with a history of uveitis or diabetes mellitus are at increased risk of macular edema.

Due to the risk of increased liver transaminases, baseline transaminase levels should be obtained. If significant liver injury is confirmed, fingolimod therapy must be discontinued; levels typically return to normal 2 months after discontinuing therapy. Due to its prolonged elimination, effective contraception should be used up to 2 months after discontinuing therapy to reduce the risk of fetal harm. Other adverse events include a decrease in pulmonary function tests. Consequently, obtain spirometry and diffusion lung capacity for carbon monoxide (DLCO). Blood pressure may increase during fingolimod therapy; monitor blood pressure during fingolimod therapy.

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. Urinary tract infections were reported more frequently in patients receiving dalfampridine (12%) compared to patients receiving placebo (8%). Dalfampridine can cause anaphylaxis and severe allergic reactions including respiratory compromise, urticaria, and angioedema and patients should discontinue dalfampridine immediately and seek medical attention if anaphylaxis occurs.

Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases on teriflunomide (Aubagio). If drug-induced liver injury is suspected, discontinue teriflunomide and start an accelerated elimination procedure with cholestyramine or charcoal. Teriflunomide may decrease white blood cell count (WBC); a recent complete blood cell count (CBC) should be available before initiating therapy. Peripheral neuropathy, acute renal failure/hyperkalemia, severe skin reactions, and elevated blood pressure are among reported warnings.

Dimethyl fumarate may decrease lymphocyte counts. In clinical trials, mean lymphocyte counts decreased approximately 30% during the first year of treatment and they increased after stopping dimethyl fumarate but did not return to baseline. Dimethyl fumarate may cause flushing (e.g., redness, itching, burning sensation). In clinical trials, 40% of patients experienced flushing which generally began soon after initiation. The majority of patients experience flushing of mild to moderate severity.

Alemtuzumab (Lemtrada) can result in the formation of autoantibodies and increase the risk of serious autoimmune-mediated conditions. Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts before and during treatment. Alemtuzumab also causes cytokine release syndrome resulting in infusion reactions, some of which may be serious and life threatening. Patients should be premedicated with a corticosteroid and monitored during treatment.

Alemtuzumab may increase the risk of malignancies including thyroid cancer, melanoma, lymphoproliferative disorders, and lymphoma. Patients and healthcare providers should monitor for signs and symptoms of malignancies. Caution should also be exercised in initiating alemtuzumab in patients with pre-existing or ongoing malignancies.

Immune thrombocytopenia (ITP), glomerular nephropathies, autoimmune thyroid disorders, pneumonitis, and autoimmune cytopenias (e.g., neutropenia, hemolytic anemia, and pancytopenia) occurred in alemtuzumab-treated patients in clinical studies. Patients should be monitored for these adverse effects.

Infections were more common in alemtuzumab-treated patients compared to patients treated with interferon beta-1a in clinical trials. Infections that occurred more often in alemtuzumab-treated patients than interferon beta-1a patients included nasopharyngitis, urinary tract infection, upper respiratory tract infection, sinusitis, herpetic infections, influenza, and bronchitis. Serious infections occurred in the alemtuzumab-treated patients, including appendicitis, gastroenteritis, pneumonia, herpes zoster, and tooth infection. Do not administer live viral vaccines following a course of alemtuzumab and consider delaying alemtuzumab administration in patients with active infection until the infection is fully controlled.

Risk Evaluation and Mitigation Strategy (REMS) Programs⁷⁷

The manufacturer of dalfampridine had a structured healthcare provider and patient education program as required by the FDA due to the risk of drug-associated seizures. The REMS requirements were removed in June 2013.⁷⁸

Fingolimod has a prescriber and patient education program. Letters to prescribers describe the risk of bradyarrhythmias and atrioventricular block at treatment initiation, infections, macular edema, posterior reversible encephalopathy syndrome (PRES), respiratory effects, hepatic effects, and fetal risk. A patient medication guide will be dispensed with each fingolimod prescription, which also includes information regarding PML.

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

Due to the risk of autoimmunity, infusion reactions, and malignancy, alemtuzumab (Lemtrada) has a prescriber, patient, pharmacy, and healthcare facility program. Prescribers must be certified with the program and complete training. Patients must enroll in the program and comply with ongoing monitoring requirements. Pharmacies must be certified and only dispense to healthcare facilities authorized to receive alemtuzumab. Healthcare facilities must enroll in the program and verify that patients are enrolled before administering alemtuzumab.

DRUG INTERACTIONS^{79,80,81,82,83,84,85}

Interactions between glatiramer (Copaxone, **Glatopa**) and other drugs have not been fully evaluated. No formal drug interaction studies have been conducted with IFN β -1a (Avonex, Rebif, Plegridy) or IFN β -1b (Betaseron, Extavia). Caution and/or additional monitoring of liver enzymes is required when using IFN β -1a with potentially hepatotoxic drugs. Drug interactions with dalfampridine have not been identified. No formal drug interaction studies have been conducted with alemtuzumab (Lemtrada). Caution should be used in patients previously treated with alemtuzumab (Campath), for B-cell chronic lymphocytic leukemia (B-CLL), due to the drug containing the same active ingredient and possible additive and long lasting effects on the immune system.

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). Co-administration of ketoconazole can increase fingolimod exposure by 70%; a higher risk of adverse effects is possible. Live attenuated vaccines during fingolimod treatment and for 2 months following discontinuation should be avoided.

Patients taking drugs metabolized by CYP2C8 and teriflunomide (Aubagio) should be monitored due to a possible increase in exposure to the CYP2C8 medication as a result of teriflunomide inhibiting the enzyme. Also, patients taking drugs metabolized by CYP1A2 and teriflunomide should be monitored due to a possible decrease in exposure to the CYP1A2 medication as a result of teriflunomide inducing the enzyme. Warfarin should be co-administered with teriflunomide with close international normalized ratio (INR) follow-up and monitoring due to a 25% decrease in peak INR when administered together. The type or dose of oral contraceptive should be considered when co-administered with teriflunomide due to an increase in contraceptive drug levels after repeated doses of teriflunomide.

ADVERSE EFFECTS^{86,87,88,89,90,91,92,93,94,95,96,97,98}

The most frequent adverse effects in patients receiving immunomodulators requiring clinical intervention were flu-like symptoms and depression. Adverse effects occurring in more than 2.5% of patients and at a rate higher than placebo are listed.

Drug	Asthenia	Depression	Flu-like Symptoms	Injection Site Reaction	Increased Liver Enzymes	Leukopenia	Pain
alemtuzumab (Lemtrada)	5	0.6*	8	92	nr	nr	12
dalfampridine (Ampyra)	7 (4)	nr	nr	n/a	nr	nr	back: 5 (2)
dimethyl fumarate (Tecfidera)	nr	nr	nr	nr	nr	nr	nr
fingolimod (Gilenya)	3 (1)	8 (7)	13 (10)	n/a	14 (5)	3 (<1)	back: 12 (7)
glatiramer (Copaxone, Glatopa) 20 mg once daily	22 (21)	reported	14 (13) [†]	2-43 [‡] (0-20)	reported	<1	20 [§] (17)
glatiramer (Copaxone) 40 mg three x weekly	nr	nr	3 (2)	2-22 [‡] (0-2)	nr	nr	2 [§] (1)
IFN β -1a IM (Avonex)	24 (18)	18-20 (13-14)	49 (29)	3-28 (6)	reported	reported	23 (21)
IFN β -1a SC (Rebif)	reported	17-25 (25-28)	56-59 (51)	89-92 (39)	10-27 (4)	28-36 (14)	10-25 (10-20)
IFN β -1a SC (pegylated) (Plegridy)	13 (8)	8 (8)	47 (13)	62 (7)	2 (1)	nr	5 (3)
IFN β -1b (Betaseron)	53 (48)	34 (34)	57 (37)	78 (26)	4-12 (1-4)	18 (6)	42 (35)
IFN β -1b (Extavia)	53 (48)	nr	57 (37)	78 (26)	4-12 (1-4)	18 (6)	42 (35)
teriflunomide (Aubagio)	nr	nr	9-12 (10)	n/a	12-14 (7)	1-2 (0.3)	upper abdominal: 5-6 (4)

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

* attempted suicide or had suicidal ideation

† influenza

‡ glatiramer 40 mg versus 20 mg package insert incidence of injection site erythema (22% versus 43%), pain (10% versus 40%), and pruritus (6% versus 27%)

§ For glatiramer 20 mg, 13% is chest pain; for glatiramer 40 mg, the 2% reflects chest pain

In pre-marketing studies, approximately 16% of patients receiving glatiramer (Copaxone, **Glatopa**) versus four% 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. Other adverse events associated with glatiramer included infection (30% versus 28% for placebo), skin rash (19% versus 11% for placebo), dyspnea (14% versus 4% for placebo), and nausea (15% versus 11% for placebo).

In a study of the dropout rate in patients with RRMS under long-term treatment with the 3 available IFN β preparations, 122 patients were divided into 4 treatment groups: IFN β -1b 24 MIU SC (Betaseron) weekly; IFN β -1a 6 MIU IM (Avonex) weekly; IFN β -1a 18 MIU SC (Rebif) weekly; and 10 patients switching from IFN β -1b to IFN β -1a IM.⁹⁹ During the 5-year observation period, 39.9% of enrolled patients dropped out. Forty-eight percent in the IFN β -1b group withdrew at a median of 758 days, 26% in the IFN β -1a IM group withdrew at a median of 356 days, 38% in the IFN β -1b SC group at a median of 421 days, and 40% in those who switched from IFN β -1b to IFN β -1a IM at a median of 259 days. The differences among the groups were not significant on survival analysis. Patients receiving higher dose treatment (IFN β -1b and IFN β -1b SC groups) dropped out mainly due to clinical adverse events; conversely, patients receiving lower dose therapy (IFN β -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 at up to 5 years of follow-up. In this study, compliance appeared to be related to the dose of the drug.

Cough, diarrhea, and headache (incidence \geq 10% and greater than placebo) have also been reported with fingolimod (Gilenya). Serious adverse events described for fingolimod include bradyarrhythmia and atrioventricular blocks, infections, macular edema, respiratory effects, and hepatic effects.

Additional frequent adverse effects associated with teriflunomide (Aubagio) (\geq 10% incidence or 2% greater than placebo) are alopecia, nausea, and paresthesia. Teriflunomide has also been associated with the following serious adverse reactions: hepatotoxicity, bone marrow and immunosuppression, peripheral neuropathy, hyperkalemia, and serious skin reactions.

Additional adverse effects reported with dimethyl fumarate (Tecfidera) ($>$ 2% incidence) are flushing, abdominal pain, diarrhea, nausea, vomiting, pruritus, rash, albumin present in urine, erythema, dyspepsia, aspartate aminotransferase increase, and lymphopenia.

Urinary tract infections were reported more frequently with dalfampridine (12%) in clinical trials compared to placebo (8%).

Additional adverse effects reported with alemtuzumab (Lemtrada) (\geq 10% of patients and more than interferon beta-1a alone) were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting.

SPECIAL POPULATIONS^{100,101,102,103,104,105,106,107,108,109,110}

Pediatrics

Alemtuzumab (Lemtrada), dalfampridine (Ampyra), dimethyl fumarate (Tecfidera), fingolimod (Gilenya), glatiramer (Copaxone, **Glatopa**), IFN β -1a IM (Avonex), IFN β -1a SC (Plegridy, Rebif), IFN β -1b (Betaseron, Extavia), and teriflunomide (Aubagio) are not indicated for use in pediatric patients.

Pregnancy

Glatiramer (Copaxone, **Glatopa**) is Pregnancy Category B. Alemtuzumab (Lemtrada), dalfampridine (Ampyra), dimethyl fumarate (Tecfidera), fingolimod (Gilenya), IFN β -1a IM (Avonex), IFN β -1a SC (Plegridy, Rebif), and IFN β -1b (Betaseron, Extavia) are Pregnancy Category C.

Fingolimod (Gilenya) may cause fetal harm. Elimination of fingolimod takes approximately 2 months upon discontinuation. Therefore, women of childbearing potential should use effective contraception to avoid pregnancy during and for 2 months after stopping fingolimod.

Teriflunomide (Aubagio) is Pregnancy Category X and contraindicated in pregnant women or women of child bearing potential not using reliable contraception. To minimize risk, female partners of men taking teriflunomide should also use reliable contraception. Although it is contraindicated, a pregnancy registry does exist for teriflunomide and pregnant women should be encouraged to enroll in order to monitor fetal outcomes.

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.

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. In patients with moderate to severe renal impairment (CrCL \leq 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.

Alemtuzumab patients with severe renal impairment should be monitored for adverse reactions due to increased drug exposure.

DOSAGES^{111,112,113,114,115,116,117,118,119,120,121,122}

Drug	Dosage	Comments	Availability
alemtuzumab (Lemtrada)	12 mg per day by intravenous (IV) infusion over 4 hours for 2 courses of therapy; course 1 is for 5 days and course 2 is for 3 days 1 year after the first course	Refrigerate; may be stored at room temperature (25 °C) for up to 8 hours before administration Protect from light	Single use vial: 12 mg/1.2 mL solution
dalfampridine (Ampyra)	10 mg by mouth twice daily about 12 hours apart	--	Tablets: 10 mg extended release tablets
dimethyl fumarate (Tecfidera)	120 mg by mouth twice daily for 7 days and then 240 mg twice daily	Should not be crushed, chewed, or sprinkled on food; Can be taken with or without food; administration with food may reduce the incidence of flushing	Capsules: 120 mg, 240 mg capsules, 30 day starter pack
fingolimod (Gilenya)	0.5 mg by mouth once daily	--	Capsules: 0.5 mg capsules
glatiramer acetate (Copaxone)	20 mg SC once daily 40 mg SC 3 times weekly (at least 48 hours apart)	Refrigerate; may be stored at room temperature for up to 1 month (refrigeration preferred)	Single-dose prefilled syringes : 20 mg/mL, 40 mg/mL (these strengths are not interchangeable)
glatiramer acetate (Glatopa*)	20 mg SC once daily		Single-dose prefilled syringe: 20 mg/mL
IFNβ-1a (Avonex)	30 mcg IM once weekly	Refrigerate; may be stored at room temperature (25 °C) for up to 7 days; Following reconstitution use immediately; however, may be refrigerated for up to 6 hours Protect from light	Powder for injection vial with diluent: – 30 mcg
IFNβ-1a (Avonex prefilled syringe)		Refrigerate; allow to come to room temperature before use (~30 minutes); may be stored at room temperature (≤ 25 °C) for up to 7 days Protect from light	Prefilled syringes: 30 mcg/0.5 mL with 23 gauge 1¼ inch needle
IFNβ-1a (Avonex pen)			Prefilled autoinjector: 30 mcg/0.5 mL with 25 gauge, 5/8 needle
IFNβ-1a (Rebif)	4.4 or 8.8 mcg SC 3 times weekly, titrated over 4 weeks up to 22 or 44 mcg SC 3 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, titration pack
IFNβ-1a (Rebif Rebidose®)			Prefilled autoinjector – 22, 44 mcg, titration pack

*Glatopa is available as a 20 mg/mL strength; it is considered therapeutically equivalent only to the 20 mg/mL formulation of glatiramer acetate (Copaxone); it is not interchangeable with Copaxone 40 mg/mL.

Dosages (continued)

Drug	Dosage	Comments	Availability
IFN β -1a SC (pegylated) (Plegridy) ¹²³	125 mcg SC every 14 days, titrated over 4 weeks with a dose of 63 mcg at initiation and 94 mcg 2 weeks later	Refrigerate; may be stored at room temperature for up to 30 days; allow to come to room temperature before use (~30 minutes) Protect from light	Prefilled syringes or autoinjector pens: 125 mcg, starter pack (63 mcg and 94 mcg syringe)
IFN β -1b (Betaseron) ¹²⁴	0.0625 mg SC every other day; increased over a 6-week period to 0.25 mg SC every other day	Store at room temperature prior to reconstitution; stable refrigerated for 3 hours after reconstitution	Powder for injection vial with diluent: 0.3 mg May be used with or without the Betaconnect™ autoinjector†
IFN β -1b (Extavia) ¹²⁵	0.0625 mg SC every other day; increased over a 6-week period to 0.25 mg SC every other day	Store at room temperature prior to reconstitution; stable refrigerated for 3 hours after reconstitution	Powder for injection vial with diluent: 0.3 mg
teriflunomide (Aubagio) ¹²⁶	7 mg or 14 mg by mouth once daily	--	Tablets: 7 mg, 14 mg tablets

† The Betaconnect electronic autoinjector is approved for use with Betaseron.¹²⁷ It is not supplied with Betaseron but is available through the Betaplus® patient support program.

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.

Significant first dose monitoring is needed for fingolimod. All patients must be observed for signs and symptoms of bradycardia for at least 6 hours after first dose with hourly pulse and blood pressure measurement. ECG must be obtained prior to dosing and at the end of the observation period.

Several monitoring parameters should be considered when administering teriflunomide. Transaminase and bilirubin levels should be taken 6 months before starting therapy and monitored monthly for at least 6 months. A complete blood cell count (CBC) should be taken 6 months before initiating therapy and further monitoring should occur based on signs and symptoms of infection. Before starting therapy, patients should be screened for tuberculosis and should have their blood pressure measured at initiation of therapy and periodically afterwards.

A recent complete blood cell (CBC) count is recommended before initiation of dimethyl fumarate therapy to identify patients with pre-existing low lymphocyte counts.

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% 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 or partially blinded manner; introduction of bias must be considered when evaluating study findings. Clinical trials of IFN β -1b (Betaseron) were used for IFN β -1b (Extavia) approval.¹²⁸

alemtuzumab (Lemtrada) versus IFN β -1a SC (Rebif)

The efficacy of alemtuzumab was demonstrated in 2 studies that evaluated alemtuzumab 12 mg in patients with relapsing-remitting multiple sclerosis (RRMS).^{129,130} Alemtuzumab was administered by intravenous (IV) infusion once daily over a 5-day course, followed 1 year later by IV infusion once daily over a 3-day course in both trials. Both studies included patients who had experienced at least 2 relapses during the 2 years prior to trial entry and at least 1 relapse during the year prior to trial entry. Neurological examinations were performed every 12 weeks and at the time of suspected relapse. Magnetic resonance imaging (MRI) evaluations were performed annually.

The first study was a 2-year randomized, open-label, rater-blinded, active comparator (interferon beta-1a 44 micrograms administered subcutaneously 3 times a week) controlled study in patients with RRMS.¹³¹ Patients entering the study had EDSS scores of 5 or less and had to have experienced at least 1 relapse while on interferon beta or glatiramer acetate therapy. Patients were randomized to receive alemtuzumab (n=426) or interferon beta-1a (n=202). The clinical outcome measures were the annualized relapse rate (ARR) over 2 years and the time to confirmed disability progression. Confirmed disability progression was defined as at least a 1 point increase above baseline EDSS sustained for 6 months. The MRI outcome measure was the change in T2 lesion volume. The ARR was significantly lower in patients treated with alemtuzumab than in patients who received interferon beta-1a (0.26 versus 0.52, p<0.0001). The proportion of patients with disability progression at year 2 was also significantly reduced in the alemtuzumab group (13% versus 21%; p<0.0084). There was no significant difference between the treatment groups for the change in T2 lesion volume (-1.3 versus -1.2; p=0.14).

The other alemtuzumab study was a 2-year randomized, open-label, rater-blinded, active comparator (interferon beta-1a 44 micrograms administered subcutaneously 3 times a week) controlled study in patients with RRMS. Patients entering Study 2 had EDSS scores of 3 or less and prior treatment for multiple sclerosis.¹³² Patients were randomized to receive alemtuzumab (n=376) or interferon beta-1a (n=187). The clinical outcome measures were the ARR over 2 years and the time to confirmed disability progression, as defined in the first study. The MRI outcome measure was the change in T2 lesion volume. The annualized relapse rate was significantly lower in patients treated with alemtuzumab than in patients who received interferon beta-1a (0.18 versus 0.39, p<0.0001). There was no statistically significant difference in the proportion of patients with disability progression at Year 2 (8% versus 11%; p=0.22) or between the treatment groups for the change in T2 lesion volume (-9.3 versus -6.5; p=0.31).

dalfampridine (Ampyra) versus placebo

A phase 3 study assessed efficacy and safety of dalfampridine in patients with ambulatory deficits due to multiple sclerosis.¹³³ This was 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 a 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%) than in the placebo group (8%; p<0.0001). Improvement in walking speed in dalfampridine-treated patients was 25.2% and 4.7% in the placebo group. A 20% or greater improvement in walking speed is frequently considered clinically meaningful.^{134,135,136}

Another randomized, multicenter, double-blind trial included 229 patients with definite MS of any type.¹³⁷ Patients were randomized to dalfampridine 10 mg twice daily or placebo. Response was defined as consistent improvement on the timed 25-foot walk with the primary outcome the percent of timed walk responders in each group. The percentage of timed walk responders was 42.9% (51/119 patients) of patients receiving dalfampridine compared to 9.3% (11/118 patients) of patients receiving placebo (p<0.0001). Average improvement in walking speed among dalfampridine-treated patients in the responders group was 24.7% from baseline (95% confidence interval [CI], 21 to 28.4). The mean improvement at the last treatment visit was 25.7% 8 to 12 hours after the previous dose. Adverse effects were consistent with previous studies.

dimethyl fumarate (Tecfidera) versus placebo

DEFINE study:¹³⁸ The DEFINE study was a 2-year, phase 3, randomized, double-blind, placebo-controlled study that compared dimethyl fumarate 240 mg twice daily, 240 mg thrice daily (not a FDA-approved dosing frequency), and placebo to demonstrate the efficacy of dimethyl fumarate in patients with relapsing-remitting multiple sclerosis (RRMS). Patients who had experienced at least 1 relapse in the previous year or had a brain MRI scan demonstrating at least 1 gadolinium-enhancing lesion within 6 weeks of randomization were included. The primary endpoint was the proportion of patients who had relapses by 2 years. Neurological evaluations were conducted at baseline, every 3 months, and at the time of a suspected relapse and safety evaluations were conducted every 4 weeks. The study had balanced baseline demographic and disease characteristics. The median time on the study drug was 96 weeks with 69% in both dimethyl fumarate groups and 65% in the placebo group completing 96 weeks. A total of 1,234 patients received at least 1 dose of the medication including 410 in the twice daily arm,

416 in the thrice daily arm, and 408 in the placebo arm. Both dimethyl fumarate groups significantly reduced relapse of MS on the basis of Kaplan-Meier estimates of 27% for the twice daily group and 26% for the thrice daily group compared to 46% in the placebo group ($p < 0.001$). No additional benefit was shown in the thrice daily group compared to the twice daily group. The incidence of adverse events was similar across the 3 groups with flushing being the most common adverse effect in the dimethyl fumarate group. Dimethyl fumarate was also associated with a decrease in lymphocyte counts.

dimethyl fumarate (Tecfidera) versus placebo with glatiramer acetate (Copaxone) as an active comparator

CONFIRM study:¹³⁹ The CONFIRM study was a 2-year, phase 3, randomized, double-blind, placebo-controlled study that compared dimethyl fumarate 240 mg twice daily, 240 mg thrice daily (not a FDA-approved dosing frequency), open label glatiramer acetate 20 mg daily, and placebo to demonstrate the efficacy of dimethyl fumarate in patients with RRMS. Patients who had experienced at least 1 relapse in the previous year or had a brain MRI scan demonstrating at least 1 gadolinium-enhancing lesion within 6 weeks of randomization were included. The primary endpoint was annualized relapse rate confirmed by an independent neurologic evaluation committee after 2 years time. The study had balanced baseline demographic and disease characteristics. The annualized relapse rate was calculated as the total number of relapses divided by patient years in the study. Standardized neurological assessments were performed every 12 weeks and at the time of suspected relapse. The median time on the study drug was 96 weeks with 72% in the dimethyl fumarate twice daily group, 70% in the dimethyl fumarate thrice daily group, 75% in the glatiramer acetate group, and 64% in the placebo group completing 96 weeks. One thousand four hundred seventeen patients were included in the intent to treat analysis including 359 in the twice daily group, 345 in the thrice daily group, 350 in the glatiramer acetate group, and 363 in the placebo group. All 3 treatment groups had a statistically significant reduction in annualized relapse rates compared to placebo including a 0.22 relapse rate ($p < 0.001$) in the twice daily group, a 0.2 ($p < 0.001$) relapse rate in the thrice daily group, and a 0.29 ($p = 0.01$) relapse rate in the glatiramer acetate compared to the 0.4 relapse rate in the placebo group. No additional benefit was shown in the thrice daily group compared to the twice daily group. **Additional benefits were also seen in MRI measures (active lesions and total lesion volume).**¹⁴⁰ Although the study was not designed to test the superiority or noninferiority of dimethyl fumarate to glatiramer acetate, the active comparator had similar results.¹⁴¹ The incidence of adverse events was similar across the groups with flushing being the most common adverse effect in the dimethyl fumarate groups. Dimethyl fumarate was also associated with a decrease in lymphocyte counts.

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

TRANSFORMS:¹⁴² The first study was a 12-month, randomized, double-blind, double-dummy, multicenter study comparing fingolimod 0.5 mg or 1.25 mg daily and INFB-1a 30 mcg IM weekly. A total of 1,292 patients had RRMS with a recent history of at least 1 relapse, median age of 36 years, and a score of 0 to 5.5 on the EDSS. The primary endpoint of annualized relapse rate was significantly lower in the fingolimod groups compared to INFB-1a: 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 INFB-1a group. MRI results supported the primary findings as measured by the mean number of new and newly enlarged T2 lesions at 1 year (1.6 for fingolimod groups versus 2.6 for INFB-1a, $p = 0.002$). There was no significant difference in the time to 3-month confirmed disability

progression between fingolimod groups and INFB-1a patients at 1 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.

A 2-year, double-blind extension of the TRANSFORMS study compared the second year with results from the first year with a focus on the patients who switched therapy from INFB-1a and to evaluate efficacy of fingolimod at 24 months relative to fingolimod efficacy at 12 months.¹⁴³ A total of 1,027 patients entered the extension phase. Patients originally randomized to fingolimod 0.5 or 1.25 mg daily continued on the same treatment. Patients who originally received INFB-1a 30 mcg IM weekly were re-randomized to fingolimod 0.5 mg or 1.25 mg daily. A total of 882 patients completed the 24 months of treatment. Endpoints included annualized relapse rate, disability progression, and MRI outcomes. Patients receiving 24 months of fingolimod had persistent benefits in annualized relapse rate (0.5 mg fingolimod [n=356], 0.12 [95% CI, 0.08 to 0.17] in months 0 to 12 versus 0.11 [95% CI, 0.08 to 0.16] in months 13 to 24; 1.25 mg fingolimod [n=330], 0.15 [95% CI, 0.1 to 0.21] versus 0.11 [95% CI, 0.08 to 0.16]). Patients who initially received INFB-1a 30 mcg IM weekly had a lower annualized relapse rate after switching to fingolimod compared to the first 12 months (INFB-1a to 0.5 mg fingolimod [n=167], 0.31 [95% CI, 0.22 to 0.43] in months 0 to 12 versus 0.22 [95% CI, 0.15 to 0.31] in months 13 to 24; p=0.049; INFB-1a to 1.25 mg fingolimod [n=174], 0.29 [95% CI, 0.2 to 0.4] versus 0.18 [95% CI, 0.12 to 0.27], p=0.024). After switching to fingolimod, numbers of new or newly enlarging T2 and gadolinium (Gd)-enhancing T1 lesions were significantly reduced compared with the previous 12 months of INFB-1a therapy (p<0.0001 for T2 lesions at both doses; p=0.002 for T1 at 0.5 mg; p=0.011 for T1 at 1.25 mg). Over the 2-year period, patients receiving continuous fingolimod had lower annualized relapse rates (0.18 [95% CI, 0.14 to 0.22] for 0.5 mg; 0.2 [95% CI, 0.16 to 0.25] for 1.25 mg; 0.33 [95% CI, 0.27 to 0.39] for the switch group; p<0.0001 for both comparisons), fewer new or newly enlarged T2 lesions (p=0.035 for 0.5 mg, p=0.068 for 1.25 mg), and fewer patients with Gd-enhancing T1 lesions (p=0.001 for 0.5 mg fingolimod versus switch group; p=0.002 for 1.25 mg fingolimod versus switch group). There was no benefit on disability progression. Adverse events were consistent with those observed for fingolimod. The manufacturer of fingolimod supported the study.

fingolimod (Gilenya) versus placebo

FREEDOMS:¹⁴⁴ A randomized, double-blind, placebo-controlled, multicenter, 24-month clinical trial evaluated 1,272 patients with relapsing-remitting MS. Patients with median age of 37 years had a score of 0 to 5.5 on the Expanded Disability Status Scale (EDSS), had 1 or more relapses the prior year, or had 2 or more relapses in the prior 2 years, and had not received any interferon-beta or glatiramer for at least the previous 3 months, nor received natalizumab for at least the previous 6 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). The key secondary endpoint was the time to disease progression which was confirmed 3 months or 6 months later. Both doses of fingolimod significantly reduced the risk of time to disability progression, (expressed as the hazard ratio [HR] relative to placebo), was 0.7 for the 0.5 mg dose and 0.68 for the 1.25 mg dose (p=0.02 for both). The cumulative probability of disability progression confirmed after 3 months was 17.7%, 16.6%, and 24.1% 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.

FREEDOMS II: A randomized, double-blind, placebo-controlled, multicenter, 24-month trial evaluated 1,083 patients with relapsing-remitting MS.¹⁴⁵ Patients aged 18 to 55 years were randomized to receive fingolimod 0.5 mg, fingolimod 1.25 mg, or placebo orally once daily (1:1:1). On Nov 12, 2009, all patients assigned to fingolimod 1.25 mg were switched to the 0.5 mg dose in a blinded manner after a review of data from other phase 3 trials and recommendation from the data and safety monitoring board, but were analyzed as being in the 1.25 mg group in the primary outcome analysis. The primary endpoint was annualized relapse rate at month 24, analyzed by intention to treat. Secondary endpoints included percentage brain volume change (PBVC) from baseline and time-to-disability-progression confirmed at 3 months. Mean annualized relapse rate was 0.4 (95% CI, 0.34 to 0.48) in patients given placebo and 0.21 (95% CI, 0.17 to 0.25) in patients given fingolimod 0.5 mg with a rate ratio of 0.52 (95% CI 0.4 to 0.66; $p < 0.0001$), corresponding to a reduction of 48% with fingolimod 0.5 mg versus placebo. Mean PBVC was -0.86 for fingolimod 0.5 mg versus -1.28 for placebo (treatment difference -0.41; 95% CI, -0.62 to -0.2; $p = 0.0002$). There was no statistically significant between group differences in confirmed disability progression. Adverse events in the fingolimod groups included lymphopenia, increased alanine aminotransferase, herpes zoster infection, hypertension, first-dose bradycardia, and first-degree atrioventricular block.

glatiramer acetate (Copaxone) and IFN β -1a IM (Avonex) versus glatiramer acetate (Copaxone) or IFN β -1a IM (Avonex)

CombiRx study:¹⁴⁶ The CombiRx study was a National Institutes of Health (NIH) sponsored 3-year, randomized, double-blind, controlled study comparing combined use of glatiramer acetate and IFN β -1a IM compared to each agent alone. Patients were randomized to 3 treatment arms of glatiramer acetate 20 mg subcutaneously daily plus placebo (GA), IFN β -1a 30 μ g intramuscularly weekly plus placebo (IFN), or 20 mg subcutaneously daily plus IFN β -1a 30 μ g intramuscularly weekly (GA + IFN). Participants were 18 to 60 years of age with an EDSS of 0 to 5.5 with an RRMS diagnosis and at least 2 exacerbations within the last 3 years. Patients received neurological assessment every 12 weeks for 3 years during the study and MRIs at months 6, 12, 24, and 36. The primary outcome of the study was the Annualized Relapse Rate (ARR) based on protocol-defined exacerbations. A total of 1,008 patients were randomized to the treatment arms with 499 patients in the GA + IFN arm, 250 in the IFN arm, and 259 in the GA arm. The patients' baseline characteristics were similar with the exception of age which was accounted for with adjustments for age. The GA + IFN treatment was not significantly better than GA treatment with 150 relapses compared to 70 relapses ($p = 0.27$), but it was significantly better than the IFN treatment with 97 relapses ($p = 0.022$). The GA treatment was significantly better than the IFN treatment with 70 relapses compared to 97 relapses ($p = 0.027$). There were no additional safety issues resulting from combination therapy and the adverse events reported were the usual adverse events associated with the single agents.

glatiramer acetate (Copaxone) (three times weekly) versus placebo

GALA study:¹⁴⁷ A randomized, double-blind, placebo-controlled study was conducted to assess the efficacy and safety of glatiramer acetate 40 mg administered 3 times weekly compared with placebo in patients with RRMS. Patients with RRMS with at least 1 documented relapse in the 12 months before screening, or at least 2 documented relapses in the 24 months before screening, and an EDSS score ≤ 5.5 , were randomized 2:1 to receive either glatiramer acetate 40 mg 3 times weekly subcutaneously or placebo for 12 months. Of 1,524 patients screened, 1,404 were randomized to receive glatiramer acetate 40 mg 3 times weekly (n=943) or placebo (n=461). Ninety-three percent and 91% of patients in the placebo and glatiramer acetate groups, respectively, completed the 12-month study. Glatiramer acetate 40 mg 3 times weekly was associated with a 33.1% annualized relapse rate compared to a 50.5% rate in the placebo group for a 34% reduction in annualized relapses (mean annualized relapse rate, 0.331 versus 0.505; $p < 0.0001$). The most common adverse event in the glatiramer acetate group was injection site reaction (35.5% of the glatiramer acetate 40 mg 3 times weekly patients versus 5% of the patients on placebo).

IFN β -1a IM (Avonex) versus IFN β -1a SC (Rebif)

The EVIDENCE (Evidence of Interferon Dose-Response: European North American Comparative Efficacy) trial was a randomized, 64-week dose effect trial of IFN β -1a 44 mcg SC 3 times weekly or IFN β -1a 30 mcg IM once weekly in 677 patients with RRMS.¹⁴⁸ 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% in the SC arm and 63% in the IM arm ($p < 0.001$). At 48 weeks, the proportion of relapse-free patients was 62% in the SC group and 52% 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% 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 IFN β -1a 44 mcg SC 3 times weekly and were followed for an average additional 32 weeks.¹⁴⁹ At the transition visit, 223 (73%) of 306 patients originally receiving 30 mcg IM weekly converted to 44 mcg SC 3 times weekly, and 272 (91%) of 299 receiving 44 mcg SC 3 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 3 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 3-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 IFN β -1a therapy had increased rates of adverse events and treatment terminations consistent with the initiation of high-dose SC IFN therapy.

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

The Independent Comparison of Interferon (INCOMIN) trial was a single-blinded, randomized comparison of IFNβ-1a IM and IFNβ-1b in 188 patients with RRMS.¹⁵⁰ IFNβ-1a was given at a dose of 30 mcg IM once weekly, and IFNβ-1b was administered at a dose of 250 mcg SC every other day. Over the 2-year study period, 36% of patients randomized to IFNβ-1a IM were relapse-free compared to 51% of patients receiving IFNβ-1b ($p=0.03$). More patients remained free from new T2 lesions, which indicate inflammatory damage on MRI, in the IFNβ-1b group (55% versus 26%, $p<0.0003$). Delay of confirmed disease progression was significantly higher in the IFNβ-1b group. Discontinuation of therapy due to disease progression was more prevalent in the IFNβ-1a IM group. Significantly more patients withdrew from therapy with IFNβ-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.

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

In an open-label study, 301 patients with RRMS were randomized to receive IFNβ-1a 22 mcg SC once weekly or IFNβ-1b 250 mcg SC every other day for 2 years.¹⁵¹ The annual relapse rates were virtually equal in the 2 arms of the randomized study (IFNβ-1a: 0.7; IFNβ-1b: 0.71), as were the time to first relapse and the time to sustained progression. In addition, no significant difference existed in proportions of relapse-free patients, 40.8% in the IFNβ-1a SC group and 45.2% in the IFNβ-1b group. Subsequent intent-to-treat analysis indicated a statistically insignificant difference in the proportion of relapse-free patients, 35% and 41% in the IFNβ-1a SC and IFNβ-1b groups, respectively.¹⁵² The IFNβ-1a dosing interval in the study was less frequent than the FDA-approved dosing regimen.

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

In a parallel group, single-blind study, 90 patients with RRMS were randomized to receive IFNβ-1a 30 mcg IM once weekly, IFNβ-1a 44 mcg SC 3 times weekly, or IFNβ-1b 250 mcg SC every other day for 24 months.¹⁵³ The EDSS scores remained stable in patients in the IFNβ-1a IM group and decreased in the groups receiving IFNβ-1a SC ($p<0.05$ versus baseline) and IFNβ-1b ($p<0.001$). In the patients treated with IFNβ-1a IM, the mean 2-year relapse rate decreased from 2 to 1.2 episodes ($p<0.001$ compared to baseline). In the patients treated with IFNβ-1a SC, the mean relapse rate decreased from 2.4 to 0.6, while the rate in those treated with IFNβ-1b decreased from 2.2 to 0.7 ($p<0.001$ for both changes from baseline). After 2 years, 20% of patients receiving IFNβ-1a IM remained relapse-free. In comparison, 57% of patients receiving IFNβ-1a SC and 43 of those receiving IFNβ-1b remained relapse-free ($p<0.05$ for both comparisons to IFNβ-1a IM).

IFNβ-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 IFNβ-1a SC 44 mcg 3 times weekly ($n=386$) or glatiramer acetate SC 20 mg daily ($n=378$) for 96 weeks.¹⁵⁴ Patients had a history of at least 1 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 IFNβ-1a group and 132 in the glatiramer acetate group) had 1 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 IFN β -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.

IFN β -1a SC pegylated (Plegridy) versus placebo

ADVANCE study:¹⁵⁵ The efficacy of pegylated IFN β -1a SC (Plegridy) was demonstrated in a randomized, double-blind, placebo-controlled trial. The trial compared clinical and MRI outcomes at 48 weeks in patients who received pegylated IFN β -1a SC 125 mcg (n=512) or placebo (n=500) subcutaneously once every 14 days. The study enrolled patients who had a baseline EDSS score from 0 to 5, who had experienced at least 2 relapses within the previous 3 years, and had experienced at least 1 relapse in the previous year. The trial excluded patients with progressive forms of multiple sclerosis. The mean age of the study population was 37 years, the mean disease duration was 3.6 years, and the mean EDSS score at baseline was 2.46. The majority of the patients were women (71%). The trial scheduled neurological evaluations at baseline, every 12 weeks, and at the time of a suspected relapse. Brain MRI evaluations were scheduled at baseline, week 24, and week 48. The primary outcome was the annualized relapse rate over 1 year. Secondary outcomes included the proportion of patients relapsing, number of new or newly enlarging T2 hyperintense lesions, and time to confirmed disability progression. Pegylated IFN β -1a SC was associated with a 26% relapse rate compared to 40% in the placebo group for a 36% relative reduction in annualized relapses (p=0.0007).

IFN β -1b SC (Betaseron) versus glatiramer acetate (Copaxone)

The BEYOND trial compared the efficacy, safety, and tolerability of IFN β -1b 250 mcg or 500 mcg with glatiramer acetate 20 mg for treating RRMS.¹⁵⁶ A total of 2,244 patients were enrolled in a prospective, multicenter, randomized trial. Patients were randomly assigned to receive IFN β -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 2 to 3.5 years. No differences were determined in relapse risk, as well as for secondary endpoints such as EDSS progression, T1-hypointensive lesion volume, or normalized brain volume among treatment groups. Flu-like symptoms were more common in patients treated with IFN β -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.

teriflunomide (Aubagio) versus placebo

TEMSE Study:^{157,158} A double-blind, placebo-controlled study evaluated 7 mg and 14 mg doses of teriflunomide in relapsing forms of MS for 108 weeks with a primary endpoint of annualized relapse rate (APR). All patients had a relapsing form of MS and had 1 relapse in the previous year or 2 relapses in the previous 2 years. Patients had not received interferon-beta for at least the past 4 months or any preventive medications in the past 6 months, nor were they permitted to receive those medications during the trial. Neurological evaluations were performed every 12 weeks during the trial in addition to visits for suspected relapse and MRIs were performed at weeks 24, 48, 72, and 108.

A total of 1,088 patients were randomized to receive 7 mg (n=366) or 14 mg (n=359) of teriflunomide or placebo (n=363). The mean age for the study was 37.9 years with a mean disease duration of 5.33 years and a EDSS of 5.5 or below with a mean baseline level of 2.68. Of the patients studied, 91.4% of the patients had RRMS and 8.6% had a progressive form of MS with relapses. A total of 796 (73.2%) of the patients completed the trial with similar dropout rates in all 3 groups. The APR and relative risk (RR) reduction were significantly reduced in the 14 mg (0.369 relapses, 31.5% RR, p=0.0005) and 7 mg (0.37 relapses, 31.2% RR, p=0.0002) teriflunomide groups compared to placebo (0.539 relapses). The reductions were noted in subgroups defined by sex, age group, prior MS therapy, and baseline disease. Although the study was not designed to demonstrate efficacy in secondary outcomes, disability progression after 12 weeks was reduced by teriflunomide 14 mg (p=0.03) and not by the 7 mg (p=0.08) arm compared to placebo. The treatment groups showed statistically favorable secondary outcomes in total lesion volume from baseline on magnetic resonance imaging (MRI). The TOWER trial, an international, randomized, double-blind, placebo-controlled trial, reinforced the results of the TEMSO, with teriflunomide 7 mg and 14 mg showing significant reduction in annualized relapse rates and teriflunomide 14 mg with a significant reduction in the accumulation of disability.¹⁵⁹ Another randomized, placebo-controlled trial, TOPIC, showed patients in the teriflunomide 7 mg and 14 mg groups had a significant reduction in time to relapse indicating clinically definite MS, relapses, and new MRI lesions, in clinically isolated syndrome indicative of early MS.¹⁶⁰

teriflunomide (Aubagio) versus IFN β -1a SC (Rebif)

TENERE Study:¹⁶¹ The TENERE study was a 48-week, randomized, rater-blinded study that compared teriflunomide 7 mg daily, 14 mg daily, and IFN β -1a 44mcg 3 times weekly. Patients 18 years of age and older who met McDonald criteria for MS, had a relapsing clinical course, with or without progression, and an EDSS score \leq 5.5 at screening were included. The primary composite endpoint was time to failure, defined as first occurrence of confirmed relapse or permanent treatment discontinuation for any cause. Relapse criteria required the appearance of a new clinical sign or symptom or clinical worsening of a previous sign or symptom that persisted for at least 24 hours without fever and each relapse was confirmed by the treating neurologist.

A total of 324 patients were randomized (IFN β -1a: 104; teriflunomide 7 mg: 109; teriflunomide 14 mg: 111) and no difference in time to failure was observed. At Week 48, the cumulative percentage of estimated failures using the Kaplan–Meier method was 37% in the IFN β -1a group, and 36% and 33% in the teriflunomide 7 mg and 14 mg groups. The contribution of permanent treatment discontinuation to the failure rate was highest in the IFN β -1a group and lowest in the teriflunomide 7 mg group. In contrast, the fewest confirmed relapses were observed in the IFN β -1a group. Overall occurrences of adverse effects were similar across groups. Common adverse effects (greater than 10% in any group) reported more frequently with teriflunomide included nasopharyngitis, diarrhea, hair thinning, paraesthesia, and back pain. Influenza-like symptoms, ALT increases, and headache occurred more frequently with IFN β -1a.

Neutralizing Antibodies: IFN β -1a IM (Avonex) versus IFN β -1a SC (Rebif) versus IFN β -1b (Betaseron)

One difference among the 3 IFN β products is the associated production of neutralizing antibodies (NAb). Data suggest that the presence of NAb against IFN β reduces the bioavailability and clinical efficacy of the drug leading to an increase in relapse rates.¹⁶² 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.^{163,164,165}

To evaluate the incidence and the prevalence of NAb in each of the 3 IFN β products, sera were tested from 125 patients with RRMS.¹⁶⁶ Patients were treated with IFN β -1b 250 mcg SC every other day, IFN β -1a 30 mcg IM once weekly, or IFN β -1a 22 mcg SC 3 times weekly. Patients with 2 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% for IFN β -1b, 15% for IFN β -1a SC, and 2% for IFN β -1a IM (p=0.001 for IFN β -1b versus IFN β -1a IM; p=0.19 for IFN β -1b versus IFN β -1a SC; p=0.04 for IFN β -1a SC versus IFN β -1a IM). In all patients with at least 1 NAb+ sample, the risk of becoming persistent NAb+ was 38% for IFN β -1b, 18% for IFN β -1a SC, and 7% for IFN β -1a IM (p=0.0007 for IFN β -1b versus IFN β -1a IM; p=0.1 for IFN β -1b versus IFN β -1a SC; p=0.07 for IFN β -1a SC versus IFN β -1a IM). At month 18, the prevalence of persistent NAb+ patients was 31.6% for IFN β -1b, 18.7% for IFN β -1a SC, and 4% for IFN β -1a IM.

In the EVIDENCE trial, NAb developed in 25% of the patients who received IFN β -1a SC compared with 2% of the patients given IFN β -1a IM.¹⁶⁷ The incidence of NAb development appears to be less with IFN β -1a than with IFN β -1b and less when given IM in comparison to SC.

META-ANALYSES

A Cochrane review of 5 clinical trials (n=2,858) assessed the efficacy of RRMS patients randomly assigned to interferons and to glatiramer acetate.¹⁶⁸ At 2 years of treatment, the number of participants with relapse (risk ratio [RR], 1.04; 95% CI, 0.87 to 1.24) and progression (RR, 1.11; 95% CI, 0.91 to 1.35) were comparable between the 2 groups. At 3 years, a single study suggested that relapse may be higher with interferons than with glatiramer (RR, 1.4; 95% CI, 1.13 to 1.7; p=0.002). Dropouts due to adverse effects were similar in both groups (RR, 0.95; 95% CI, 0.64 to 1.4). MRI results were also considered. At 2 years, the effects on new or enlarging T2- or gadolinium (Gd)-enhancing lesions at 124 months (mean difference [MD], -0.01; 95% CI, -0.28 to 0.26; and MD, -0.14; 95% CI, -0.3 to 0.02; respectively) were similar, but they differed in reduction in T2- and T1-weighted lesion volume as it was significant greater with interferon than with glatiramer (MD, -0.58; 95% CI, -0.99 to -0.18; p=0.004; and MD, -0.2; 95% CI, -0.33 to -0.07; p=0.003; respectively).

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 IFN β 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 IFN β in patients with SPMS but without relapses is uncertain. Plegridy, is a pegylated formulation of interferon beta 1a, which allows for a longer duration, therefore Plegridy is dosed subcutaneously once every 2 weeks. These guidelines also favor glatiramer (Copaxone) treatment to help reduce the number of attacks for patients with RRMS. **Glatopa 20 mg/mL is a therapeutically equivalent glatiramer acetate generic of Copaxone 20 mg/mL.** 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. The 3 oral agents, dimethyl fumarate (Tecfidera), fingolimod (Gilenya), and teriflunomide (Aubagio), and the second-line therapy, alemtuzumab (Lemtrada), were not available at the time of guideline review. Alemtuzumab is approved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS.

There is sufficient evidence to indicate that either the dose or the frequency of IFN β administration, or both, significantly influences the short-term outcome in patients with RRMS. The route of administration of IFN β 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 IFN β reduce the 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 IFN β -1a than with IFN β -1b and less when given IM in comparison to SC. Some studies suggest that NAb, once present, might disappear over time with continued treatment.

Based on trial evidence, interferons and glatiramer acetate have similar clinical utility in MS. The results of the CombiRx trial suggest that combination glatiramer acetate (Copaxone) and IFN β -1a IM (Avonex) is not more effective than glatiramer acetate therapy alone, but glatiramer acetate may be more effective than IFN β -1a IM in reducing risk of exacerbations. Additional trials are needed to confirm this result and the comparative efficacy of glatiramer acetate to other IFN β s.

Three oral agents, dimethyl fumarate (Tecfidera), fingolimod (Gilenya), and teriflunomide (Aubagio), are available for the treatment of MS. Dimethyl fumarate has been shown to reduce MS relapse rates compared to placebo in 2 trials. Dimethyl fumarate also had similar results to glatiramer acetate in a study although the study was not designed to test the superiority or noninferiority of dimethyl fumarate to glatiramer acetate. Fingolimod has shown significant efficacy compared to placebo by reducing relapse rates, MRI measures, and lowering risk of disability progression. Compared to IFN β -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. Due to fingolimod's adverse event profile, significant monitoring is required. Teriflunomide has shown significant efficacy compared to placebo by reducing annual relapse rates in patients with MS. No trials have been published comparing it to other MS agents. The long-term safety and efficacy of these oral agents are unknown.

Another oral agent, dalfampridine (Ampyra), improves walking speed but it has no effect on the underlying disease.

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