Therapeutic Class Overview
Multiple Sclerosis Agents

Therapeutic Class

- **Overview/Summary:** Several biologic response modifiers are Food and Drug Administration (FDA)-approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) including dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®), glatiramer acetate (Copaxone®), interferon β (IFNβ)-1b (Betaseron®, Extavia®), intramuscular (IM) IFNβ-1a (Avonex®), subcutaneous (SC) IFNβ-1a (Rebif®) and teriflunomide (Aubagio®).[1-8] In addition, glatiramer acetate, IFNβ-1b and IM IFNβ-1a are FDA-approved for the treatment of patients experiencing a first clinical episode with magnetic resonance imaging evidence of multiple sclerosis (MS), referred to as a clinically isolated syndrome.[3-7,8] The exact mechanisms of dimethyl fumarate, glatiramer acetate, the IFNβs and teriflunomide have not been fully established; however, they are likely due to their antiproliferative and immunomodulatory effects.[1,3-8] Glatiramer acetate is a polymer containing four amino acids that are found in the myelin basic protein.[3] The IFNβ products are produced by recombinant deoxyribonucleic acid technology in different cell systems, resulting in differences in amino acid sequence, molecular weight and degree of glycosylation.[9] Three orally administered agents are currently available including fingolimod, a first-in-class sphingosine 1-phosphate receptor modulator, dimethyl fumarate and teriflunomide. Fingolimod and teriflunomide are administered once daily, while dimethyl fumarate should be administered twice daily.[1,2,8] Each IFNβ has a different FDA-approved dosing and administration schedule. Avonex® is administered IM once weekly, while Rebif® is administered SC three times weekly and Betaseron® and Extavia® are administered SC every other day.[4-7] MS is a chronic and potentially disabling neurological disease characterized by repeated episodes of inflammation within the nervous tissue of the brain and spinal cord, resulting in injury to the myelin sheaths and subsequently the nerve cell axons.[10] Of the four clinical subtypes of MS (primary progressive, progressive relapsing, RRMS and secondary progressive), RRMS is the most common and is characterized by acute relapses followed by partial or full recovery.[10-12] The most common adverse events associated with IFNβ therapy are influenza-type symptoms, injection site reactions, headache, nausea and musculoskeletal pain. Hepatotoxicity has rarely been reported in patients treated with IFNβ therapy.[4-7] Therapy with IFNβ should be used cautiously in patients with depression or other mood disorders. Patients receiving glatiramer acetate therapy may experience a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction and urticaria.[3] Substantial cardiac monitoring is required when initiating treatment with fingolimod as post-marketing cases of cardiac-related death have been reported. In addition, fingolimod is contraindicated in patients with certain pre-existing cardiovascular conditions.[2] The labeling of teriflunomide contains two black box warnings regarding the risk of hepatotoxicity and teratogenicity.[8] Dimethyl fumarate, although it has limited post-marketing data, appears to have the most mild adverse event profile with flushing and gastrointestinal effects reported most frequently.[1]

Table 1. Current Medications Available in the Therapeutic Class[1-8]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Dimethyl fumarate (Tecfidera®)	Relapsing-remitting multiple sclerosis*	Delayed-release capsule: 120 mg 240 mg	-
Fingolimod (Gilenya®)	Relapsing-remitting multiple sclerosis†	Capsule: 0.5 mg	-
Glatiramer acetate (Copaxone®)	Relapsing-remitting multiple sclerosis‡, treatment of first clinical episode with magnetic resonance imaging features consistent with multiple sclerosis	Prefilled syringe: 20 mg	-
Interferon β-1b	Relapsing-remitting multiple sclerosis§,	Single use vial:	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
(Betaseron®, Extavia®)	treatment of first clinical episode with magnetic resonance imaging features consistent with multiple sclerosis	0.3 mg lyophilized powder	
Interferon β-1a (Rebif®)	Relapsing-remitting multiple sclerosis‖	Prefilled syringe: 8.8 µg 22 µg 44 µg	-
Interferon β-1a (Avonex®, Avonex Administration Pack®)	Relapsing-remitting multiple sclerosis¶, treatment of first clinical episode with magnetic resonance imaging features consistent with multiple sclerosis	Prefilled syringe: 30 µg Single use vial: 30 µg lyophilized powder	-
Teriflunomide (Aubagio®)	Relapsing-remitting multiple sclerosis*	Tablet: 7 mg 14 mg	-

*Treatment of patients with relapsing forms of multiple sclerosis.
†Treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.
‡Reduction of the frequency of relapses in patients with relapsing-remitting multiple sclerosis.
§Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.
‖Treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.
¶ Treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations.

Evidence-based Medicine

- The safety and efficacy of glatiramer acetate and interferon (IFNβ) products are well established. Recent clinical trials have not produced clinically different results compared to trials published previously.
- In two large, randomized trials with dimethyl fumarate 240 mg twice-daily or three times daily compared to placebo, there were statistically significant reductions in the annualized relapse rate (ARR) with both dimethyl fumarate regimens compared to placebo ($P \leq 0.001$ for both).[13,14] Fox et al also included an open-label glatiramer acetate comparator group. In a post-hoc analysis, there were significant improvements favoring dimethyl fumarate over glatiramer acetate with regard to ARR (three times daily group only), new or enlarging T2 hyperintense lesions and new T1 hypointense lesions (three times daily group only).[14]
- In the 24-month, placebo-controlled FREEDOMS trial, treatment with fingolimod 0.5 or 1.25 mg once daily significantly reduced ARR compared to placebo (54 and 60%, respectively; $P<0.001$ for both).[15]
- In the 12-month TRANSFORMS trial, fingolimod 0.5 or 1.25 mg once-daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 µg intramuscularly (IM) once-weekly ($P<0.001$ for both).[16] In a 12-month extension of TRANSFORMS, patients initially randomized to IM IFNβ-1a were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IM IFNβ-1a.[17]
- In the TEMSO trial, treatment with teriflunomide 7 or 14 mg was associated with significantly greater relative reductions in ARR compared to placebo (31.2 and 31.5%. respectively; $P<0.001$).[18] In an unpublished extension study, ARR remained low after five years and the adverse event rates were similar to those reported in previous trials.[19,20]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The American Academy of Neurology and the National Multiple Sclerosis (MS) Society guidelines recommend the use of interferon β (IFNβ) products or glatiramer acetate as first-

line therapy in all patients with clinically definite relapsing-remitting MS (RRMS) and in select patients with clinically isolated syndrome.[21,22]
    - The most appropriate agent may be selected on an individual basis and monitored for clinical response and tolerability.[21]
    - Consensus guidelines have not been updated to address the role of dimethyl fumarate or teriflunomide in the treatment of MS.[21]
    - The National Institute for Clinical Excellence has recommended that due to its adverse event profile, fingolimod be reserved as an option for highly active RRMS in adults, only if patients have an unchanged or increased relapse rate or ongoing severe relapses compared to the previous year despite treatment with IFNβ.[23]
- Other Key Facts:
    - No generic products are currently available.
    - There are no head-to-head trials comparing IFNβ-1b products (Betaseron® and Extavia®) and the drugs are not interchangeable despite Extavia® being approved with the same active ingredient and registration trials as Betaseron®.[4,5]
    - Extavia® comes with a 27-gauge needle, packaged with 15 vials for a 30 day supply, while the Betaseron® has 30-gauge needles, packaged with 14 vials for a 28 day supply.[4,5]

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Therapeutic Class Review
Multiple Sclerosis Agents

Overview/Summary

Several biologic response modifiers are Food and Drug Administration (FDA)-approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) and include dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®), glatiramer acetate (Copaxone®), interferon β (IFNβ)-1b (Betaseron®, Extavia®), intramuscular (IM) IFNβ-1a (Avonex®), subcutaneous (SC) IFNβ-1a (Rebif®) and teriflunomide (Aubagio®).[1-9] In addition, glatiramer acetate, IFNβ-1b and IM IFNβ-1a are FDA-approved for the treatment of patients experiencing a first clinical episode with magnetic resonance imaging (MRI) evidence of multiple sclerosis (MS), often referred to as a clinically isolated syndrome.[3-7,8] Fingolimod, a first-in-class sphingosine 1-phosphate receptor modulator, was approved by the FDA in September 2010, and is the first oral agent indicated for MS.[10] Two more oral agents, teriflunomide and dimethyl fumarate, were approved in September 2012 and March 2013, respectively.[10] The exact mechanisms of action of dimethyl fumarate, teriflunomide, the INFs, and glatiramer acetate are unknown but are likely due to their antiproliferative and immunomodulatory effects.[1,3-8] Glatiramer acetate is a polymer containing four amino acids that are found in the myelin basic protein.[3,11] IFNs are produced by recombinant deoxyribonucleic acid technology in different cell systems, resulting in slight differences in amino acid sequence, molecular weight, degree of glycosylation, and specific activity.[12] Each IFNβ product has a different FDA-approved dosing and administration schedule. IFNβ-1a (Avonex®) 30 µg is administered IM once-weekly, while IFNβ-1a (Rebif®) 22 to 44 µg is administered SC three times weekly and IFNβ-1b (Betaseron®, Extavia®) 250 µg is administered SC every other day.[4-7]

MS is a chronic and potentially disabling neurological disease characterized by repeated episodes of inflammation within the nervous tissue of the brain and spinal cord, resulting in injury to the myelin sheaths and subsequently the nerve cell axons.[11-13] There are four clinical subtypes of MS: RRMS, primary progressive (PPMS), progressive relapsing (PRMS), and secondary progressive (SPMS).[13-15] The most common form is RRMS, characterized by acute relapses followed by partial or full recovery.[14,15] Patients with PPMS have a continuous and gradual decline in function without evidence of acute attacks. Patients with PRMS also have a continuous decline in function while experiencing occasional attacks. Finally, SPMS begins as RRMS, but as time progresses the attack rate declines and patients experience a gradual deterioration.[15]

The approach to treating MS includes the management of symptoms, treatment of acute relapses, and utilization of disease-modifying therapies to reduce the frequency and severity of relapses, and delay disease and disability progression.[11,13,15] The American Academy of Neurology and the National MS Society guidelines recommend the use of IFNβ products or glatiramer acetate as first-line therapy in all patients with clinically definite RRMS and in select patients with clinically isolated syndrome.[15] It is suggested that the most appropriate agent may be selected on an individual basis and monitored for clinical response and tolerability. Consensus guidelines have not been updated to address the role of dimethyl fumarate or teriflunomide in the treatment of MS. The National Institute for Clinical Excellence has recommended that due to its adverse effect profile, fingolimod be reserved as an option for highly active RRMS in adults, only if patients have an unchanged or increased relapse rate, or ongoing severe relapses compared to the previous year despite treatment with IFNβ.[16]

Results from head-to-head studies have found IFNβ products and glatiramer acetate to be comparable in terms of annualized relapse rate (ARR) reduction, and disease and disability progression.[11,13,15,17] Patients treated with fingolimod in clinical trials experienced a reduction in ARR from 40 to 60%, improved MRI outcomes and slowed progression to disability when compared to patients treated with placebo and IM IFNβ-1a, respectively.[13] Both dimethyl fumarate and teriflunomide treatment have shown to also significantly reduce ARR, improve MRI outcomes, and slow progression to disability compared to placebo, but each have limited head-to-head studies with alternative MS treatments.[13] Lower doses of IFNβ products may be more tolerable for some patients, yet they may be associated with a reduced efficacy. The development of neutralizing antibodies to IFNβ (more commonly seen with IFNβ-1b

compared to IFNβ-1a) may lead to decreased efficacy of these agents.[18,19] However, the long-term impact of neutralizing antibodies on clinical outcomes has not been fully determined. Consensus guidelines do not recommend a change of therapy in patients positive for neutralizing antibodies who are responding to IFN therapy, noting that neutralizing antibodies disappear with continued treatment in the majority of patients.[15,17-19] Generally, patients treated with either IFNβ or glatiramer acetate experience a 30% reduction in ARR.[17] However, many patients do not optimally respond to the initial biologic response modifier therapy.[20,21] Clinical data suggests that a change of therapy may be considered in patients experiencing a suboptimal response or intolerable adverse effects. In studies, patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor response, achieved a significant reduction in relapse rate and a delay in disease and disability progression.[20,22,23] The IFNβ products or glatiramer acetate therapy may be considered in patients with progressive forms of the disease, although safety and efficacy have not been established in this patient population.

The most frequently reported adverse events associated with IFNβ therapy are influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain. Rare cases of hepatic toxicity have occurred in patients who were treated with IFN therapy.[4-7] Therapy with IFNβ should be used cautiously in patients with depression or other mood disorders. Patients receiving glatiramer acetate therapy may experience a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria.[3] Glatiramer acetate does not have any known drug interactions, and is not associated with an increased risk of hepatotoxicity or depression.[3] Fingolimod has been associated with post-marketing cases of cardiac-related death and thus requires substantial cardiac monitoring and is contraindicated in patients with certain pre-existing cardiovascular conditions.[2] Teriflunomide has two black box warnings regarding hepatotoxicity and its risk of teratogenicity.[8] Dimethyl fumarate, although it has limited post-marketing data, it appears to have the most mild side effect profile with its most common adverse events being flushing and gastrointestinal effects.[1]

Of note, natalizumab (Tysabri®) and mitoxantrone (Novantrone®) are also FDA-approved for the treatment of RRMS. However, these agents are not recommended for first-line use due to safety concerns with progressive multifocal leukoencephalopathy and cardiotoxicity, respectively.[24,25] Natalizumab is reserved for patients with rapidly advancing disease who have failed other therapies and can only be obtained through a restricted access program.[24]

Medications

Table 1. Medications Included Within Class Review[1-8]

Generic Name (Trade name)	Medication Class	Generic Availability
Dimethyl fumarate (Tecfidera®)	Biological response modifiers	-
Fingolimod (Gilenya®)	Biological response modifiers	-
Glatiramer acetate (Copaxone®)	Biological response modifiers	-
Interferon β-1b (Betaseron®, Extavia®)	Biological response modifiers	-
Interferon β-1a (Rebif®)	Biological response modifiers	-
Interferon β-1a (Avonex®, Avonex Administration Pack®)	Biological response modifiers	-
Teriflunomide (Aubagio®)	Biological response modifiers	-

Indications

Table 2. Food and Drug Administration Approved Indications[1-8]

Generic Name (Trade name)	Relapsing-Remitting Multiple Sclerosis	Treatment of First Clinical Episode with Magnetic Resonance Imaging Features Consistent With Multiple Sclerosis
Dimethyl fumarate (Tecfidera®)	✔ *	-
Fingolimod (Gilenya®)	✔ †	-

Generic Name (Trade name)	Relapsing-Remitting Multiple Sclerosis	Treatment of First Clinical Episode with Magnetic Resonance Imaging Features Consistent With Multiple Sclerosis
Glatiramer acetate (Copaxone®)	✔ ‡	✔
Interferon β-1b (Betaseron®, Extavia®)	✔ §	✔
Interferon β-1a (Rebif®)	✔ ‖	-
Interferon β-1a (Avonex®, Avonex Administration Pack®)	✔ ¶	✔
Teriflunomide (Aubagio®)	✔ *	-

*Treatment of patients with relapsing forms of multiple sclerosis.
†Treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.
‡Reduction of the frequency of relapses in patients with relapsing-remitting multiple sclerosis.
§Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.
‖Treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.
¶ Treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations.

Potential off-label uses of the biologic response modifiers include secondary progressive multiple sclerosis with relapses, and in children with relapsing-remitting multiple sclerosis.[11,13,14]

Pharmacokinetics

Table 3. Pharmacokinetics[1-8,11]

Generic Name (Trade name)	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Dimethyl fumarate (Tecfidera®)	Not reported	Not reported	16	Monomethyl fumarate	1
Fingolimod (Gilenya®)	93	Not reported	81	Fingolimod phosphate	144 to 216
Glatiramer acetate (Copaxone®)	Not reported	Not reported	Not reported	Not reported	Not reported
Interferon β-1b (Betaseron®, Extavia®)	50	50	Not reported	Not reported	0.13 to 4.30
Interferon β-1a (Rebif®)	Not reported	Not reported	Not reported	Not reported	69
Interferon β-1a (Avonex®, Avonex Administration Pack®)	Not reported	Not reported	Not reported	Not reported	10
Teriflunomide (Aubagio®)	Not reported	Not reported	22.6	Not reported	432 to 456

Clinical Trials

Numerous studies of the agents in the management of multiple sclerosis (MS) have been published.[26-87] In the management of MS, several clinical trials have established the safety and efficacy of the biologic response modifiers in reducing the frequency of relapses and delaying disease progression and disability.[17,26-76] Moreover, there is substantial evidence of benefit for using biologic response modifiers in patients with clinically isolated syndrome. In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a clinically definite MS diagnosis by 45% compared to placebo in patients with clinically isolated syndrome (*P*=0.005). In addition, the time for 25% of patients to convert to clinically definite MS was significantly prolonged with glatiramer acetate compared to placebo (722 vs 336 days;

P=0.0041).[77] A meta-analysis of randomized, double-blind, placebo-controlled trials in patients with clinically isolated syndrome found a significantly lower risk of clinically definite MS with interferon (IFN) therapy compared to placebo (*P*<0.0001).[78] The role of the MS biologic response modifiers in the treatment of primary or secondary progressive MS has not been determined, and these agents are not Food and Drug Administration (FDA)-approved for treating these forms of MS. The results of studies with these agents have failed to consistently demonstrate a benefit in progressive forms of MS and due to being off-label uses are not included in Table 4. In the PROMISE trial, glatiramer acetate was no more effective than placebo in delaying the time to accumulated disability for patients with primary progressive MS.[82] Several IFN trials, including a systematic review, in this population have yielded conflicting results.[83,87]

The safety and efficacy of dimethyl fumarate were demonstrated in two large, randomized, controlled trials that compared dimethyl fumarate 240 mg twice daily and three times daily to placebo. Both trials were approximately two years in duration and each found that the twice daily dose significantly reduced the annualized relapse rate (ARR) compared to placebo (*P*≤0.001 for both).[26,50] Fox et al. also included an open label glatiramer acetate comparator group. In a post-hoc analysis, it was found there were significant differences favoring dimethyl fumarate over glatiramer for ARR (dimethyl fumarate three times daily only), new or enlarging T2 hyperintense lesions (both doses of dimethyl fumarate) and new T1 hypointense lesions (dimethyl fumarate three times daily only).[50]

Fingolimod has been evaluated in two large, randomized, controlled trials against placebo and against intramuscular (IM) IFNβ-1a. In FREEDOMS, a 24-month placebo-controlled trial, fingolimod (0.5% and 1.25 mg once-daily) was associated with significant reductions in ARR compared to placebo (54% and 60%, respectively; *P*<0.001 for both).[27] Another subgroup analysis of FREEDOMS found that the significant reductions in ARR were maintained in all groups except in patients older than 40 years of age.[28] Moreover, fingolimod was associated with reductions in disability progression and a prolonged time to first relapse compared to placebo.[27] In the 12-month TRANSFORMS trial, fingolimod 0.5 and 1.25 mg once-daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 µg IM once-weekly (*P*<0.001 for both).[32] In a 12-month extension of TRANSFORMS, patients initially randomized to IM IFNβ-1a were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IM IFNβ-1a. No new fingolimod-associated adverse events were reported in the extension phase, although patients initially treated with IFNβ-1a had fewer IFN-associated adverse events and an increase events associated with fingolimod.[33]

Teriflunomide has been evaluated as monotherapy treatment in one large phase III trial, TEMSO, and an extension study. In TEMSO, the ARR was significantly reduced in both the 7 mg and 14 mg treatment groups compared to placebo (0.37 vs. 0.54, for both treatment arms compared to placebo; *P*<0.001).[45] In the unpublished extension study, ARR remained low after five years and the adverse event rates were similar to those reported in previous trials.[46,47] An unpublished, head-to-head phase III trial compared teriflunomide 7 mg and 14 mg to Rebif®. It was reported that the primary endpoint, time to failure (relapse of MS or permanent discontinuation of study treatment for any reason), was not significantly different between groups. However, the most frequent reason for failure in the teriflunomide groups trended toward relapse, while the most frequent reason for failure in the Rebif® (IFNβ-1a) group trended toward treatment discontinuation.[76]

Head-to-head trials have found glatiramer acetate, subcutaneously (SC) IFNβ-1a, and IFNβ-1b to be comparable in terms of relapse rate reduction and disease and disability progression.[40,41,53,54] The results of several studies suggest that lower IFNβ-1a strengths (30 µg IM once-weekly) may be less efficacious while being more tolerable compared to higher IFN doses (SC three times weekly, or every other day) or glatiramer acetate.[55,56,62,63,66-69] A meta-analysis of six placebo-controlled trials failed to find a significant advantage of IFNβ-1a 30 µg IM once-weekly compared to placebo in the number of relapse-free patients after one year of therapy.[43] In contrast, other studies found IFNβ-1a 30 µg IM once-weekly to be comparable to the other IFN products in terms of relapse rate reduction, disability progression and secondary progressive MS development.[58,64,72-75] Moreover, IFN therapy, especially the higher dose products, are associated with the production of neutralizing antibodies which may result in decreased

radiographic and clinical effectiveness of treatment.[18,19] Exploratory post-hoc analyses of the PRISMS trial linked the development of neutralizing antibodies with reduced efficacy.[84] Development of neutralizing antibodies among patients (N=368) randomized to receive IFNβ-1a 44 or 22 µg SC three times weekly for four years was associated with higher relapse rates (adjusted relapse rate ratio, 1.41; 95% confidence interval [CI], 1.12 to 1.78; *P*=0.004) and a greater number of active lesions and percentage change in T2 lesion burden from baseline on magnetic resonance imaging scan (*P*<0.001).

It is estimated that within a few years of treatment, at least 30% and 15% of patients discontinue MS biological response modifiers due to perceived lack of efficacy or side effects, respectively.[20,21] According to several observational studies, switching patients who have failed to adequately respond on initial treatment, to another first-line therapy is safe and effective.[22,23,58] Patients switching to glatiramer acetate after experiencing inadequate response on IFNβ-1a therapy experienced a reduction in relapse rates and disability progression. Likewise, switching to IFNβ-1a therapy after suboptimal efficacy with glatiramer acetate increased the number of relapse-free patients in one study.[58] The smallest reduction in the annualized relapse rate was seen in patients who had switched from one IFNβ-1a preparation to another.

Despite evidence showing these treatments to be effective in slowing MS progression, and reducing relapses, significant side effects and high costs associated with treatment can be burdensome for patients and payers. Three cost-effectiveness studies evaluating glatiramer acetate and IFN therapy in patients with relapsing-remitting MS have been conducted in the United States. One study found glatiramer acetate to be the most cost-effective biological response modifier for MS, while the remaining two reported that IM IFNβ-1a is the most cost-effective agent, in 10 year disease progression models. Of note, none of the oral multiple sclerosis agents were included in these cost-effectiveness studies.[79-81]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Relapsing-Remitting Multiple Sclerosis				
Gold et al[26] DEFINE Dimethyl fumarate 240 mg BID vs Dimethyl fumarate 240 mg TID vs placebo	DB, MC, PC, RCT Patients aged 18 to 55 years with a diagnosis of RRMS, an EDSS score of 0 to 5, and at least one clinically documented relapse in the previous 12 months or at least one gadolinium-enhancing lesion 0 to 6 weeks before randomization	N=1,237 96 weeks	Primary: Proportion of patients who had a relapse by two years Secondary: ARR, time to progression of disability, number of gadolinium-enhancing lesions and of new or enlarging hyperintense T2 lesions	Primary: Relapses after two years were observed in 27% and 26% of the patients in the twice daily and three times daily dimethyl fumarate groups, respectively, compared to 46% of patients in the placebo group (HR, 0.51; 95% CI: 0.39 to 0.65 and 0.50; 95% CI: 0.39 to 0.65, respectively). Secondary: Time to first relapse was prolonged by 87 and 91 weeks in patients in the twice and three times daily groups, respectively, compared to placebo. Relative to placebo, the ARR was reduced by 53% and 48% in the twice daily and three times daily groups, respectively (*P*=0.001). Additionally, the time to progression of disability was reduced by 38% in the twice daily group (HR, 0.62; 95% CI: 0.44 to 0.87) and by 34% in the three times daily group (HR, 0.66; 95% CI: 0.48 to 0.92. Relative to placebo, the number of new or enlarging hyperintense T2 lesions and the number of gadolinium-enhancing lesions was decreased by 85% and 90%, respectively in patients receiving dimethyl fumarate twice daily and by 74% and 73% in patients receiving dimethyl fumarate three times daily (P<0.001 for all) The most common adverse events in patients receiving dimethyl fumarate were flushing, gastrointestinal events, proteinuria and pruritus.
Kappos et al[27] FREEDOMS Fingolimod 0.5 mg once daily vs fingolimod 1.25 mg once	DB, MC, PC, RCT Patients 18 to 55 years of age with RRMS and an EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past 2 years	N=1,272 24 months	Primary: ARR Secondary: Time to first relapse, proportion of patients relapse free after 24 months, time to confirmed	Primary: The aggregate ARR was lower with fingolimod 0.5 (0.18; 95% CI, 0.15 to 0.22) and 1.25 mg (0.16; 95% CI, 0.13 to 0.19) compared to placebo (0.40; 95% CI, 0.34 to 0.47; *P*<0.001 for both comparisons). This represents a reduction of 54 and 60%, respectively, in the ARR for fingolimod. A subgroup analysis comparing ARRs among treatment naïve patients and those previously treated found significant reductions compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily vs placebo			disability (an increase ≥1 in EDSS) progression confirmed after three and six months, changes in EDSS and MSFC score from baseline to 24 months, number of gadolinium-enhancing lesions, proportion of patients free from gadolinium-enhancing lesions, number of new or enlarged lesions on T2-weighted MRI scans, proportion of patients free from new or enlarged lesions on T2-weighted scans, volumes of hyperintense lesions on T2-weighted scans and hypointense lesions on T1-weighted scans, change in brain volume between baseline and 24 months, safety and tolerability	placebo (*P*<0.01 for all comparisons). Secondary: In the fingolimod groups compared to the placebo group, the time to a first relapse was longer (*P*<0.001 for both comparisons), the risk of relapse was reduced (0.5 mg vs placebo: HR, 0.48; 95% CI, 0.39 to 0.61; *P*<0.001 and 1.25 mg vs placebo: HR, 0.38; 95% CI, 0.30 to 0.48; *P*<0.001) and significantly more patients remained free of relapse during the 24 month period (0.5 mg: 70.4±2.3%; 95% CI, 66.0 to 74.8; *P*<0.001, 1.25 mg: 74.7±2.2%; 95% CI, 70.4 to 2.3; *P*<0.001, placebo: 45.6±2.3%; 95% CI, 40.7 to 50.6). The time to disability progression was longer in patients treated with fingolimod compared to patients treated with placebo. Treatment with fingolimod reduced the risk of disability progression, confirmed after three months, over the 24 month study period (HR, 0.70 for 0.5 mg and HR, 0.68 for 1.25 mg; *P* values not reported). The cumulative probability of disability progression (confirmed after three months) was 17.7% for fingolimod 0.5 mg, 16.6% for fingolimod 1.25 mg and 24.1% for placebo (*P* values not reported). Regarding disability progression that was confirmed after six months, the risk was also reduced with fingolimod over the 24 month study period (HR, 0.63 for 0.5 mg and HR, 0.60 for 1.25 mg; *P* values not reported), and the cumulative probability of progression was 12.5% for fingolimod 0.5 mg, 11.5% for fingolimod 1.25 mg and 19.0% for placebo (*P* values not reported). During the study period, the EDSS and MSFC scores remained stable or improved slightly in the fingolimod groups and worsened in the placebo group (*P*<0.02 for all comparisons). All MRI based secondary endpoints including number and proportion of patients demonstrating gadolinium-enhancing lesions, changes in hypointense and hyperintense lesions on T1- or T2-weighted scans and changes in brain volume favored the fingolimod groups compared to the placebo group (*P*≤0.03 for all comparisons).

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>The rates of adverse events were reported to be similar (93 to 94%) among the three treatment groups. Adverse events that led to treatment discontinuation were more common with fingolimod 1.25 mg (14.2%) compared to fingolimod 0.5 mg (7.5%) and placebo (7.7%).

The most common serious adverse events, each reported for eight patients, were bradycardia, MS relapse and basal-cell carcinoma. The overall incidence of infection was similar in the fingolimod and placebo groups (69 to 72%); serious infections occurred in 1.6 and 2.6% of patients.

Transient, dose-related decreases in heart rate occurred after the first dose of fingolimod was administered. Bradycardia was reported in nine patients receiving 0.5 mg of fingolimod, 14 patients receiving 1.25 mg of fingolimod and three patients receiving placebo.

Macular edema was diagnosed in seven patients, all of whom were receiving 1.25 mg of fingolimod. Three of these events were reported as serious adverse events.

Peripheral-blood lymphocyte counts were reduced from the baseline counts by an average of 73% with 0.5 mg of fingolimod and 76% with 1.25 mg of fingolimod, remaining stable after one month. Increases in ALT to three times the upper limit of normal or more were more frequent in the fingolimod groups (8.5% of patients in the 0.5 mg group and 12.5% of patients in the 1.25 mg group) than in the placebo group (1.7% of patients) and occurred predominantly in men.</td></tr>
<tr><td>Devonshire et al[28]
Subgroup analysis of FREEDOMS

Fingolimod 0.5 mg once daily

vs</td><td>DB, MC, PC, RCT

Patients 18 to 55 years of age with RRMS and an EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past 2 years</td><td>N=1,272

24 months</td><td>Primary:
ARR

Secondary:
Confirmed disability progression</td><td>Primary:
Fingolimod 0.5 mg treatment significantly reduced ARR compared to placebo in all subgroups except for patients older than 40 years of age.

ARR
<table>
<tr><th>Subgroup</th><th>HR, (95% CI)</th></tr>
<tr><td>Sex</td><td></td></tr>
<tr><td>Men</td><td>0.33, (0.22 to 0.50)</td></tr>
<tr><td>Women</td><td>0.50, (0.39 to 0.65)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>placebo

Subgroup analysis based on demographic factors (sex, gender, treatment history), disease characteristics (baseline disability scores, relapse rates, and lesion parameters), and response to previous therapy.</td><td></td><td></td><td></td><td>
<table>
<tr><td colspan="2">Age</td></tr>
<tr><td>>40 years</td><td>0.76, (0.54 to 1.09)</td></tr>
<tr><td>≤40 years</td><td>0.33, (0.25 to 0.43)</td></tr>
<tr><td colspan="2">Treatment history</td></tr>
<tr><td>Previously treated</td><td>0.54, (0.39 to 0.74)</td></tr>
<tr><td>Treatment naïve</td><td>0.36, (0.27 to 0.49)</td></tr>
<tr><td colspan="2">Number of relapses in year before study</td></tr>
<tr><td>>1</td><td>0.37, (0.27 to 0.51)</td></tr>
<tr><td>≤1</td><td>0.52, (0.39 to 0.69)</td></tr>
<tr><td colspan="2">Number of relapses in two years before study</td></tr>
<tr><td>>2</td><td>0.50, (0.34 to 0.72)</td></tr>
<tr><td>2</td><td>0.45, (0.32 to 0.63)</td></tr>
<tr><td>1</td><td>0.37, (0.24 to 0.58)</td></tr>
<tr><td colspan="2">Baseline disability</td></tr>
<tr><td>EDSS >3.5</td><td>0.34, (0.20 to 0.58)</td></tr>
<tr><td>EDSS 0 to 3.5</td><td>0.48, (0.38 to 0.60)</td></tr>
<tr><td colspan="2">Number of gadolinium-enhancing lesions</td></tr>
<tr><td>≥1</td><td>0.40, (0.29 to 0.55)</td></tr>
<tr><td>0</td><td>0.48, (0.36 to 0.65)</td></tr>
<tr><td colspan="2">T2 lesion volume</td></tr>
<tr><td>>3,300 mm</td><td>0.47, (0.36 to 0.63)</td></tr>
<tr><td>≤3,300 mm</td><td>0.40, (0.29 to 0.57)</td></tr>
<tr><td colspan="2">Disease activity in treatment-naïve or previously treated patients</td></tr>
<tr><td>Group A*</td><td>0.29, (0.16 to 0.52)</td></tr>
<tr><td>Group B†</td><td>0.38, (0.24 to 0.62)</td></tr>
<tr><td>Group C‡</td><td>0.38, (0.21 to 0.68)</td></tr>
<tr><td>Group D§</td><td>0.49, (0.31 to 0.78)</td></tr>
<tr><td>Group E‖</td><td>0.33, (0.18 to 0.62)</td></tr>
</table>

Secondary:
Disability progression confirmed after three months
<table>
<tr><th>Subgroup</th><th>HR, (95% CI)</th></tr>
<tr><td colspan="2">Sex</td></tr>
<tr><td>Men</td><td>0.43, (0.22 to 0.81)</td></tr>
</table>
</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results

Women	0.77, (0.53 to 1.10)
Age	
>40 years	0.74, (0.46 to 1.19)
≤40 years	0.68, (0.45 to 1.02)
Treatment history	
Previously treated	0.70, (0.43 to 1.14)
Treatment naïve	0.63, (0.41 to 0.95)
Number of relapses in year before study	
>1	0.62, (0.37 to 1.05)
≤1	0.70, (0.47 to 1.03)
Number of relapses in two years before study	
>2	0.40, (0.21 to 0.77)
2	0.71, (0.44 to 1.13)
1	0.84, (0.46 to 1.52)
Baseline disability	
EDSS >3.5	0.32, (0.14 to 0.73)
EDSS 0 to 3.5	0.77, (0.55 to 1.09)
Number of gadolinium-enhancing lesions	
≥1	0.62, (0.37 to 1.04)
0	0.75, (0.50 to 1.11)
T2 lesion volume	
>3,300 mm	0.59, (0.38 to 0.90)
≤3,300 mm	0.85, (0.53 to 1.36)
Disease activity in treatment-naïve or previously treated patients	
Group A*	0.64, (0.27 to 1.51)
Group B†	0.59, (0.29 to 1.20)
Group C‡	0.68, (0.29 to 1.62)
Group D§	0.54, (0.26 to 1.10)
Group E‖	0.73, (0.25 to 2.07)

*Patients who received interferon beta during the year before study enrollment but who had as many or more relapses in the year immediately before the study than in the two years before the study.
†Patients who received any disease modifying therapy during the year before study enrollment but who had as many or more relapses in the year immediately before the study than in the two years before the study.
‡ Patients who received interferon beta during the year before study enrollment and had at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline. § Patients who received any disease modifying therapy during the year before study enrollment and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or nine T2 lesions at baseline. ‖Treatment-naïve rapidly evolving severe RRMS with at least two relapses within the year before baseline and at least one gadolinium-enhancing lesion at baseline.
Kappos et al[29] Fingolimod 1.25 mg once daily vs fingolimod 5 mg once daily vs placebo Patients who were randomized to placebo for the first six months were randomized to active treatment during the six month ES (placebo/fingolimod group).	DB, ES, MC, PC, RCT Patients 18 to 60 years of age with RRMS, an EDSS score 0 to 6, neurologically stable condition with no evidence of relapse for ≥30 days before screening and ≥2 documented relapses during the previous two years; ≥1 documented relapse in the year before enrollment or ≥1 gadolinium-enhanced lesions detected by MRI at screening	N=281 6 months (followed by a 6 month ES)	Primary: Total number of gadolinium-enhanced lesions/ patient recorded on T1-weighted MRI intervals for six months Secondary: Total number of gadolinium-enhanced lesions per patient, the proportion of patients with gadolinium-enhanced lesions, total number of new lesions per patient on T2-weighted images, changes in lesion volume on T2-weighted images, brain volume from baseline to month six, number of patients remaining free of relapse,	Primary: The total cumulative numbers of lesions per patient on post-baseline, monthly gadolinium-enhanced T1-weighted MRI scans were lower in both fingolimod groups compared to the placebo group (*P*<0.001 for 1.25 mg and *P*=0.006 for 5 mg). Secondary: At 12 months, the number of lesions remained low in the two groups of patients who received continuous treatment with fingolimod, whereas the number decreased significantly in the placebo-to-fingolimod group (*P* value not reported). At six months, the proportion of patients who were free of gadolinium-enhanced lesions was greater in both fingolimod groups than with the placebo group (*P*<0.001 for both comparisons), with a separation between the curves becoming evident after two months of treatment. With the exception of the change in brain volume from baseline, all secondary MRI endpoints differed significantly between the fingolimod groups and the placebo group, in each case favoring treatment with fingolimod. At 12 months, MRI variables consistently demonstrated that fingolimod continued to have a marked effect on inflammatory activity, as reflected by MRI findings. At 12 months, more than 80% of patients who received fingolimod were free of gadolinium-enhanced lesions. The trial was not powered to detect a treatment effect on relapse endpoints; however, in both groups of patients who received continuous fingolimod, 79% were free of relapse at month 12, whereas 65 to 67%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			ARR, time to first relapse, disability scores	were free of relapse in the placebo-to-fingolimod group. Significant improvements over placebo were observed in the fingolimod groups, including a reduction in the ARR (by 53% in the 5 mg group and by 55% in the 1.25 mg group). For the placebo-to-fingolimod group, the ARR was lower during the period of treatment with fingolimod. The relapse rates for patients who received continuous fingolimod remained low during months seven to 12, with overall 12 month relapse rates of 0.31 and 0.29 for the 1.25 and 5 mg dose, respectively. The estimated time to a first relapse was significantly prolonged in the fingolimod groups (*P* value not reported). There were no significant differences in EDSS scores at 12 months between the fingolimod groups and the placebo/fingolimod group (*P*=0.74 for 1.25 mg and *P*=0.64 for 5 mg).
Radue et al[30] Fingolimod 0.5 mg QD vs Fingolimod 1.25 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 55 years of age with RRMS and an EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past 2 years	N=1,272 2 years	Primary: Proportion of patients free from gadolinium-enhancing lesions, proportion of patients free from gadolinium-enhancing T1 lesions or new anti-inflammatory activity, proportion of patients free from new or enlarged T2 lesions, change from baseline in the total volume of T2 lesions or T1 hypointense lesions, change in PBVC	Primary: Both fingolimod 0.5 mg and 1.25 mg significantly decreased the number of new/newly enlarged T2 lesions, the number of gadolinium-enhancing lesions and the volume of gadolinium-enhancing lesions from baseline over 24 months compared to placebo (*P*<0.001 for all). Additionally, the proportion of patients free from new/newly enlarged T2 lesions, gadolinium-enhancing lesions or both was significantly greater in patients receiving fingolimod compared to placebo (*P*<0.001 for all) Change in T2 lesion volume was significantly reduced in each fingolimod group compared to placebo at both 12 and 24 months (*P*<0.001 for all). The actual T2 lesions volume slightly decreased in each fingolimod group, but increased in the placebo group. After 24 months, T1 hypointense lesion volume increased in the placebo group, but remained stable in each fingolimod group (absolute change vs placebo, *P*<0.001 for each). Both fingolimod groups significantly reduced PBVC compared to placebo from months 0 to 6, 0 to 12 and 12 to 24 (*P*<0.05 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	Secondary: Not reported
Saida et al[31] Fingolimod 0.5 mg QD vs Fingolimod 1.25 mg QD vs placebo	PC, PG, RCT Patients aged 18 to 60 years, a diagnosis of MS according to the revised McDonald criteria and a relapsing course of the disease	N=171 6 months	Primary: Percentage of patients free from gadolinium-enhanced lesions at months three and six Secondary: Relapses over six months, safety	Primary: The proportion of patients who were free from gadolinium-enhanced lesions at months three and six was significantly greater in the fingolimod 0.5 mg (70%) and 1.25 mg (86%) groups compared to placebo (40%; *P*<0.004 and *P*<0.001, respectively). Secondary: The proportion of patients who were relapse free in the fingolimod 0.5 mg and 1.25 mg groups was 78.9% and 83.3%, respectively, compared to 64.9% in the placebo group (OR, 1.94; 95% CI: 0.82 to 4.63 and OR, 2.49; 95% CI: 0.99 to 6.29, respectively). An adverse event was reported in 91.2% and 94.4% of patients receiving fingolimod 0.5 mg and 1.25 mg, respectively, compared to 78.9% of patients receiving placebo (No *P* values reported). Additionally, a serious adverse event was reported in 8.8% and 20.4% of patients receiving fingolimod 0.5 mg and 1.25 mg, respectively, compared to 5.3% of patients receiving placebo (No *P* values reported). Adverse events related to fingolimod included transient bradycardia and atrioventricular block at treatment initiation and elevated liver enzymes.
Cohen et al[32] TRANSFORMS Fingolimod 0.5 mg once daily vs fingolimod 1.25 mg once daily vs	DB, DD, MC, PG, RCT Patients 18 to 55 years of age with RRMS, EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past two years	N=1,292 12 months	Primary: ARR Secondary: The number of new or enlarged hyperintense lesions on T2-weighted MRI scans at 12 months, time to confirmed disability progression and adverse events	Primary: There were significantly greater reductions in ARR for both fingolimod groups compared to the IFNβ-1a group (fingolimod 1.25 mg: ARR, 0.20; 95% CI, 0.16 to 0.26; *P*<0.001, fingolimod 0.5 mg: ARR, 0.16; 95% CI, 0.12 to 0.21; *P*<0.001, IFNβ-1a: ARR, 0.33; 95% CI, 0.26 to 0.42). There was no significant difference in the magnitude of the treatment effect between patients who had previously undergone disease treatment and those who had not. Secondary: Patients in the two fingolimod groups had significantly fewer new or enlarged hyperintense lesions on T2-weighted images at 12 months

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IFNβ-1a (Avonex®) 30 µg IM once-weekly Previous or recent therapy with any type of IFNβ or GA was not a criterion for exclusion.				compared to those in the IFN group (fingolimod 1.25 mg: 1.5±2.7; *P*<0.001, fingolimod 0.5 mg: 1.7±3.9; *P*=0.004 and IFNβ-1a: 2.6±5.8). Confirmed disability progression was infrequent in all the treatment groups. There were no significant differences in the time to the progression of disability or in the proportion of patients with confirmed progression among the treatment groups (*P* values not reported). Adverse events were reported in similar proportions of patients in the three treatment groups, ranging from 86 to 92%. Serious adverse events and those leading to the discontinuation of a study drug were most frequent in patients assigned to fingolimod 1.25 mg. The most common adverse events observed were bradycardia and atrioventricular block. The overall incidence of infection was similar across the treatment groups (ranging from 51 to 53%). Increases in mean arterial pressure occurred in both fingolimod groups (3 mm Hg in the 1.25 mg group and 2 mm Hg in the 0.5 mg group) during the first six months and remained stable between six and 12 months. Macular edema was confirmed in six patients receiving fingolimod; four patients in the 1.25 mg group (1%) and two patients in the 0.5 mg group (0.5%). A mild reduction (2 to 3%) in the mean forced respiratory volume in one second was observed in both fingolimod groups at one month, with no further reductions for the remainder of treatment.
Khatri et al[33] TRANSFORMS Fingolimod 0.5 mg once daily vs	DB, DD, ES, MC, PG, RCT A 12-month extension of TRANSFORMS; patients 18 to 55 years of age with	N=1,027 12 months	Primary: ARR Secondary: The number of new or enlarged hyperintense lesions	Primary: Patients initially randomized to fingolimod 0.5 or 1.25 mg in the core study continued to experience reductions in ARR throughout the extension study (months 13 to 24). The estimated ARR for patients receiving fingolimod 0.5 mg was not different between the core study and 12 month extension period (0.12 vs 0.11, respectively; *P*=0.80). Similarly, there was no difference in the ARR for patients continuing the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fingolimod 1.25 mg once daily Patients initially randomized to either fingolimod dose in the core study continued treatment throughout the extension period. Patients initially randomized IFNβ-1a 30 µg IM once-weekly were randomly reassigned (1:1) to receive fingolimod 0.5 or 1.25 mg daily for the duration of the extension period.	RRMS, EDSS score 0 to 5.5 and ≥1 relapse in the past year or ≥2 relapses in the past two years; all patients must have completed the core study on assigned treatments		on T2-weighted MRI scans at 12 months, time to confirmed disability progression, adverse events	1.25 mg dose through month 24 compared to the core study (0.15 vs 0.11 for, respectively; *P*=0.12). Patients switched from IFNβ-1a to either fingolimod dose in the extension period experienced greater reductions in ARR compared to initial treatment with IFNβ-1a. Patients switched to fingolimod 0.5 mg experience a lower ARR in the extension period compared to treatment with IFNβ-1a during the core trial (0.22 vs 0.31; *P*=0.049). Patients switched from IFNβ-1a to fingolimod 1.25 mg had lower ARR in the extension period with fingolimod treatment compared to treatment with IFNβ-1a in the core trial (0.18 vs 0.29; *P*=0.024). Switching from IFNβ-1a to fingolimod 0.5 mg was associated with a 30% reduction in relapse rates (ARR, 0.70; 95% CI, 0.49 to 1.00), while patients switched to the 1.25 mg dose experienced a 36% reduction in relapses (ARR, 0.64; 95% CI, 0.43 to 0.94). Secondary: Patients in the fingolimod 1.25 mg continuous treatment group had significantly fewer (mean) new or enlarged hyperintense lesions on T2-weighted images at 24 months compared to the end of the core study (1.0±2.3 vs 1.4±2.37; *P*=0.0003). Significant reductions in new or enlarged lesions were also observed in patients treated with the 0.5 mg dose at 24 months compared to month 12 (0.9±1.87 vs 1.6±3.60; *P*=0.0001). Patients switched from IFNβ-1a to either fingolimod dose for the extension period experienced significant reductions in new or enhanced T2 lesions at 24 months compared to initial treatment with IFNβ-1a in the core study (1.0 vs 2.4 and 0.7 vs 2.1 for the 1.25 and 0.5 mg doses, respectively; *P*<0.0001 for both comparisons). There were no significant changes in EDSS scores in the extension period compared to the core study for any of the treatments. Patients switched from IFNβ-1a to fingolimod experienced fewer adverse events compared to treatment with IFNβ-1a in the core study (86 vs 91% and 91 vs 94% for the 0.5 and 1.25 mg groups, respectively;

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>*P* values not reported). Fewer patients continuing fingolimod from the core study reported adverse events in the extension period compared to the core study. (72 vs 86% and 71 vs 90% for the 0.5 and 1.25 mg doses, respectively; *P* values not reported).

There was a rise in serious cardiac-related adverse events after switching to fingolimod 1.25 mg (from 0% with IFNβ-1a to 2% with fingolimod) but not with the 0.5 mg dose (1% for both time periods).</td></tr>
<tr><td>Meca-Lallana et al[34]

GA

Patients must have switched from treatment with IFNβ and been on GA for at least 24 weeks.</td><td>MC, OS

Patients aged 18 to 60 years with a diagnosis of RRMS, a score of ≤5.5 on the Kurtzke EDSS and confirmed spasticity</td><td>N=68

6 months</td><td>Primary:
Changes on the PSFS, MAS, ATRS and GPS after three and six months

Secondary:
Change in disability, number of relapses, working days' leave, adverse events</td><td>Primary:
Significant reductions from baseline in mean scores on all spasticity measurement scales were observed after three and six months.

<table><tr><th>Scale</th><th>Baseline</th><th>Three Months</th><th>*P* Value (Three Months)</th><th>Six Months</th><th>*P* Value (Six Months)</th></tr><tr><td>PSFS</td><td>1.7</td><td>1.4</td><td><0.01</td><td>1.3</td><td><0.01</td></tr><tr><td>MAS</td><td>0.7</td><td>0.6</td><td><0.01</td><td>0.5</td><td><0.01</td></tr><tr><td>ATRS</td><td>1.6</td><td>1.4</td><td><0.01</td><td>1.3</td><td><0.01</td></tr><tr><td>GPS</td><td>29.4</td><td>24.7</td><td><0.01</td><td>19.1</td><td><0.01</td></tr></table>
Secondary:
EDSS scores were significantly decreased after three months but not after six months (*P*<0.05 and *P*=0.385, respectively). A relapse was observed in 10.3% of patients over six months.

After three months, 19.1% of patients reported missing work and after SIX months, 13.2% more patients reported missing work. The mean number of working days' leave used was 15.4 and 26.5 days, at three and six months, respectively.

At least one adverse event was reported in five (7.4%) of patients, however only one was considered possibly related to GA.</td></tr>
<tr><td>Ford et al[35]

GA 20 mg SC daily</td><td>ES, OL, PRO

Patients with RRMS</td><td>N=100

180 months</td><td>Primary:
Change from baseline in ARR,</td><td>Primary:
The cohort of patients continuing to receive GA for 15 year had a lower ARR compared to their baseline values (0.25±0.34 vs 1.12±0.82; *P*</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	who had experienced ≥2 medically documented relapses in the previous two years and had EDSS scores 0 to 5 at study entry		change in EDSS scores, yearly EDSS scores Secondary: Not reported	value not reported). These results appear to be lower compared to reductions in AAR for patients completing the original study but who did not remain on treatment for 15 years (0.43±0.58 vs 1.18±0.82; *P* value not reported), although the significance the lowered relapse rate in these patients is unknown. Of patients who withdrew from the original study, the ARR associated with GA treatment was 0.56±0.68 compared to baseline relapse rates of 1.23±0.83 (*P* value not reported). The cohort of patients continuing GA treatment for 15 years had a slower progression in EDSS scores compared to the modified ITT population of patients completing the original study, and the population of patients who withdrew from the original study (0.6±2.0 vs 0.9±1.8 and 1.0±1.7 points, respectively; *P* value not reported). Moreover, the average yearly change in EDSS was smaller with the cohort of patients continuing GA treatment for 15 years compared to the original modified ITT population completing the original study, and the population of patients who withdrew from the original study (0.1±0.2 vs 0.2±0.6 and 0.5±0.8, respectively; *P* value not reported) Secondary: Not reported
Boneschi et al[36] GA 20 mg SC daily vs placebo	MA DB, PC, RCTs of patients 18 to 50 years of age with RRMS for at least one year with ≥1 relapse in the previous two years	N=540 (3 studies) Up to 35 months	Primary: ARR Secondary: Total number of relapses, time to first relapse and disability progression	Primary: Treatment with GA was associated with a statistically significant 28% reduction in the ARR compared to treatment with placebo (0.82 vs 1.14; *P*=0.004). Secondary: Treatment with GA was associated with a statistically significant 36% reduction in the total number of relapses compared to treatment with placebo (*P*<0.0001). Treatment with GA was associated with a statistically significant 32% delay in the time to first relapse compared to treatment with placebo (322 vs 219 days; *P*=0.01).

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				Treatment with GA was associated with a beneficial effect on disability progression compared to treatment with placebo (RR, 0.6; 95% CI, 0.4 to 0.9; *P*=0.02).
Caon et al[22] GA 20 mg SC daily Administered for up to 42 months to patients who had previously received IFNβ-1a 30 µg IM once-weekly therapy for up to 24 months.	OL, PRO Patients 18 years of age or older with RRMS	N=85 Up to 24 months	Primary: ARR Secondary: Change in EDSS	Primary: Switching to GA was associated with a statistically significant 57% reduction in the ARR from 1.23 to 0.53 (*P*=0.0001). In a subgroup of patients who switched to GA due to lack of efficacy with IFNβ-1a, the ARR was reduced from 1.32 to 0.52 (61%; *P*=0.0001). There was no statistically significant reduction in the ARR among patients who switched from IFNβ-1a to GA due to adverse effects (*P*=NS). Secondary: After 37.5 months of GA there was a statistically significant improvement in mean EDSS scores (*P*=0.0001).
Zwibel et al[23] GA 20 mg SC daily administered to treatment naive patients vs GA 20 mg SC daily administered to patients who had previously received IFNβ-1b therapy	MC, OL, PRO Patients 18 years of age or older with RRMS and an EDSS disability score ≤6	N=805 3.5 years	Primary: ARR, proportion of relapse-free patients, time to first relapse, progression of neurological disability (measured by change in EDSS score from baseline) and proportion of patients with sustained progression (≥1 EDSS point increase for six months) Secondary: Not reported	Primary: There was no significant difference between the prior IFNβ-1b and treatment-naïve groups in the reduction of ARR from two years before study entry (75% in both groups; *P*=0.148). No significant difference was reported between the prior IFNβ-1b and treatment-naïve groups in the proportion of relapse-free patients throughout the study (68.4 vs 69.5%; *P*>0.90). There were no differences in the estimated time to first relapse for 25% of patients in the prior IFNβ-1b and treatment-naïve groups (245 vs 328 days, respectively; *P*=0.28). Patients with a prior history of IFNβ-1b therapy exhibited a higher rate of neurological disability progression at 12 and 18-months and last observation compared to treatment-naïve patients (*P*=0.0070, *P*=0.0155 and *P*=0.0018, respectively). There were no significant differences between the study groups in

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				regards to the proportion of patients with sustained progression (*P*=0.209). Secondary: Not reported
Miller et al[37] GA 20 mg SC daily	OL, PRO Patients with RRMS	N=46 Up to 22 years	Primary: ARR, percentage of relapse-free patients, change in EDSS and adverse events Secondary: Not reported	Primary: Throughout the course of the study patients experienced a statistically significant reduction in the ARR from 2.9 to 0.1 at last observation (*P*<0.0001). Of patients who continued therapy through the end of the study 72% were free of relapses (*P* value not reported). There were no significant changes in the mean EDSS scores from baseline (*P*=0.076) with the majority (67%) of continuing patients exhibiting improved or stable EDSS scores. The most commonly reported adverse events were injection site reactions. Six patients who received GA for up to 22 years reported lipoatrophy. Skin necrosis was not observed. A discontinuation rate of 61% was observed. The most common reason for discontinuing the study was withdrawal of consent. Secondary: Not reported
La Mantia et al[38] GA 20 mg SC daily vs placebo	MA RCTs comparing GA and placebo in patients of any age or gender with definite MS of any severity according to Poser criteria	N=1,458 (540 with RRMS) Up to 35 months	Primary: Patient disease progression (defined as worsening of at least one point in EDSS for six months), mean changes in EDSS score, frequency of clinical relapses, patients who	Primary: Treatment with GA did not significantly reduce the risk of disease progression at two years (RR, 0.75; 95% CI, 0.51 to 1.12; *P*=0.16) or at 35 months (RR, 0.81; 95% CI, 0.50 to 1.29; *P*=0.37). Patients randomized to receive GA experienced small yet significant decreases in EDSS scores at two years (WMD, -0.33; 95% CI, -0.58 to -0.08; *P*=0.009) and at 35 months (WMD, -0.45; 95% CI, -0.77 to -0.13; *P*=0.006). Compared to placebo, there was a significant reduction in the frequency

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			remained relapse-free, frequency of adverse events and quality of life Secondary: Number of patients requiring steroid courses, hospital admissions and length of stay	of clinical relapses reported with GA use at one year (-0.35; *P*=0.0002), at two years (-0.51; *P*=0.0006) and at 35 months (-0.64; *P*=0.002). Patients randomized to receive GA were more likely to remain relapse-free after one year of treatment compared to patients randomized to receive placebo (RR, 1.28; 95% CI, 1.02 to 1.62; *P*=0.03). The risk of being relapse-free after two years and 35 months continued to be higher in the GA treatment group, although the difference was not statistically significant (RR, 1.39; 95% CI, 0.99 to 1.94; *P*=0.06 and RR, 1.33; 95% CI, 0.86 to 2.06; *P*=0.19, at two years and 35 months, respectively). Injection-site reactions including itching, swelling, redness and pain occurred more frequently with GA compared to placebo (*P*<0.05 for all comparisons). Secondary: There was a significantly lower risk of requiring steroids in patients treated with GA compared to patients treated with placebo over nine months (RR, 0.65; 95% CI, 0.52 to 0.82; *P*=0.0002), although only one study evaluated this outcome. Data from hospital admission rates showed that patients receiving GA experienced fewer hospitalization by the end of follow-up compared to patients who were treated with placebo (RR, 0.54; 95% CI, 0.31 to 0.93; *P*=0.02).
Khan O et al[85] GALA GA 40 mg SC three times weekly vs placebo	DB, MC, PC, PG, Phase III, RCT Patients 18 to 55 years of age with RRMS with at least 1 documented relapse in the 12 months before screening, or at least 2 documented relapses in the 24	N=1,404 12 months	Primary: Total number of confirmed relapses during the 12-month PC phase Secondary: Cumulative number of new/newly enlarging T2 lesions as months 6 and 12,	Primary: GA group had a 34% reduction in the risk of relapse compared to placebo group (mean ARR, 0.331 vs 0.505; RR, 0.656; 95% CI, 0.539 to 0.799; *P*<0.0001). Secondary: The time to first confirmed relapse was significantly longer in the GA group compared to placebo group (393 days vs 377 days; HR, 0.606; 95% CI, 0.493 to 0.744; *P*<0.0001). GA group (77.0%) compared to placebo group (65.5%) had a greater

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	months before screening, and an EDSS score ≤5.5 with relapse-free for ≥30 days		cumulative number of Gd-enhancing lesions on T1-WI taken at months 6 and 12, brain atrophy defined as the percentage brain volume change from baseline to month 12, time to the first confirmed relapse, proportion of relapse-free patients, total number of severe confirmed relapses defined as those requiring hospitalizations or intravenous steroids	proportion of relapse-free patients (OR, 1.928; 95% CI, 1.491 to 2.494; *P*<0.0001). GA group was associated with 35% reduction in annualized rate of severe relapse (0.301 vs 0.466; RR, 0.644; 95% CI, 0.526 to 0.790; *P*<0.0001). Patients in the GA group experienced 45% reduction in the cumulative number of Gd-enhancing T1 lesions compared to placebo (RR, 0.552; 95% CI, 0.436 to 0.699; *P*<0.0001) and 35% reduction in the cumulative number of new or newly enlarging T2 lesions (RR, 0.653; 95% CI, 0.546 to 0.780; *P*<0.0001) at months 6 and 12. The percentage change in normalized brain volume at month 12 from baseline was similar between treatment arms (20.706 with GA group vs 20.645 with placebo group; *P*=0.2058). The most common adverse reactions were injection-site reactions with 35.2% in the GA group vs 5.0% in the placebo group with 99.9% reactions being mild or moderate in severity. The most common injection-site reactions with an incidence of >5% in the GA group were erythema (20.9%), injection site pain (10.4%) and pruritis (5.9%). Total number of severe confirmed relapses defined as those requiring hospitalizations or intravenous steroids results were not noted.
Carmona et al[39] IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs no treatment	OL, PRO Patients with clinically definite RRMS and a history of ≥2 relapses in the previous two years	N=159 Up to 5 years	Primary: Percentage of relapse-free patients, ARR, time to first relapse, disability progression (assessed by change in EDSS scores) and time to progression	Primary: The percentage of patients treated with IFNβ-1b who were relapse-free at the end of follow-up was 21.7% (*P* value not reported). At two years of follow-up, 32.5% of patients in the IFNβ-1b group were relapse-free compared to 22.7% of patients in the control group (*P*=NS). The mean ARR in the IFNβ-1b group was 0.70 relapses per year (*P* value not reported). The mean ARR at two year follow-up in the IFNβ-1b group was 0.74 compared to 2.20 in the control group (*P*=0.001). The median time to first relapse in the IFNβ-1b group was 375 days

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			Secondary: Not reported	compared to 313 days in the control group (*P*=0.26). The mean number of relapses after two years of treatment decreased by 47% (from 3.2 at baseline to 1.7; *P* value not reported). At 59 months of follow-up, 25% of IFNβ-1b treated patients progressed by one point on the EDSS from baseline (*P* value not reported). The mean time that it took for the IFNβ-1b treated patients to progress by one point on the EDSS was longer compared to the control group (72.94 vs 36.94 months; *P*=0.002). Higher EDSS scores were observed at the end of follow-up among patients who had experienced a relapse during the first 12 months of treatment compared to those patients who did not have a relapse (3.37 vs 2.36; *P*=0.003). At the end of follow-up, 70% of patients remained on IFNβ-1b therapy with sustained efficacy and good tolerance. Secondary: Not reported
PRISMS study group[40] IFNβ-1a (Rebif®) 22 µg SC three times weekly vs IFNβ-1a (Rebif®) 44 µg SC three times weekly vs placebo	DB, I, MC, PC, RCT Adult patients, median age 34.9 years, with RRMS and EDSS scores 0 to 5 and ≥2 relapses in the preceding two years	N=560 2 years	Primary: Mean number of relapses Secondary: Relapse rate, percentage of patients relapse-free at one and two years, mean number of moderate to severe relapses, mean number of hospital admissions, mean change in EDSS, median time	Primary: Patients randomized to IFNβ-1a 22 and 44 µg groups experienced significantly fewer mean number of relapses compared to patients receiving placebo at two years of therapy (1.82 and 1.73 vs 2.56, respectively; *P*<0.005). Secondary: Compared to the placebo group, the relapse rate was reduced by 29% in the IFNβ-1a 22 µg group and 32% in the IFNβ-1a 44 µg group (*P* value not reported). At one year, a significantly greater percentage of patients in the IFNβ-1a 22 and 44 µg groups were relapse-free compared to those receiving placebo (37 and 45 vs 22%, respectively; *P*<0.005). At two years, a significantly greater percentage of patients in the IFNβ-

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			to first relapse, time to sustained progression, burden of disease and adverse events	1a 22 µg (27 vs 16%; *P*≤0.05) and IFNβ-1a 44 µg (32 vs 16%; *P*<0.005) groups were relapse-free compared to those receiving placebo. The mean number of moderate to severe relapses was significantly lower in the IFNβ-1a 22 and 44 µg groups compared to the placebo group (0.71 and 0.62 vs 0.99; *P*<0.005). The mean number of hospital admissions was significantly lower in the IFNβ-1a 44 µg group compared to patients receiving placebo (0.25 vs 0.48, respectively; *P*<0.005). The mean change in EDSS was significantly smaller in the IFNβ-1a 22 and 44 µg groups compared to patients receiving placebo (0.23 and 0.24 vs 0.48, respectively; *P*≤0.05). The median time to first relapse was delayed by three and five months in the IFNβ-1a 22 and 44 µg groups, respectively (*P* value not reported). The time to sustained progression was significantly longer in both the IFNβ-1a 22 and 44 µg groups compared to the placebo group (*P*<0.05). The burden of disease was significantly increased in the placebo group compared to the IFNβ-1a 22 and 44 µg groups (10.9 vs -1.2 and -3.8%, respectively; *P*<0.0001 for both compared to placebo). The following adverse events occurred more frequency with IFNβ-1a treatment compared to placebo: injection-site reactions, lymphopenia, increased ALT, leukopenia and granulocytopenia (*P*≤0.05).
Kappos et al[41] PRISMS IFNβ-1a (Rebif®) 22 µg SC three times weekly vs	DB, ES, I, PC, RCT This was a PRISMS extension study; patients with RRMS and EDSS scores 0 to 5 and ≥2 relapses within two years prior	N=382 Up to 8 years	Primary: Mean change in EDSS scores, progression to SPMS, ARR, percentage of relapse-free patients, annualized	Primary: Among patients returning for follow-up after eight years of therapy, mean EDSS scores increased by 1.1 points. Approximately 31.3% of patients progressed by two EDSS points. The longest time to reach disability progression was observed among patients initially randomized to IFNβ-1a 44 µg (2.3 vs 1.0 year for the late treatment group). Progression to SPMS occurred in 19.7% of patients. The time to

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IFNβ-1a (Rebif®) 44 µg SC three times weekly vs placebo for initial two years, followed by IFNβ-1a 22 or 44 µg (Rebif®) SC three times a week for additional six years (later treatment group)	to study onset		change in T2 burden of disease, change in brain parenchymal volume, adverse events and antibody development Secondary: Not reported	developing SPMS was 5.3 years. The ARR was lower in the IFNβ-1a 44 µg (0.60 vs 0.78; *P*=0.014) and IFNβ-1a 22 µg (0.63 vs 0.78; *P*<0.001) treatment groups compared to patients in the late treatment group. The greatest percentage of patients remaining relapse-free at follow-up were those receiving IFNβ-1a 44 µg (15.4%) compared to patients in the IFNβ-1a 22 µg (8.1%) and late treatment groups (6.5%; *P* value not reported). Compared to the late treatment group, patients initially randomized to IFNβ-1a 44 µg therapy had a lower increase in T2 burden of disease (5.0 vs 24.5%; *P*=0.002). At two years of follow-up, patients receiving placebo experienced a greater median annualized increase in T2 burden of disease compared to the IFNβ-1a 22 and 44 µg groups (6.5 vs -0.7 and -2.8%, respectively; *P* value not reported). At eight-year follow-up, all treatment groups experienced a median relative reduction in brain parenchymal volume of 3.9% from baseline (*P* value not reported). At eight-year follow-up, the most frequently reported adverse events were injection-site disorders, reported by 44% of patients. Flu-like symptoms occurred in 11.7% of patients. Elevated ALT was the most common liver abnormality, affecting approximately 8.4% of patients on IFNβ-1a therapy. Lymphopenia and leukopenia were reported by 19.6 and 14.0% of patients receiving IFNβ-1a therapy, respectively. Of patients who developed antibodies, 90% did so during the first two years of therapy. Of patients returning for follow-up after eight years of therapy 72% remained on SC IFNβ-1a.

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				Secondary: Not reported
Rice et al[42] IFNα-2a (Roferon-A®) 9 MIU IM every other day vs IFNβ-1a (Avonex®) 6 to 12 MIU IM once-weekly vs IFNβ-1a (Rebif®) 6 to 12 MIU SC three times weekly vs IFNβ-1b (Betaseron®) 0.6 to 8 MIU SC every other day vs placebo	MA DB, PC, RCTs of patients with RRMS who were treated with recombinant IFN, given by the SC or the IM route	N=1,301 (8 studies) Up to 24 months	Primary: Exacerbation rate during treatment and follow-up, percent of patients who progressed during treatment, mean change in EDSS score and the percent of patients unable to walk without aid at the end of treatment (EDSS >5.5) Secondary: Time to first exacerbation, time to progression in disability, percent of patients requiring steroid administration during IFN treatment and follow-up, hospitalizations during treatment and follow-up, number of patients reporting adverse events, mean change of total lesion load on T2	Primary: Patients treated with IFN therapy were significantly less likely to experience an exacerbation during the first year of treatment compared to patients receiving placebo (pooled RR, 0.73; 95% CI, 0.55 to 0.97; *P*=0.03). During the first two years, IFN treatment was associated with lower rates of exacerbations compared to placebo (55 vs 69%; RR, 0.80; 95% CI, 0.73 to 0.88; *P*<0.001). The type of IFN administered or route of administration did not appear to affect the number of patients experiencing exacerbations. Disease progression, defined as ≥1 EDSS point increase for three to six months, occurred in 20% of the patients receiving IFN treatment compared to 29% of patients receiving placebo over two years (RR, 0.69; 95%CI, 0.55 to 0.87; *P*=0.002). Patients treated with IFN experienced a small but significant decrease in EDSS score relative to patients treated with placebo (WMD, -0.25; 95% CI, -0.05 to -0.46; *P*=0.01). Notably, this outcome was only reported in two studies. No data was available for the number of patients who were unable to walk without aid. Secondary: The frequency of steroid administration over the first year of treatment was only reported in two studies. Result from one study found a non-significant reduction in steroid requirements between IFN treatment and placebo, while the second study reported no difference between treatments. One study evaluated steroid requirements over two years and concluded that patients treated with IFN were less likely to require steroid administration compared to patients treated with placebo (RR, 0.70; 95% CI, 0.56 to 0.87; *P*=0.001).

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			weighted images, and the number of patients continuing to show gadolinium-enhancing lesions during treatment and follow-up	There was no reduction in the frequency of hospitalization between participants treated with IFN and those treated with placebo (RR, 0.44; 95% CI, 0.08 to 2.36; *P*=0.30). Flu-like symptoms, injection site reactions, development of psychiatric disorders, leukopenia, lymphopenia and elevated liver enzymes were all reported more frequently in IFN groups compared to the placebo group (*P*<0.05 for all). The evolution in MRI technology in the decade in which these studies were conducted and varied data reporting in the studies made it impossible to perform a quantitative analysis of the MRI results. A reduction in gadolinium enhancing lesions was apparent after one year of treatment in two studies, but the benefit was not apparent at two years. No data were available for the time to first exacerbation or time to progression in disability.
Freedman et al[43] GA 20 mg SC weekly vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 to 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	MA DB, MC, PC, RCTs with a sample size >30 patients, that included patients at least 18 years of age diagnosed with a clinically-definite RRMS	N=2,351 (6 studies) Up to 2 years	Primary: The proportion of patients relapse-free at one year, proportion of patients relapse-free at two years, proportion of patients progression-free at two years, proportion of patients free of gadolinium-enhancing lesions at one year Secondary: Not reported	Primary: Compared to placebo, a significantly greater proportion of patients receiving IFNβ-1a 22 to 44 µg SC (AAR, 0.23; 95% CI, 0.14 to 0.33; *P* value not reported) and natalizumab were relapse-free at one year (AAR, 0.23; 95% CI, 0.17 to 0.30; *P* value not reported). The proportion of patients receiving IFNβ-1a 30 µg IM or GA that were relapse-free at one year of therapy was not statistically different from those receiving placebo (*P* value not reported). Compared to placebo, a significantly greater proportion of patients receiving IFNβ-1a 22 to 44 µg SC (AAR, 0.17; 95% CI, 0.09 to 0.26; *P* value not reported), IFNβ-1b (AAR, 0.14; 95% CI, 0.04 to 0.25; *P* value not reported), and natalizumab were relapse-free at two years (AAR, 0.26; 95% CI, 0.20 to 0.33; *P* value not reported). The proportion of patients receiving GA who were relapse-free at two years of therapy was not statistically different from those receiving placebo (*P* value not reported). Compared to placebo, a significantly greater proportion of patients were progression-free at two years among patients receiving IFNβ-1a 22 to 44

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vs natalizumab 300 mg IV infusion every four weeks vs placebo				µg SC (AAR, 0.11; 95% CI, 0.01 to 0.20; *P* value not reported), IFNβ-1a 30 µg IM (AAR, 0.13; 95% CI, 0.03 to 0.23; *P* value not reported) and natalizumab (AAR, 0.12; 95% CI, 0.06 to 0.18; *P* value not reported). The proportion of patients progression-free at two years among patients receiving IFNβ-1b or GA was not statistically different from those receiving placebo (*P* value not reported). Compared to placebo, a significantly greater proportion of patients were free of gadolinium-enhancing lesions at one year among patients receiving IFNβ-1a 22 to 44 µg SC (AAR, 0.31; 95% CI, 0.17 to 0.44; *P* value not reported), IFNβ-1a 30 µg IM (AAR, 0.12; 95% CI, 0.01 to 0.24; *P* value not reported) and natalizumab (AAR, 0.28; 95% CI, 0.23 to 0.33; *P* value not reported). The proportion of patients free of gadolinium-enhancing lesions at one year among patients receiving GA was not statistically different from patients receiving placebo (*P* value not reported). Secondary: Not reported
Coppola et al[44] IFNβ-1a (Avonex®) 30 µg IM once-weekly	OS, PRO Patients with a clinically definite or laboratory-confirmed MS	N=255 Mean of 31.7 months	Primary: Percentage of patients progression-free, percentage of patients relapse-free, relapse rate, change in EDSS scores and estimated time to disability progression Secondary: Not reported	Primary: At three years of therapy, 58% of patients remained progression-free, and 39.6% of patients remained relapse-free (*P* values not reported). At three years of therapy, 88% of patients had an improved relapse rate compared to baseline (*P* value not reported). After three years of therapy, mean EDSS scores increased by 0.4 points from baseline (*P* value not reported). The estimated median time to disability progression among patients receiving IFNβ-1a therapy was 4.5 years (*P* value not reported). Within the three-year follow-up period, 31% of patients discontinued the study. Reasons for discontinuation were disease activity (66%), voluntary decision (23%) and adverse events (11%). Secondary:

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				Not reported
O'Connor et al[45] TEMSO Teriflunomide 7 mg QD vs teriflunomide 14 mg QD vs placebo	DB, MC, PC, PG, RCT Patients aged 18 to 55 years who met McDonald criteria for MS diagnosis and had relapsing clinical course with or without progression, EDSS score ≤5.5 and 1 relapse in previous year or 2 relapses in previous 2 years	N=1,088 108 weeks	Primary: ARR Secondary: Disability progression, change in total MRI lesion volume from baseline	Primary: ARR was significantly reduced in both teriflunomide 7 mg (0.37; CI, 0.32 to 0.43) and 14 mg groups (0.37; CI, 0.31 to 0.44) compared to placebo (0.54; CI 0.47 to 0.62; *P*<0.001 for both). This represented a RRR of 16.7% and 31.2%, respectively. Secondary: The percentage of patients with confirmed progression of disability in the 14 mg group (20.2%; CI, 15.6 to 24.7) was marginally lower than the placebo group (27.3%; CI, 22.3 to 32.3; *P*=0.03). The percentage of patients with confirmed progression of disability was not significantly different than placebo in the 7 mg group. The changes in total MRI brain lesion volume from baseline were reduced in both the 7 mg group (1.31±6.80 mL) and the 14 mg group (0.72±7.59 mL) compared to the placebo group (2.21±7.00 mL; *P*=0.03 and *P*<0.001, respectively).
O'Connor el al[46,47] TEMSO Extension Teriflunomide 7 mg QD vs placebo/teriflunomide 7 mg QD vs teriflunomide 14 mg QD vs placebo/teriflunomide 14 mg QD	DB, ES, MC Patients who completed TEMSO entered the long-term extension and patients originally receiving placebo were re-randomized to teriflunomide 7 mg or 14 mg, while patients receiving active treatment continued on the original dose	N=742 Primary: 4 years Secondary: 3 years	Primary: Safety and tolerability of teriflunomide Secondary: ARR, disability progression, change in total lesion volume on MRI from baseline	Primary: The overall incidence of TEAEs was similar across study groups (7 mg: 83.6%; 14 mg: 84.6%) at 4 year follow-up. The most common TEAEs reported for teriflunomide 7 mg and 14 mg groups, respectively, were nasopharyngitis (21.4% and 23.5%), headache (11.0% and 12.3%), ALT increase (12.0% and 11.8%), pain in extremity (7.6% and 10.6%), back pain (7.6% and 10.4%), diarrhea (6.3% and 10.4%), urinary tract infection (7.3% and 9.5%), influenza (9.7% and 9.2%), paresthesia (6.3% and 8.4%) and fatigue (11.2% and 7.8%). The overall rates of serious TEAEs were 15.4% for the 7 mg group and 11.5% for the 14 mg group. Two deaths occurred during the trial, but were not determined to be treatment related. Secondary: ARR was 0.25 for the placebo/7 mg group, 0.23 for the 7 mg group, 0.18 for the placebo/14 mg group and 0.21 for the 14 mg group. The percentage of patients with confirmed progression of disability was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				numerically lower in patients originally treated with teriflunomide than in patients originally treated with placebo. The changes in total MRI lesion volume from baseline were numerically lower in the 7 mg group compared to the placebo/7 mg group and were numerically lower in the 14 mg group compared to the placebo/14 mg group.
Freedman MS et al[48] Teriflunomide 7 mg vs teriflunomide 14 mg vs placebo All patients received IFNβ (Avonex® [IFNβ-1a] 30 µg IM QW or Rebif® [IFNβ-1a] 22 µg or 44 µg SC TIW or Betaseron® [IFNβ-1b] 0.25 mg SC QOD)	DB, MC, PC, RCT, ES Patients aged 18 to 55 years who met McDonald criteria for MS diagnosis and had relapsing clinical course with or without progression, EDSS score ≤5.5 and had received a stable dose of IFNβ for 26 weeks before screening After initial randomization and treatment for 24 weeks, patients could enter the 24 week blinded extension study in which patients remained on their initial treatment regimen	N=118 24 weeks N=86 24 week extension	Primary: Safety and tolerability Secondary: ARR, total number T1-gadolinium-enhancing lesions, total T1- gadolinium-enhancing lesion volume per MRI scan	Primary: The overall incidence of patients experiencing at least one TEAE was similar across all groups (placebo: 85.4%; teriflunomide 7 mg: 89.2%; teriflunomide 14 mg: 84.2%). TEAEs occurring more frequently in the teriflunomide groups (incidence ≥10%) in any group were increased ALT/AST, decreased white blood cells counts, nasopharyngitis, fatigue, nausea and hypertension. The number of patients experiencing serious TEAEs during the initial 24 week study was similar across groups (placebo: 1; 7 mg: 2; 14 mg: 0), but the incidence was slightly higher in the 7 mg group during the 24 week extension study (placebo: 4.9%; 7 mg: 10.8%; 14 mg: 2.6%). Discontinuation due to TEAEs was low and similar across all groups. No deaths occurred during 48 weeks. Secondary: ARRs at 24 weeks and 48 weeks were not significantly different between groups. At baseline, 21.7% of patients had at least one T1-gadolinium-enhancing lesion. The total number of T1-gadolinium-enhancing lesions per MRI scan during the initial 24 week study was decreased in the teriflunomide groups, corresponding to a RRR compared to placebo of 82.6% (*P*=0.0009) for 7 mg and 84.4% (*P*=0.0001) for 14 mg. These RRRs were maintained at 48 weeks. Total T1-gadolinium-enhancing lesion volume per MRI scan was reduced in the teriflunomide groups, but only the 14 mg group reached a significant RRR at 24 weeks (7 mg: 67.6%, *P*=0.19; 14 mg: 64.7%, *P*=0.007). These reductions were maintained at 48 weeks.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Confavreux et al[49] Teriflunomide 7 mg vs teriflunomide14 mg	ES, OL Patients aged 18 to 65 years with RRMS, a EDSS ≤6 and at least two clinical relapses in the previous three years and one during the preceding year	N=147 0.05 to 8.5 years	Primary: Long-term safety Secondary: Relapses, EDSS, T2 lesion volume, cerebral volume	Primary: The most commonly reported treatment emergent adverse events included infections, hepatic disorders, gastrointestinal disorders, neurological disorders, psychiatric disorders and hematologic disorders. The incidence of serious adverse events was slightly higher in the 7 mg group (35.8%) than the 14 mg group (28.8%) and included increased hepatic enzymes, loss of consciousness, neutropenia, pneumonia, MS relapse and breast cancer (No *P* values reported). The proportion of patients who discontinued treatment to due to an adverse event was 13.6% in both the 7 and 14 mg groups. One death due to a sudden cardiac disorder was reported in a patient who had been taking teriflunomide 14 mg for 4.8 years. This death was not directly attributed to the study drug. Secondary: The AARs decreased over time in the 7 and 14 mg groups and were 0.279 and 0.200 overall, respectively. The mean change (SD) in EDSS from baseline were 0.50 (1.29) and 0.34 (1.20), respectively (No *P* values reported). Mean cerebral volume decreased slightly more in the 7 mg group than in the 14 mg group at the end of the study. Mean (SD) percentage change from baseline in T2 volume was 62.66 (84.84)% and 72.28 (99.13)% in the 7 mg and 14 mg groups, respectively No *P* values reported).
Fox et al[50] CONFIRM Dimethyl fumarate 240 mg BID vs dimethyl fumarate 240 mg TID vs	DB, MC, PC, RCT Patients aged 18 to 55 years with a diagnosis of RRMS, an EDSS score of 0 to 5, and at least one clinically documented relapse in the previous 12 months or at least one gadolinium-enhancing lesion 0 to 6 weeks	N=1,430 96 weeks	Primary: ARR over two years Secondary: Number of new or enlarging hyperintense T2 lesions, number of new hypointense T1 lesions, proportion of patients with a relapse, time to	Primary: The ARR in patients receiving dimethyl fumarate twice daily and three times daily was 0.22 and 0.20, respectively. This corresponded to a reduction relative to placebo of 44% and 51% (*P*<0.001 for both). GAr was associated with a relative ARR reduction of 29% compared to placebo (*P*=0.001). Secondary: Dimethyl fumarate twice daily, three times daily and GA reduced the number of T2 lesions by 71%, 73% and 54%, respectively (all *P*<0.001 compared to placebo). The number of T1 lesions was reduced by 57%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GA 20 mg QD vs placebo The glatiramer acetate group was not an active comparator, but used as a referenced group. Patients receiving glatiramer were not blinded to treatment regimen.	before randomization		disability progression	(*P*<0.001), 65% (*P*<0.001) and 41% (*P*=0.002) relative to placebo, respectively. Compared to placebo, dimethyl fumarate twice daily, three times daily and GA significantly reduced the risk of relapse by 34% (*P*=0.002), 45% (*P*<0.001) and 29% (*P*<0.01), respectively. However, disability progression was not significantly reduced in any group compared to placebo. Post hoc analysis directly comparing dimethyl fumarate twice daily and three times daily to glatiramer determined that a comparison of ARR resulted in *P* values of 0.10 and 0.02, respectively favoring dimethyl fumarate. The overall incidence of adverse events, serious adverse events and adverse events leading to discontinuation was similar in all groups. The most common adverse events reported in patients receiving dimethyl fumarate were flushing, gastrointestinal events, upper respiratory tract infections and erythema.
Castelli-Haley et al[51] GA SC vs IFNβ-1a (Rebif®) SC Doses not reported for either treatment arm.	CE, RETRO Patients (mean age 43) diagnosed with MS, with a procedure code, or outpatient prescription for GA or IFNβ-1a, and insurance coverage starting at least six months before and extending through 24 months after the index date; in addition, a continuous use cohort could not have used other disease-	N=845 (ITT); N=410 (continuous use) 24 months	Primary: Costs (direct medical costs, including inpatient, outpatient and prescription drug cost) and relapse rate (defined as hospitalization with an MS diagnosis or a seven-day steroid therapy) Secondary: Not reported	Primary: Compared to IFNβ-1a therapy, patients in the ITT cohort receiving GA experienced a significantly lower two-year relapse rate (5.92 vs 10.89%; *P*=0.0305). Compared to IFNβ-1a therapy, patients in the continuous use cohort receiving GA experienced a significantly lower two-year relapse rate (1.94 vs 9.09%; *P*=0.0049). Compared to IFNβ-1a therapy, patients in the ITT cohort receiving GA had significantly lower twp-year estimated direct medical expenses ($41,786 vs $49,030; *P*=0.0002). Compared to IFNβ-1a therapy, patients in the continuous use cohort receiving GA had significantly lower two-year estimated direct medical expenses ($45,213 vs $57,311; *P*=0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	modifying therapy within the study period and were required to have received the study medication within 28 days of study end			Secondary: Not reported
Cadavid et al[52] BECOME GA 20 mg SC daily vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day	DB, MC, OL, PG, RCT Treatment-naïve patients with RRMS or clinically isolated syndrome suggestive of MS	N=75 24 months	Primary: Number of combined active lesions per patient per scan during year one, combined active lesions includes all enhancing lesions and nonenhancing new T2/fluid-attenuated inversion recovery lesions Secondary: Number of new lesions and clinical relapses over two years	Primary: The median number of combined active lesions per patient per scan during year one was not significantly different between patients receiving treatment with GA or IFNβ-1b (0.58 vs 0.63, respectively; *P*=0.58). Moreover, the number of patients who were active-lesion-free during the first year was similar among GA and IFNβ-1b-treated patients (19 vs 26%, respectively; *P*=0.59). Secondary: Over 24 months, the number of new lesions per patient per month was lower with GA compared to IFNβ-1b, but did not reach statistical significance (0.23 vs 0.46; *P*=0.13). The total number of relapses between GA and IFNβ-1b over two years was similar between treatments (23 vs 25, respectively; *P* value not reported). Both treatments were similar in regards to their effect on ARR (*P*=0.68).
Mikol et al[53] REGARD GA 20 mg SC daily vs IFNβ-1a (Rebif®) 44 µg SC three times weekly	MC, OL, PG, RCT Patients between 18 and 60 years of age, naïve to both study drugs, diagnosed with RRMS with the McDonald criteria, an EDSS score 0 to 5.5,	N=764 96 weeks	Primary: Time to first relapse (defined as new or worsening neurological symptoms, without fever, lasting at least 48 hours and accompanied by a	Primary: There was no significant difference in the time to first relapse between the IFNβ-1a and GA groups (HR, 0.94; 95% CI, 0.74 to 1.21; *P*=0.64). Secondary: There was no significant difference between treatment groups in the proportion of patients who were free from relapse over study period (*P*=0.96).There was no statistically significant difference between treatment groups in the ARR over the study period (*P*=0.828).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	≥1 attack within past 12 months and clinically stable or neurologically improving during the four weeks before study onset		change in KFS score) Secondary: Proportion of patients relapse-free over study period, relapse rate, number of active T2 lesions (defined as new or enlarging per patient per scan over 96 weeks), mean number of gadolinium-enhancing lesions/patient/scan, change in the volume of gadolinium-enhancing lesions, change in T2 volume, combined unique active lesions, new T1 hypointensities, T1 hypointense lesion volume, brain volume, disability progression, adverse effects	There were no differences between treatment groups in the number of active T2 lesions (new or enlarging) per patient per scan over 96 weeks of therapy (*P*=0.18). No significant difference was reported between treatment groups in the mean change in T2 lesion volume over 96 weeks of therapy (*P*=0.26). Patients randomized to IFNβ-1a experienced a significantly lower number of gadolinium-enhancing lesions per patient per scan compared to the GA-treated group (0.24 vs 0.41; *P*=0.0002). Over the 96 weeks of therapy, a significantly greater number of patients randomized to IFNβ-1a were free of gadolinium-enhancing lesions compared to the GA-treated groups (81 vs 67%; *P*=0.0005). There were no significant difference between the groups in the mean change in gadolinium-enhancing lesion volume over 96 weeks of therapy (*P*=0.42). Patients randomized to IFNβ-1a experienced a significantly lower number of combined unique active lesions per patient per scan compared to the GA-treated group (0.91 vs 1.22; *P*=0.01). There were no significant differences between treatment groups in the number of new T1 hypointense lesions per patient per scan over 96 weeks of therapy (*P*=0.15). No differences were reported between treatment groups in the mean change in new T1 hypointense lesion volume over 96 weeks of therapy (*P*=0.29). There was a significant reduction in brain volume among patients randomized to IFNβ-1a compared to the GA-treated group (*P*=0.018). There was no significant difference between the IFNβ-1a and GA groups in the proportion of patients with a six-month confirmed EDSS progression (11.7 vs 8.7%; *P*=0.117). Patients randomized to IFNβ-1a and GA experienced 632 and 618 treatment-related adverse effects, respectively (*P* value not reported). Treatment-related adverse events occurring significantly more often in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the IFNβ-1a group than in the GA group included influenza-like illness, headache, myalgia and increased ALT (*P*<0.05). Treatment-related adverse events occurring significantly more often in the GA group than in the IFNβ-1a group included pruritus, swelling, induration at the injection site, dyspnea and post-injection systemic reactions (*P*<0.05).
Flechter et al[54] GA 20 mg SC daily vs GA 20 mg SC every other day vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day	OL, PRO Patients 18 years of age and older with clinically definite MS and ≥2 exacerbations within the previous two years	N=58 2 years	Primary: Relapse rate, change in EDSS score and adverse effects Secondary: Not reported	Primary: At one and two years of follow-up, the relapse rate decreased significantly in all three treatment groups compared to baseline (*P*<0.05). While there were no significant changes in the EDSS scores from baseline at two years in the IFNβ-1b group (*P*=0.30), patients receiving GA daily or every other day experienced significantly higher (worsening) EDSS scores from baseline (*P*=0.007, *P*=0.04, respectively). There was no statistically significant difference in adverse events among the three treatment groups (*P*=NS). IFNβ-1b groups reported the following adverse effects: flu-like symptoms, increased spasticity, injection-site reactions and systemic reactions. The treatment group receiving GA daily experienced the following adverse effects: flu-like symptoms, injection-site reactions, systemic reaction, lymphadenopathy and lipodystrophy. Side effects were generally reported within the first six months of therapy and resolved with continued therapy. Secondary: Not reported
Khan et al[55] GA 20 mg SC daily vs	MC, OL, PRO Patients with RRMS, ≥1 relapses in past two years and EDSS score ≤4	N=156 12 months	Primary: Relapse rate Secondary: Changes in EDSS scores, relapse rate	Primary: Relapse rates were 0.97, 0.85, 0.61 and 0.62 for patients receiving no treatment, IFNβ-1a, IFNβ-1b and GA, respectively. Reductions in the relapse rate compared to no treatment was only significant with IFNβ-1b (*P*<0.002) and GA (*P*<0.003) groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs no treatment			during each half of study, proportion of relapse-free patients and proportion of relapse-free patients during each half of the study	Secondary: Mean EDSS scores were significantly reduced with IFNβ-1b (*P*<0.01) and GA (*P*<0.001) compared to no treatment. There were no significant reductions in relapse rates in the first half of the study and only GA-treated patients displayed a significant reduction in the second half (*P*=0.004). The proportions of relapse-free patients were 15, 20, 39 and 38% in the no treatment, IFNβ-1a, IFNβ-1b and GA groups, respectively. The differences between the IFNβ-1b and GA groups were statistically significant compared to the placebo group (*P*=0.037 and *P*=0.038, respectively). There was no significant difference between IFNβ-1a and placebo (*P*=NS). Of the 156 patients, 33 patients elected no treatment, 40 patients elected IFNβ-1a, 41 patients elected IFNβ-1b and 42 patients elected GA.
Khan et al[56] GA 20 mg SC daily vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs no treatment	MC, OL, PRO 18 months follow up study in patients with RRMS and ≥1 relapse in the past two years and an EDSS score ≤4	N=156 18 months	Primary: Relapse rate Secondary: Change in EDSS scores, proportion of relapse-free patients	Primary: Relapse rates were 1.02, 0.81, 0.55 and 0.49 in the no treatment, IFNβ-1a, IFNβ-1b and GA groups, respectively. Reduction in the relapse rate compared to receiving no treatment was statistically significant only in the IFNβ-1b and GA (*P*=0.001 for both comparisons) groups. Secondary: Mean EDSS scores were significantly reduced only in the IFNβ-1b (*P*<0.01) and GA (*P*=0.003) groups compared to the no treatment group. The proportions of relapse-free patients were 6.7, 11.8, 32.4 and 33.3% in the no treatment, IFNβ-1a, IFNβ-1b and GA groups, respectively. A significantly greater proportion of patients in the IFNβ-1b and GA groups were relapse-free over 18 months of follow-up compared to patients receiving no treatment group (*P*=0.05). There was no significant difference in the proportion of relapse-free patients between IFNβ-1a and patients receiving no treatment (*P*>0.999).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
O'Connor et al[57] BEYOND GA 20 mg SC daily vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1b (Betaseron®) 0.50 mg SC every other day	DB, MC, PG, PRO, RCT Patients 18 to 55 years of age with RRMS, EDSS score 0 to 5.5 and ≥1 relapse in the past year	N=2,244 24 months	Primary: Relapse risk Secondary: Progression on EDSS scale and change in T1-hypointense lesion volume	Primary: There were no differences in ARR between IFNβ-1b 0.25 and 0.50 mg (0.36 vs 0.33, respectively; *P*=0.10). In addition, no significant reductions in ARR were reported between GA and either dose of IFNβ-1b (0.34 vs 0.36 and 0.33 for the GA and the 0.25 and 0.50 mg doses of IFNβ-1b, respectively; *P*=0.42 and *P*=0.79). Secondary: The rate of progression on the EDSS scale was not significantly different between the IFNβ-1b groups and the GA group (21 to 27% across groups; *P*=0.55 to 0.71). Similarly, there were no differences in T1 hypointense lesion volume among treatment groups after two years compared to baseline values (*P*=0.18 to 0.68).
Carra et al[58] GA 20 mg SC weekly for three years, subsequently switched to IFNβ or mitoxantrone therapy for additional three years vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day for three years, subsequently switched to GA or mitoxantrone therapy for additional three years vs	MC, OS, PRO Patients 18 years of age or older with RRMS, an EDSS disability score <6 and ≥1 relapse in the previous year	N=114 3-year, before switch period; 3-year, after switch period	Primary: ARR over the three-year post-switch treatment period Secondary: The proportion of patients relapse-free during the three-year post-switch treatment period and mean change in EDSS score over six years	Primary: The ARR was reduced by 77% (from 0.63 to 0.14) among patients who switched from IFNβ to GA therapy (*P* value not reported). The ARR was reduced by 71% (from 0.53 to 0.15) among patients who switched from IFNβ to mitoxantrone therapy (*P* value not reported). The ARR was reduced by 67% (from 0.52 to 0.17) among patients who switched from IFNβ to GA therapy (*P* value not reported). The smallest reduction (57%, from 0.37 to 0.16) in the ARR was observed in patients switched between different IFNβ preparations (*P* value not reported). The ARR was reduced by 75% (from 0.8 to 0.2) in the reference group over six years of therapy (*P* value not reported). Secondary: The proportion of relapse-free patients increased from 55 to 68% after switching from one IFNβ preparation to another (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IFNβ-1a (Rebif®) 22 µg SC three times weekly for three years, subsequently switched to GA, IFNβ-1a 44 µg SC, IFNβ-1b, or mitoxantrone therapy for additional three years vs IFNβ-1a (Rebif®) 44 µg SC three times weekly for three years, subsequently switched to IFNβ-1b, GA or mitoxantrone therapy for additional three years vs IFNβ-1a (Avonex®) 30 µg IM once-weekly for three years, subsequently switched to IFNβ-1b, IFNβ-1a 44 µg SC, GA or mitoxantrone therapy for additional three years vs IFNβ or GA therapy for six years (reference cohort)				The proportion of relapse-free patients increased from 16 to 68% after switching from IFNβ to GA therapy due to inadequate efficacy (*P* value not reported).The proportion of relapse-free patients increased from 71 to 80% after switching from IFNβ to GA therapy due to adverse events (*P* value not reported). The proportion of relapse-free patients increased from 33 to 81% after switching from IFNβ to mitoxantrone therapy (*P* value not reported). The proportion of relapse-free patients increased from 27 to 63% after switching from GA to IFNβ therapy due to inadequate efficacy (*P* value not reported).The proportion of relapse-free patients decreased from 75 to 50% after switching from GA to IFNβ therapy due to adverse events (*P* value not reported). There was no evidence of disability progression as evidenced by a lack of statistically significant change in EDSS scores among patients switching from IFNβ to GA due to inadequate efficacy or those switching from IFNβ to mitoxantrone ($P>0.05$). However, patients switching from one IFNβ to another or GA to IFNβ demonstrated a statistically significant disability progression ($P<0.05$). The change in EDSS scores was significantly higher among patients switching from GA to IFNβ compared to those switching from IFNβ to GA therapy ($P=0.0035$), suggesting a higher rate of disability progression in the latter group. There was no statistically significant change from baseline in EDSS score in the reference group six months after therapy initiation (*P* value not reported).

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Haas et al[59] GA 20 mg SC weekly vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	OL, RETRO Patients with RRMS who have had one to three exacerbations within previous year and an EDSS score ≤3.5	N=308 24 months	Primary: Relapse rate Secondary: Number of relapse-free patients, mean EDSS change and progression rate	Primary: The relapse rates decreased significantly for all drugs (*P*<0.05), with an ARR of 0.80, 0.69, 0.66 and 0.36 for IFNβ-1a 30 µg IM, IFNβ-1b, IFNβ-1a 22 µg SC and GA, respectively. There were no significant differences between the groups at six months, but the decline in relapse rate at 24 months was highest with GA (0.81; *P*<0.001). Secondary: The percentage of relapse-free patients at 24 months was 35.4, 45.5, 45.8 and 58.2% for IFNβ-1a 30 µg IM, IFNβ-1b, IFNβ-1a 22 µg SC and GA, respectively (*P*=NS). There were no significant differences in EDSS between groups (*P*=NS). The progression index declined in all treatment groups (*P* values were not reported). The discontinuation rate between six and 24 months was highest for IFNβ-1a 30 µg IM and lowest for GA (33 vs 9%; *P*<0.001).
Lublin FD et al[86] IFNβ-1a (Avonex®) 30 µg IM once-weekly + GA 20 mg SC daily vs IFNβ-1a (Avonex®) 30 µg IM once-weekly + placebo SC daily vs GA 20 mg SC daily + placebo IM once-weekly	DB, MC, PC, Phase III, RCT Patients between the ages of 18 and 60 years with EDSS score of 0 to 5.5 and diagnosis of RRMS by Poser or McDonald criteria, with at least 2 exacerbations in the prior 3 years with no prior history of seizure activity	N=1,008 36 months	Primary: Reduction in ARR as measured by protocol-defined exacerbations Secondary: Time to confirmed disability, MSFC score, MRI metrics, safety	Primary: ARR of IFNβ-1a + GA combination treatment group was similar to the ARR of GA + placebo treatment group (*P*=0.27). GA + placebo treatment group was significantly better than IFNβ-1a + placebo treatment group, reducing the risk of exacerbation by 31% (*P*=0.027) and the IFNβ-1a + GA combination treatment group was significantly better than IFNβ-1a + placebo treatment group, reducing the risk of exacerbation by 25% (*P*=0.022). There was no difference between the three treatment groups in time to first exacerbation (*P*=0.19). There was no difference between the groups in proportion of patients with relapses (IFNβ-1a + placebo vs GA + placebo, *P*=0.14; IFNβ-1a + GA vs IFNβ-1a + placebo, *P*=0.19; IFNβ-1a + GA vs GA + placebo, *P*=0.21). Secondary: There was no difference between the three treatment groups showing 6-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				month confirmed progression of EDSS with 23.9%, 21.6%, and 24.8% of patients with EDSS progression in the IFNβ-1a + GA, IFNβ-1a + placebo, and GA + placebo treatment groups, respectively. There was no difference between the three treatment groups in the MSFC score over 36 months with all groups showing small increases. Change in a composite score constructed from 4 MRI measures, Z4, from baseline to month 36 did not differ between the IFNβ-1a + placebo and GA + placebo groups (*P*=0.52) or IFNβ-1a + GA and IFNβ-1a + placebo groups (*P*=0.23). Similarly, there were no differences between the groups at months 6, 12 and 24. The treatment groups were all effective in reducing MRI-defined disease activity measured by enhanced lesion numbers within 6 months of their initiation. The IFNβ-1a + GA combination treatment group reduced enhancement numbers more than IFNβ-1a + placebo group (*P*=0.01) when adjusted for baseline age and number of enhancements. There was no difference in the change in the number of enhancements from months 0 to 36 between IFNβ-1a + placebo and GA + placebo groups (*P*=0.82). The combination therapy with IFNβ-1a + GA did not result in any additional safety issues with the exception of the usual adverse events that were seen with the single agents. There were three deaths in the core study one in the extension study.
Koch-Henriksen et al[60] IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg SC once-weekly	MC, OL, RCT Patients with RMSS who have had ≥2 relapses within two years and an EDSS score ≤5.5	N=421 24 months	Primary: ARR, time to first relapse and NAb formation Secondary: Time to sustained progression	Primary: The ARR, time to first relapse and NAb formation were similar between patients taking either IFNβ therapy (*P*=NS). Secondary: There was no difference in the time to sustained progression between treatment arms (*P*=NS). Other: Side effects (15%) were the most frequent cause of withdrawal in the IFNβ-1b group and treatment failure was the most frequent cause of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				withdrawal in the IFNβ-1a group.
Baum et al[61] BRIGHT IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 44 µg SC three times weekly	I, MC, OS, PRO Patients, mean age 36 years with RRMS and treated with either one of the study regimens	N=445 15 consecutive injections (follow-up period, four to five weeks)	Primary: The proportion of patients pain-free during all injections (immediately, 30 minutes and 60 minutes post-injection) Secondary: Proportion of injections that were pain free per patient, the mean visual analog scale per patient, impact of injection site pain on comfort and satisfaction with treatment	Primary: A significantly greater proportion of patients receiving IFNβ-1b compared to IFNβ-1a were free from pain immediately, 30 minutes and 60 minutes after injection (*P*<0.0001 at all time points). Secondary: The proportion of pain-free injections per patient was significantly greater with IFNβ-1b compared to IFNβ-1a immediately, 30 minutes and 60 minutes after injection (*P*<0.0001 at all time points). Mean visual analog scale scores per patient were significantly lower with IFNβ-1b compared to IFNβ-1a immediately, 30 minutes and 60 minutes after injection (*P*<0.0001 at all time points). Injection site reactions occurred in significantly fewer patients treated with IFNβ-1b compared to IFNβ-1a (*P*<0.05). A significantly greater proportion of patients treated with IFNβ-1a compared to IFNβ-1b reported that pain after injection negatively impacted their satisfaction with treatment (35.9 vs 23.1%; *P*=0.006). Adverse effects were reported by 33.3% of patients treated with IFNβ-1b compared to 32.4% of patients receiving IFNβ-1a therapy (*P* value not reported).
Barbero et al[62] INCOMIN IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	MC, PG, PRO, RCT IFNβ-naïve patients with RRMS, ≥2 exacerbations in prior two years and EDSS scores 1 to 3.5	N=188 2 years	Primary: Proportion of patients with ≥1 active MRI lesion Secondary: Total area/volume of brain lesions or burden of disease, correlation between primary outcome	Primary: Significantly fewer patients had ≥1 active lesion in the IFNβ-1b arm compared to the IFNβ-1a arm (17 vs 34%; *P*<0.014). Secondary: The mean T2 burden of disease showed a progressive decrease from baseline in patients treated with IFNβ-1b and a progressive increase in patients treated with IFNβ-1a (*P*<0.001). The development of NAbs did not appear to have any impact on changes in MRI activity associated with IFNβ-1b treatment during the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and NAb status	entire study period (*P*=NS).
Durelli et al[63] INCOMIN IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	MC, PG, PRO, RCT IFNβ-naïve patients with RRMS and ≥2 exacerbations in prior two years and EDSS scores 1 to 3.5	N=188 2 years	Primary: Proportion of patients free from relapses Secondary: ARR, annualized treated relapse rate, proportion of patients free from sustained and confirmed progression in disability, EDSS score and time to sustained and confirmed progression in disability	Primary: Fifty-one percent of patients taking IFNβ-1b remained relapse-free compared to 36% of patients taking IFNβ-1a who remained relapse-free (*P*=0.03). Secondary: IFNβ-1b treatment resulted in fewer relapses per patient (0.5 vs 0.7; *P*=0.03), fewer treated relapses (0.38 vs 0.50; *P*=0.09), lower EDSS scores (2.1 vs 2.5; *P*=0.004), lower proportion of patients with progression in EDSS score of one point sustained for six months and confirmed at end of study (13 vs 30%; *P*=0.005) and longer time to sustained and confirmed disability progression (*P*<0.01) than IFNβ-1a treatment. Most adverse events (flu-like syndrome, fever, fatigue and increased liver enzymes) declined following six months of treatment. The frequency of adverse events was similar between groups. Local skin reactions and NAbs were more common in patients treated with IFNβ-1b compared to patients treated with IFNβ-1a (*P* values not reported). NAb were reduced during the second year of treatment and did not appear to have any correlation with relapse rate.
Minagara et al[64,65] PROOF IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	DB, MC, OS, PRO, RETRO Patients between 18 and 50 years of age with RRMS and an EDSS score 0 to 5.5, at least two documented relapses during the three years before study onset, receiving IFNβ-1a 30 µg IM once-weekly or	N=136 12 to 24 months (RETRO phase) 6 month (PRO phase)	Primary: Change in brain parenchymal fraction Secondary: Proportion of patients who experienced relapses at six months, ARR, change in EDSS, NAb formation and	Primary: There was no significant difference between the groups in the change in brain parenchymal fraction (*P* value not reported). Secondary: There was no significant difference between the treatment groups in the rate of relapse (*P* value not reported). There was no significant difference between the groups in the change in EDSS scores, suggesting similar sustained disability progression in both the IM IFNβ-1a and IFNβ-1a 44 µg SC groups (25.8 vs 26.7%; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	IFNβ-1a 44 µg SC three times weekly for at least 12 months and up to 24 months before enrollment		adverse effects	More patients in the IFNβ-1a 44 µg SC group developed NAbs compared to patients in the IM IFNβ-1a group (19 vs 0%; *P* value not reported). More patients positive for NAbs compared to those negative for NAbs had disability progression (40.0 vs 27.8%; *P*>0.05), new or enlarging T2 lesions (63.6 vs 40.7%; *P*=0.003) and gadolinium-enhancing lesions after 12 to 24 months of therapy (36.4 vs 15.0%; *P*=0.001). While general tolerability was comparable between the study drugs, IFNβ-1a 44 µg SC was associated with a greater incidence of injection-site reactions compared to the IM formulation (6.0 vs 2.9%; *P* value not reported).
Panitch et al[66] EVIDENCE IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	MC, PG, RCT IFNβ-naïve patients with RRMS, ≥2 exacerbations in prior two years and EDSS score 0 to 5.5	N=677 48 weeks	Primary: Proportion of patients who were relapse-free at 24 weeks Secondary: Relapse rate, time to first relapse and number of active lesions per patient per scan on MRI	Primary: More patients in the IFNβ-1a 44 µg SC treatment group compared to the IFNβ-1a 30 µg IM group remained relapse free at 24 (75 vs 63%; *P*=0.0005) and 48 weeks (62 vs 52%; *P*=0.009). Secondary: The time to first relapse was significantly prolonged in the IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group (*P*=0.003). Patients receiving IFNβ-1a 44 µg SC compared to IFNβ-1a 30 µg IM had significantly fewer active MRI lesions (*P*<0.001). Injection-site reactions, asymptomatic abnormalities of liver enzymes, and altered leukocyte counts were more frequent with IFNβ-1a 44 µg SC compared to IFNβ-1a 30 µg IM (83 vs 28%; *P*<0.001, 18 vs 9%; *P*<0.002 and 11 vs 5%; *P*<0.003), respectively. NAbs developed in 25% of the IFNβ-1a 44 µg SC group compared to 2% of the IFNβ-1a 30 µg IM group (*P*<0.001).
Panitch et al[67] EVIDENCE IFNβ-1a (Rebif®) 44 µg SC three times weekly	MC, PG, RCT A 64-week follow-up of the EVIDENCE trial; IFNβ-naïve patients	N=677 64 weeks	Primary: Proportion of patients who were relapse-free at 24 weeks	Primary: At study endpoint, 56% of patients in the IFNβ-1a 44 µg SC group and 48% of patients in the IFNβ-1a 30 µg IM group remained relapse-free (*P*=0.023).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	with RRMS, ≥2 exacerbations in prior two years and an EDSS score 0 to 5.5		Secondary: Relapse rate, time to first and second relapse, number of T2 active lesions per patient per scan, percentage of active scans per patient and proportion of patients with no active lesions	Secondary: In the IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group, there was a 17% reduction in relapse rate, a delayed time to first relapse (HR, 0.70), and a 32% reduction in steroid use to treat relapses (*P* value not reported). Patients in the IFNβ-1a 44 µg SC group had decreased MRI activity with reductions in T2 active lesions and a lower proportion of active scans and increases in patients with no active scans compared to patients in the IFNβ-1a 30 µg IM treatment group (*P*<0.001, for all comparisons). The presence of NAbs was associated with reduced efficacy for MRI measures and fewer IFNβ-related adverse effects, but did not have a significant impact on relapse measures.
Schwid et al[68] EVIDENCE IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly increased to 44 µg SC three times weekly Patients initially randomized to 30 µg IM once-weekly were allowed to switch to 44 µg SC three times a week after 48 weeks of therapy while patients initially randomized to 44 µg SC three times a	ES, MC, PG, RCT An eight-month extension of the EVIDENCE trial; IFNβ-naïve patients with RRMS, ≥2 exacerbations in prior two years and an EDSS score 0 to 5.5	N=677 80 weeks	Primary: Change in relapse rate Secondary: Change in the number of T2 active lesions per patient per scan, proportion of T2 active scans per patient and proportion of patients without T2 active scans	Primary: The relapse rate decreased from 0.64 to 0.32 for patients changing therapy (*P*<0.001) and from 0.46 to 0.34 for patients continuing therapy (*P*=0.03). The reduction in relapse rate was greater among patients switching to a higher dose and frequency IFNβ regimen (*P*=0.047). Secondary: Patients converting to the higher dose and frequency IFNβ regimen had fewer active lesions on T2-weighted MRI (*P*=0.02), fewer active scans (*P*=0.01) and no significant changes in the proportion of patients without active scans (*P*=NS). There were no significant changes in the continuing therapy group (*P*=NS). Seventy-three percent of the 306 patients receiving IFNβ-1a 30 µg IM switched to the IFNβ-1a 44 µg SC treatment and 91% of patients continued IFNβ-1a 44 µg SC therapy. Patients converting to the increased dose and frequency regimen experienced a higher incidence of adverse effects.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
week could withdraw from the study or continue on the regimen for an additional eight months.				
Schwid et al[69] EVIDENCE IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly, increased to 44 µg SC three times weekly Patients initially randomized to 30 µg IM once-weekly were allowed to switch to 44 µg SC three times a week after 48 weeks of therapy while patients initially randomized to 44 µg SC three times a week could withdraw from the study or continue on the regimen for an additional eight months.	AB, I, MC, PG, RCT, XO Full results of the EVIDENCE trial; IFNβ-naïve patients, between 18 and 55 years of age, with RRMS, ≥2 exacerbations in prior two years and an EDSS score 0 to 5.5	N=677 80 weeks	Primary: Proportion of patients free of relapses Secondary: Time to first relapse, ARR, number of steroid courses, number of T2 active lesions per patient per scan, percentage of active scans per patient, proportion of patients with no active scans, adverse events and NAbs detected	Primary: A significantly greater proportion of patients randomized to receive IFNβ-1a 44 µg SC remained free from relapses during the comparative phase of the study, compared to patients receiving IFNβ-1a 30 µg IM once-weekly (56 vs 48%; OR, 1.5; 95% CI, 1.1 to 2.0; *P*=0.023). Secondary: Compared to patients in the IFNβ-1a 30 µg IM group, patients in the high-dose IFNβ-1a 44 µg SC group experienced a 30% reduction in the time to first relapse (HR, 0.70; *P*=0.002) during the comparative phase of the study. Compared to patients in the IFNβ-1a 30 µg IM group, patients in the high-dose, IFNβ-1a 44 µg SC group experienced a 17% reduction in ARR (*P*=0.033) during the comparative phase of the study. A 50% reduction in the mean ARR occurred among patients who switched from IFNβ-1a 30 µg IM to IFNβ-1a 44 µg SC (*P*<0.001) during the XO phase of the study. A 26% reduction in the mean ARR occurred among patients who continued to receive IFNβ-1a 44 µg SC (*P*=0.028) during the XO phase of the study. A significantly lower number of steroid courses per patient per year were used in the high-dose IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group (0.19 vs 0.28; *P*=0.009) during the comparative phase of the study. Patients in the IFNβ-1a 44 µg SC group had a significantly fewer mean number of T2-active lesions compared to patients in the IFNβ-1a 30 µg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				IM group (0.9 vs 1.4; *P*<0.001) during the comparative phase of the study. A significant reduction in the mean number of T2-active lesions occurred among patients who converted from IFNβ-1a 30 µg IM to IFNβ-1a 44 µg SC during the XO phase of the study (*P*=0.022). Patients in the IFNβ-1a 44 µg SC group had a significantly lower percentage of T2-active scans per patient compared to patients in the IFNβ-1a 30 µg IM group (27 vs 44%; *P*<0.001) during the comparative phase of the study. Patients who converted from IFNβ-1a 30 µg IM to IFNβ-1a 44 µg SC experienced a statistically significant reduction in the percentage of T2-active scans per patient during the XO phase of the study (*P*<0.001). A significantly greater percentage of patients randomized to the IFNβ-1a 44 µg SC group did not have a T2-active scan compared to patients in the IFNβ-1a 30 µg IM group (58 vs 38%; OR, 2.4; 95% CI, 1.7 to 3.3; *P*<0.001) during the comparative phase of the study. Converting from IFNβ-1a 30 µg IM to IFNβ-1a 44 µg SC was not correlated with a significant change in the percentage of patients with no T2-active scans (*P*=0.803). Patients who continued IFNβ-1a 44 µg SC therapy from the start of the study did not have significant changes in any of the MRI measures (*P* value not reported). Injection-site reactions were significantly more common in patients receiving IFNβ-1a 44 µg SC compared to patients receiving IFNβ-1a 30 µg IM (85 vs 33%; *P*<0.001). Flu-like symptoms were significantly more common in patients receiving IFNβ-1a 30 µg IM than in patients receiving IFNβ-1a 44 µg SC (53 vs 45%; *P*=0.031). Abnormal liver function test results were significantly more common in patients receiving IFNβ-1a 44 µg SC than in patients receiving IFNβ-1a 30 µg IM

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(18 vs 10%; *P*=0.003). Most liver enzyme elevations resolved with continued therapy. Abnormal WBC counts were significantly more common in patients receiving IFNβ-1a 44 µg SC compared to patients receiving IFNβ-1a 30 µg IM (14 vs 5%; *P*<0.001). WBC counts normalized in most patients with continued therapy. The development of NAbs occurred in a significantly greater percentage of patients receiving IFNβ-1a 44 µg SC compared to patients receiving IFNβ-1a 30 µg IM (26 vs 3%; *P*<0.001). However, relapse rate was not affected by the NAb status (*P*=0.203).
Traboulsee et al[70] EVIDENCE IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly, increased to 44 µg SC three times weekly	PH This was a PH analysis of the EVIDENCE study; patients were included if had received at least one dose of the study drug and had an evaluable T2-weighted MRI scan obtained at baseline and week-48	N=533 48 weeks	Primary: Percentage change in T2 burden of disease from baseline to week-48 Secondary: Absolute change in burden of disease, percentage and absolute change in burden of disease when stratified by NAb status from baseline to week-48	Primary: Median percentage decreases in burden of disease were greater in the IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group (-6.7 vs -0.6%; *P* value not reported). The adjusted mean treatment difference in percentage change in burden of disease from baseline to week-48 showed a significant treatment benefit for patients treated with IFNβ-1a 44 µg SC compared to patients treated with IFNβ-1a 30 µg IM (-4.6%; SE, 2.6%; *P*=0.002). Secondary: A greater median absolute reduction from baseline in BOD was observed in the IFNβ-1a 44 µg SC group compared to IFNβ-1a 30 µg IM (-189.5 vs -19.0; *P* value not reported). Among patients randomized to IFNβ-1a 44 µg SC, median percentage decreases in burden of disease were smaller in patients positive for NAbs compared to those with a negative NAb status (-0.8 vs -8.0; *P* value not reported). Among patients randomized to IFNβ-1a 44 µg SC, absolute decreases in burden of disease were smaller in patients positive for NAbs compared to those with a negative NAb status (-46.2 vs -254.6; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The adjusted mean treatment difference in percentage change in burden of disease from baseline to week-48 showed a significant treatment benefit for NAb negative patients treated with IFNβ-1a 44 µg SC compared to IFNβ-1a 30 µg IM treated patients (-6.6%; SE, 2.8%; *P*<0.0001). The adjusted mean treatment difference in percentage change in burden of disease from baseline to week-48 showed comparable treatment benefit for NAb positive patients treated with IFNβ-1a 44 µg SC compared to IFNβ-1a 30 µg IM treated patients (-0.5%; SE, 3.9%; *P*=0.583).
Etemadifar et al[71] IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly	MC, RCT, SB Patients with RRMS with ≥2 relapses in past two years and EDSS score ≤5	N=90 24 months	Primary: Number of relapses, proportion of relapse-free patients and EDSS scores Secondary: Not reported	Primary: Mean relapse rates were reduced from 2.0 to 1.2, 2.4 to 0.6 and 2.2 to 0.7 episodes (*P*<0.001 for each) for the IFNβ-1a 30 µg IM, IFNβ-1a 44 µg SC, and IFNβ-1b groups, respectively. The proportions of relapse-free patients were 20, 43 and 57% for IFNβ-1a 30 µg IM, IFNβ-1a 44 µg SC, and IFNβ-1b, respectively. The mean number of relapses were lower with IFNβ-1a 44 µg SC and IFNβ-1b compared to IFNβ-1a 30 µg IM treatment (*P*<0.05). EDSS scores decreased by 0.3 in the IFNβ-1a 44 µg SC group (*P*<0.05) and 0.7 in the IFNβ-1b group (*P*<0.001) while the IFNβ-1a 30 µg IM group remained stable. Secondary: Not reported
Rio et al[72] IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg	OL, OS, PM Patients with RRMS with ≥2 relapses in the previous two years and an EDSS score 0 to 5.5	N=495 Up to 8 years	Primary: Proportion of relapse-free patients, proportion of patients with confirmed and sustained disability progression, ARR, proportion of	Primary: At two years 59, 59 and 50% of patients were relapse-free in the IFNβ-1a 30 µg IM, IFNβ-1a 22 µg SC, and IFNβ-1b groups, respectively. At four years 52, 39 and 35% of patients were relapse-free in the IFNβ-1a 30 µg IM, IFNβ-1a 22 µg SC and IFNβ-1b groups, respectively. Each group showed a significant reduction in relapse rate (*P*<0.0001). The number of relapses decreased with treatment at two years from 2.24 to 0.80 for IFNβ-1a 30 µg IM, from 2.51 to 0.64 for IFNβ-1a 22 µg SC and from 2.86 to 0.87 for IFNβ-1b. The relapse rates decreased at four years

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly			decrease in relapse rate, proportion of patients reaching EDSS of six and number of patients who discontinued treatment due to inefficacy Secondary: Not reported	(from 1.07 to 0.33 for IFNβ-1a 30 µg IM, 1.21 to 0.41 for IFNβ-1a 22 µg SC, and from 1.36 to 0.38 for IFNβ-1b; *P*<0.0001 for all comparisons). The proportions of patients with confirmed and sustained disability at two and four years respectively, were 17 and 23% for IFNβ-1a 30 µg IM, 19 and 35% for IFNβ-1a 22 µg SC, and 10 and 24% for IFNβ-1b. There were no significant differences between the treatment groups (*P*=NS). Thirteen percent of patients had an EDSS ≥6 following four years of therapy, but there were no significant differences between groups (*P*=NS). The proportions of patients discontinuing treatment due to lack of efficacy were 8% for IFNβ-1a 30 µg IM, 3% for IFNβ-1a 22 µg SC and 10% for IFNβ-1b (*P* values not reported). Patients selecting therapy with IFNβ-1a 30 µg IM were older than those selecting IFNβ-1a 22 µg SC. Patients selecting IFNβ-1b had greater disease activity and disability at baseline compared to the other treatments. Secondary: Not reported
Trojano et al[73] IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg	MC, OL, OS, PM Patients with RRMS	N=1,033 24 months	Primary: Proportion of relapse-free patients and number of patients with ≥1 point progression in EDSS Secondary: Changes from baseline in ARR and EDSS score	Primary: The proportions of patients who were relapse free in each group were similar (54% with IFNβ-1a 30 µg IM, 49% with IFNβ-1a 22 µg SC and 54% with IFNβ-1b at 12 months *(P* value not reported). The proportions of patients who remained relapse free at 24 months were 33% with IFNβ-1a 30 µg IM and 38% with IFNβ-1b (*P*=NS). The number of patients experiencing ≥1 point progression in EDSS was 3% with IFNβ-1a 30 µg IM, 5% with IFNβ-1a 22 µg SC and 4% with IFNβ-1b at 12 months (*P*=NS). The number of patients with ≥1 point progression in EDSS at 24 months was 7% with IFNβ-1a 30 µg IM and 11% with IFNβ-1b (*P*=NS). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IM once-weekly				Relapse rates were 0.71 with IFNβ-1a 30 µg IM and 0.65 with IFNβ-1b (*P*=0.16). Mean changes in EDSS score were similar among the groups (*P*=NS).
Trojano et al[74] IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg SC three times weekly vs IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs no treatment	OS Patients with RRMS	N=1,504 7 years	Primary: Incidence of SPMS Secondary: EDSS score of four and an EDSS score of six	Primary: Patients treated with IFNβ patients showed a reduction in the incidence of SPMS compared to untreated patients (*P*<0.0001) in terms of time from first visit (HR, 0.38) and current age (HR, 0.36). Secondary: There was a significant difference in favor of IFNβ-treated patients for EDSS score of four (*P*<0.02) and EDSS score of six (*P*≤0.03).
Limmroth et al[75] QUASIMS IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs	MC, OS Patients 18 to 65 years of age with RRMS and uninterrupted ≥2 year history of therapy with one of the study regimens	N=4,754 ≥2 years	Primary: Change from baseline EDSS score, percentage of progression-free patients (defined as <1 point increase in EDSS score over two years of	Primary: There were no differences in the change from baseline EDSS scores among patients who received IFNβ-1a 30 µg IM, IFNβ-1b, IFNβ-1a 22 µg SC and IFNβ-1a 44 µg SC regimens over two years of therapy (0.17 vs 0.25 vs 0.20 vs 0.35, respectively; *P* value not reported). The percentage of progression-free patients was significantly lower in the IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group (*P*<0.001) and IFNβ-1a 22 µg SC group (*P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IFNβ-1a (Rebif®) 22 µg SC three times weekly vs IFNβ-1a (Rebif®) 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly			therapy), percentage of relapse-free patients, ARR and reasons for therapy change Secondary: Not reported	The percentage of progression-free patients was significantly lower in the IFNβ-1b group compared to the IFNβ-1a 30 µg IM group (*P*=0.001). The percentage of relapse-free patients was significantly lower in the IFNβ-1a 44 µg SC group compared to the IFNβ-1a 30 µg IM group (34.6 vs 48.5%; *P*=0.002) and IFNβ-1b group (34.6 vs 45.7%; *P*=0.007). The percentage of relapse-free patients was significantly lower in the IFNβ-1a 22 µg SC group compared to the IFNβ-1a 30 µg IM group (39.8 vs 48.5%; *P*=0.005). There were no significant differences in ARR over two years among treatment-naïve patients who received IFNβ-1a 30 µg IM, IFNβ-1b, IFNβ-1a 22 µg SC and IFNβ-1a 44 µg SC regimens (0.51 vs 0.52 vs 0.53 vs 0.63, respectively; *P*=NS). The most common reason for therapy change was a perceived lack of efficacy (7.1%). A significantly greater percentage of patients changed therapy due to perceived lack of efficacy in the IFNβ-1a 22 µg SC group compared to either IFNβ-1a 30 µg IM (*P*=0.0027) or IFNβ-1b group (*P*<0.0001). Therapy change due to injection-site reactions was significantly less frequent among patients receiving IFNβ-1a 30 µg IM compared to IFNβ-1b (*P*<0.0001) and IFNβ-1a 22 µg SC groups (*P*=0.0001). In addition, a significantly greater percentage of patients in the IFNβ-1b group changed therapy due to flu-like symptoms compared to patients in the IFNβ-1a 22 µg SC group (1.2 vs 0.2 %; *P*=0.0038). Secondary: Not reported
TENERE[76] Teriflunomide 7 mg vs	DB, MC, PG, RCT Patients aged 18 years or older who met McDonald criteria	N=324 48 weeks	Primary: Time to failure Secondary: Safety and	Primary: Time to failure was not significantly different between groups (Rebif®: 42.3%; teriflunomide 7 mg: 48.6%, *P*=0.52; teriflunomide 14 mg: 37.8%, *P*=0.60).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
teriflunomide 14 mg vs Rebif® (IFNβ-1a) SC titrated to 8.8 µg for 2 weeks, 22 µg for 2 weeks then 44 µg; those who could not tolerate 44 µg were reduced to 22 µg	for MS diagnosis and had relapsing clinical course, EDSS score of 5.5 or lower and no systemic corticosteroid use in 2 weeks prior to randomization		tolerability of teriflunomide, ARR, fatigue impact scale, global satisfaction score	Secondary: The overall incidence of patients experiencing at least one TEAE was similar across all groups. The most common, potentially teriflunomide-related TEAEs were nasopharyngitis, diarrhea, alopecia, paresthesia and back pain and the most common potentially Rebif®-related TEAEs were headache, influenza-like illness and increased ALT. ARR was marginally lower in the Rebif® group (0.216) than the 7 mg group (0.410; *P*=0.03) and was not significantly different from the 14 mg group (0.259; *P*=0.59). The increase from baseline in fatigue impact score was marginally lower in the Rebif® group (9.10) than the 7 mg group (0.97; *P*=0.03) and not statistically different than the 14 mg group (4.10; *P*=0.18). Patients in the Rebif® group expressed marginally lower global satisfaction scores (60.98) than patients in the 7 mg and 14 mg groups (68.29 and 68.82; *P*=0.02 for both).
Other				
Comi et al[77] PRECISE GA 20 mg SC daily vs placebo	DB, DD, MC, PG, PRO, RCT Patients aged 18 to 45 years of age, with one unifocal neurological event in the previous 90 days, and positive brain MRI (defined as at least two cerebral lesions on the T2-weighted images at least 6 mm in diameter)	N=481 Up to 36 months	Primary: Time to conversion to clinically definite MS Secondary: Number of new T2 lesions detected at last scan, T2 lesion volume at last scan, percent change in brain volume (atrophy) and proportion of patients converting to clinically definite MS	Primary: There was a 45% reduction in the risk of conversion to clinically definite MS associated with GA compared to placebo (HR, 0.55; 95% CI, 0.40 to 0.77; *P*=0.0005). In addition, the time for 25% of patients to convert to clinically definite MS was significantly longer with GA compared to placebo (722 vs 336 days; *P*=0.0041). Secondary: The new number of new T2 lesions on MRI at the last visit was significantly reduced in patients treated with GA compared to patients randomized to placebo (0.7 vs 1.8; *P*<0.001). In PH analyses of patients completing two years of treatment without conversion to clinically definite MS, the cumulative number of new T2 lesions was reduced by 43% (RR, 0.57; 95% CI, 0.45 to 0.72; *P*<0.0001) of the MRI activity during the first year and by 52% (RR, 0.48; 95% CI, 0.3 to 0.61; *P*<0.0001) during the entire two years with GA compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo. The reduction in the number of new T2 lesions corresponded with a reduction in lesion volume for patients treated with GA compared to patients randomized to placebo (geometric means ratio, 0.75; 95% CI, 0.64 to 0.87; *P*=0.0002). Fewer patients who were treated with GA experienced a second attack and converted to clinically definite MS compared to patients randomized to placebo (24.7 vs 42.9%; *P*<0.0001).
Clerico et al[78] IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFNβ-1a (Rebif®) 22 µg SC weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs placebo	MA DB, PC, RCTs of patients with clinically isolated syndrome treated with either IFNβ or GA therapy	N=1,160 (3 studies) 2 to 3 years	Primary: The proportion of patients who converted to clinically definite MS Secondary: Side effects/adverse events	Primary: The proportion of patients converting to clinically definite MS was significantly lower in the IFNβ group compared to the placebo-treated group both at one year (OR, 0.53; 95% CI, 0.40 to 0.71; *P*<0.0001) and two years of follow-up (OR, 0.52; 95% CI, 0.38 to 0.70; *P*<0.0001). Secondary: Flu-like syndrome and injection site reactions occurred more frequently in patients receiving IFNβ compared to placebo: flu-like syndrome and injection-site reactions (*P*<0.00001). There was no significant difference in the incidence of serious adverse events between the two groups (*P* value not reported).
Bell et al[79] GA 20 mg SC daily vs IFNβ-1b (Betaseron®)	CE Patients diagnosed with RRMS in the United States	N=3,151 Up to 10 years	Primary: Incremental cost per QALY gained, cost per year spent in EDSS 0 to 5.5, cost per relapse-free year, cost per life-	Primary: The incremental cost per QALY gained was $258,465, $337,968, $416,301, and $310,691 for GA, IFNβ-1a 30 µg IM, IFNβ-1a 22 to 44 µg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management. The incremental cost per year spent in EDSS 0 to 5.5 was $21,667,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
0.25 mg SC every other day vs IFN-1a (Rebif®) 22 to 44 µg SC three times weekly vs AA IFNβ-1a (Avonex®) 30 µg IM once-weekly vs symptomatic management			year gained Secondary: Not reported	$28,293, $41,008, and $27,860 for GA, IFNβ-1a 30 µg IM, IFNβ-1a 22 to 44 µg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management. The incremental cost per relapse-free year was $17,599, $24,327, $32,207, and $23,065 for GA, IFNβ-1a 30 µg IM, IFNβ-1a 22 to 44 µg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management. The incremental cost per life-year gained was $2,076,622, $2,588,087, $3,378,626, and $2,452,616 for GA, IFNβ-1a 30 µg IM, IFNβ-1a 22 to 44 µg SC and IFNβ-1b 0.25 mg, respectively, compared to symptomatic management. Consequently, compared to symptomatic management alone, GA was found to be the most CE immunomodulatory therapy option for MS. Secondary: Not reported
Prosser et al[80] GA vs IFNβ-1b (Betaseron®) vs IFNβ-1a (Avonex®) vs no treatment Details of the clinical	CE Hypothetical cohorts of patients with non-primary progressive MS	N=not reported 10 years	Primary: Gain in quality-adjusted life expectancy, incremental CE ratios in dollars per QALY gained Secondary: Not reported	Primary: Ten-year therapy with IFNβ-1a was associated with the largest gain in quality-adjusted life expectancy (QALY, 7.955) with an incremental CE ratio of $2,200,000/QALY for women and $1,800,000/QALY for men, compared to no treatment. For five-year treatment duration, no treatment strategy was associated with more quality-adjusted life years compared to alternative treatments. CE ratios were similar across all treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
studies, including medication doses, used for the CE were not reported.				
Noyes et al[81] GA 20 mg SC daily vs IFNβ-1b (Betaseron®) 0.25 mg SC every other day vs IFN-1a (Rebif®) 22 to 44 µg SC three times weekly vs IFNβ-1a (Avonex®) 30 µg IM once-weekly vs symptomatic management	CE Patients diagnosed with RRMS and SPMS in the United States	N=1,121 10-year simulated disease progression cohort	Primary: Net gain in quality-adjusted life expectancy, incremental CE ratios in dollars per QALY gained Secondary: Not reported	Primary: The net gain in QALYs after 10 years of treatment with disease modifying therapy compared to supportive treatment was 0.192, 0.173, 0.082 and 0.126 years for IFNβ-1a 30 µg IM, IFNβ-1b 0.25 mg, IFNβ-1a 22 to 44 µg SC and GA, respectively. The CE of all disease modifying treatments exceeded $900,000/QALY. IM IFNβ-1a 30 µg was associated with the lowest incremental cost per QALY at $901,319. The incremental cost/QALY for IFNβ-1b 0.25 mg and IFNβ-1a 22 to 44 µg SC were similar, costing $1,123,162 and $1,487,306, respectively. Treatment with GA was calculated to cost $2,178,555 per QALY. Investigators reported that disease modifying therapies were associated with reduced costs/QALY and were more likely to become CE when drug costs were reduced and treatment was initiated earlier in the disease. Secondary: Not reported
Boneschi et al[36] GA 20 mg SC daily vs placebo	MA DB, PC, RCTs of patients 18 to 50 years of age with RRMS for at least one year with ≥1 relapse in the previous two years	N=540 (3 studies) Up to 35 months	Primary: ARR Secondary: Total number of relapses, time to first relapse and disability	Primary: Treatment with GA was associated with a statistically significant 28% reduction in the ARR compared to treatment with placebo (0.82 vs 1.14; *P*=0.004). Secondary: Treatment with GA was associated with a statistically significant 36% reduction in the total number of relapses compared to treatment with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			progression	placebo (*P*<0.0001). Treatment with GA was associated with a statistically significant 32% delay in the time to first relapse compared to treatment with placebo (322 vs 219 days; *P*=0.01). Treatment with GA was associated with a beneficial effect on disability progression compared to treatment with placebo (RR, 0.6; 95% CI, 0.4 to 0.9; *P*=0.02).

Drug regimen abbreviations: BID=twice daily, GA=glatiramer acetate, IFNβ=interferon beta, IM=intramuscularly, IV=intravenous, QD=once daily, SC=subcutaneously, TID=three times daily
Study abbreviations: AAR=absolute risk reduction, AB=assessor-blind, CE=cost-effectiveness study, CI=confidence interval, DB=double blind, DD=double dummy, ES=extension study, HR=hazard ratio, I=international, ITT=intention-to-treat, MA=meta-analysis, MC=multi-center, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PH=post-hoc analysis, PM=post-marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, RRR=relative risk reduction, SB=single-blind, SE=standard error, SR=systematic review, XO=crossover
Miscellaneous abbreviations: ALT=alanine aminotransferase, ARR=annualized relapse rate, ATRS=Adductor Tone Rating Scale, EDSS=expanded disability status scale, GPS=global pain score, KFS=Kurtzke functional score, MAS=Modified Ashworth Scale, MRI=magnetic resonance imaging, MS=multiple Sclerosis, MSFC=multiple sclerosis functional composite, NAb=neutralizing antibody, PBVC=percent brain volume change, PSFS=Penn Spasm Frequency Scale, QALY=quality-adjusted life years, RRMS=relapsing-remitting MS, SPMS=secondary progressive MS, TEAE=treatment emergent adverse event, WBC=white blood cell, WHO=world health organization, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[1-8]

Generic Name (Trade name)	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Dimethyl fumarate (Tecfidera®)	Safety and efficacy in the elderly and in children <18 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Not known; importance of drug administration to mother should be determined.
Fingolimod (Gilenya®)	Safety and efficacy in the elderly and in children <18 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required for patients with mild or moderate hepatic impairment.	C	Not known; importance of drug administration to mother should be determined.
Glatiramer acetate (Copaxone®)	Safety and efficacy in the elderly and in children <18 years of age have not been established.	Not reported	Not reported.	B	Not known; importance of drug administration to mother should be determined.
Interferon β-1b (Betaseron®, Extavia®)	Safety and efficacy in the elderly and in children <18 years of age have not been established.	Not reported	Not reported.	C	Not known; importance of drug administration to mother should be determined.
Interferon β-1a (Rebif®)	Safety and efficacy in the elderly and in children <18 years of age have not been established.	Not reported	Hepatic dose adjustment may be necessary.	C	Not known; importance of drug administration to mother should be determined.
Interferon β-1a (Avonex®, Avonex Administration Pack®)	Safety and efficacy in the elderly and in children <18 years of age have not been established.	Not reported	Hepatic dysfunction is a precaution.	C	Not known; importance of drug administration to mother should be determined.
Teriflunomide (Aubagio®)	Safety and efficacy in the elderly and in children <18 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required for patients with mild or moderate hepatic impairment.	X	Not known; importance of drug administration to mother should be determined.

Adverse Drug Events

The most commonly reported adverse events for the multiple sclerosis (MS) biologic response modifiers are listed in Table 6. In clinical trials, the most frequently reported adverse events associated with dimethyl fumarate were flushing, abdominal pain, diarrhea and nausea. The most commonly associated events with fingolimod treatment were headache, influenza, diarrhea and back pain. Increases in serum transaminases occurred in 14% of patients and led to discontinuing treatment in 3.8% of patients.[1] Influenza-like symptoms including injection site reactions, musculoskeletal pain, fatigue and headache are frequently reported with interferon β (IFNβ) treatment. Adverse events related to IFNβ therapy appear to be dose-related and transient.[3-6] In pre-marketing studies, 10% of patients treated with glatiramer acetate experienced a transient, self-limited, systemic reaction of flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria immediately following injection.[2] The most commonly observed adverse events with teriflunomide were increases in serum transaminases, alopecia, diarrhea, influenza, nausea, and paresthesia.

Table 6. Adverse Drug Events (%)[1-8]

Adverse Event	Dimethyl Fumarate	Fingolimod	Glatiramer Acetate	Interferon β-1b*	Interferon β-1a†	Interferon β-1a‡	Teriflunomide
Cardiovascular							
Atrioventricular block	-	0.1§	-	-	-	-	-
Bradycardia	-	4	-	-	-	-	-
Chest pain	-	-	13	9	6 to 8	5	-
Hypertension	-	6	-	6	-	-	4
Palpitations	-	-	9	-	-	-	2 to 3
Tachycardia	-	-	5	-	-	-	-
Vasodilatation	-	-	20	-	-	2	-
Central Nervous System							
Burning sensation	-	-	-	-	-	-	2 to 3
Convulsions	-	-	-	-	4 to 5	-	-
Dizziness	-	7	-	-	-	14	-
Fatigue	-	-	-	-	33 to 41	-	-
Fever	-	-	-	31	-	-	-
Headache	-	25	-	50	65 to 70	58	19 to 22
Malaise	-	-	-	6	4 to 5	-	-
Migraine	-	5	4	-	-	5	-
Incoordination	-	-	-	17	4 to 5	-	-
Insomnia	-	-	-	21	-	-	-
Paresthesia	-	5	-	-	-	-	9 to 10
Pyrexia	-	-	6	-	-	-	-
Sciatica	-	-	-	-	-	-	1 to 3
Somnolence	-	-	-	-	4 to 5	-	-
Speech disorder	-	-	2	-	-	-	-
Syncope	-	-	3	-	-	-	-

Adverse Event	Dimethyl Fumarate	Fingolimod	Glatiramer Acetate	Interferon β-1b*	Interferon β-1a†	Interferon β-1a‡	Teriflunomide
Tremor	-	-	4	-	-	-	-
Weight decreased	-	-	-	-	-	-	2 to 3
Endocrine							
Thyroid disorder	-	-	-	-	4 to 6	-	-
Gastrointestinal							
Abdominal pain	18	-	-	16	20 to 22	8	5 to 6
Diarrhea	14	12	-	-	-	-	15 to 18
Dry mouth	-	-	-	-	1 to 5	-	-
Dyspepsia	5	-	-	-	-	-	-
Distension	-	-	-	-	-	-	1 to 2
Nausea	12	-	15	-	-	23	9 to 14
Toothache	-	-	-	-	-	-	4
Vomiting	9	-	7	-	-	-	-
Hematologic							
Anemia	-	-	-	-	3 to 5	4	-
Hypertriglyceridemia	-	3	-	-	-	-	-
Injection site ecchymosis	-	-	-	-	-	6	-
Leukopenia	-	3	-	13	28 to 36	-	1 to 2
Lymphadenopathy	-	-	7	6	11 to 12	-	-
Lymphomas	-	✔‖	-	-	-	-	-
Lymphopenia	2	4	-	86	-	-	1 to 3
Neutropenia	-	-	-	13	-	-	2 to 4
Thrombocytopenia	-	-	-	-	2 to 8	-	-
Hepatic							
Abnormal hepatic function	-	-	-	-	4 to 9	-	-
Alanine aminotransferase liver enzymes increased	-	14	-	12	20 to 27	-	12 to 14
Aspartate aminotransferase liver enzymes increased	4	14	-	4	10 to 17	-	2 to 3
Bilirubinemia	-	-	-	-	2 to 3	-	-
Gamma-glutamyl transpeptidase liver enzymes increased	-	5	-	-	-	-	-
Gamma-glutamyltransferase increased	-	-	-	-	-	-	3 to 5

Adverse Event	Dimethyl Fumarate	Fingolimod	Glatiramer Acetate	Interferon β-1b*	Interferon β-1a†	Interferon β-1a‡	Teriflunomide
Infections							
Bronchitis	-	-	-	-	-	-	5 to 8
Cystitis	-	-	-	-	-	-	2 to 4
Gastroenteritis	-	5	6	-	-	-	2 to 4
Herpes viral infection	-	9	-	-	-	-	2 to 4
Influenza-like symptoms	-	13	14	57	56 to 59	49	9 to 12
Sinusitis	-	-	-	-	-	-	4 to 6
Tinea infections	-	4	-	-	-	-	-
Upper respiratory tract infection	-	-	-	-	-	-	9
Vaginal candidiasis	-	-	4	-	-	-	-
Musculoskeletal							
Arthralgia or myalgia	-	-	24	23	25	9 to 29	3 to 4
Asthenia	-	3	41	53	-	24	-
Back pain	-	12	12	-	23 to 25	-	-
Chills	-	-	3	21	-	-	-
Hypertonia	-	-	22	40	6 to 7	-	-
Pain	-	-	28	42	-	23	4 to 5
Skeletal pain	-	-	-	-	10 to 15	-	-
Ophthalmic							
Abnormal vision	-	-	-	-	7 to 13	-	-
Blurred vision	-	4	-	-	-	-	3
Conjunctivitis	-	-	-	-	-	-	1 to 3
Diplopia	-	-	3	-	-	-	-
Eye disorder	-	-	3	-	-	4	-
Eye pain	-	3	-	-	-	-	-
Xerophthalmia	-	-	-	-	1 to 3	-	-
Psychiatric							
Anxiety	-	-	13	-	-	-	3 to 4
Depression	-	8	-	-	-	18	-
Nervousness	-	-	2	-	-	-	
Respiratory							
Bronchitis	-	8	6	-	-	8	-
Cough	-	10	6	-	-	-	-
Dyspnea	-	8	14	6	-	-	-
Laryngospasm	-	-	2	-	-	-	-

Adverse Event	Dimethyl Fumarate	Fingolimod	Glatiramer Acetate	Interferon β-1b*	Interferon β-1a†	Interferon β-1a‡	Teriflunomide
Seasonal allergy	-	-	-	-	-	-	2 to 3
Sinusitis	-	7	7	-	-	14	-
Upper respiratory tract infection	-	-	-	-	-	14	-
Skin and Subcutaneous Tissue							
Acne	-	-	-	-	-	-	1 to 3
Alopecia	-	4	-	-	-	4	10 to 13
Eczema	-	3	-	-	-	-	-
Edema	-	-	8	-	-	-	-
Erythema	5	-	-	-	-	-	-
Flushing	40	-	-	-	-	-	-
Hyperhidrosis	-	-	7	-	-	-	-
Hypersensitivity	-	-	3	-	-	-	-
Injection site necrosis	-	-	-	4	1 to 3	-	-
Injection site reactions	-	-	4 to 64	78	89 to 92	6 to 8	-
Pruritus	8	3	5	-	-	-	3 to 4
Rash	8	-	19	21	4 to 7	-	-
Skin disorder	-	-	3	10	-	-	-
Urticaria	-	-	3	-	-	-	-
Urogenital							
Albumin urine present	6	-	-	-	-	-	-
Impotence	-	-	-	8	-	-	-
Metrorrhagia	-	-	-	9	-	-	-
Micturition urgency	-	-	5	-	2 to 7	-	-
Urinary incontinence	-	-	-	-	2 to 4	-	-
Urinary tract infection	-	-	-	-	-	17	-
Urine constituents abnormal	-	-	-	-	-	3	-

✓ Percent not specified.
- Event not reported.
* Betaseron®, Extavia®
†Rebif®
‡ Avonex®
§ Initiation of fingolimod treatment has resulted in transient atrioventricular (AV) conduction delays. In clinical trials, first degree AV block (prolonged PR interval on electrocardiogram) following the first dose was reported in 0.1% of patients receiving fingolimod 0.5 mg, but in no patient receiving placebo. Second degree AV block following the first dose was also identified in 0.1% of patients receiving fingolimod 0.5 mg but in no patient receiving placebo.
‖Cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma) were reported in premarketing clinical trials in multiple sclerosis patients receiving fingolimod at, or above, the recommended dose of 0.5 mg. Based on the small number of cases and short duration of exposure, the relationship to fingolimod remains uncertain.

Contraindications[1-8]

All of the biologic response modifiers used for the treatment of multiple sclerosis (MS) are contraindicated in patients with a known hypersensitivity to the drug, while interferon β (IFNβ) products are all contraindicated in patients with a hypersensitivity to albumin. Glatiramer acetate is contraindicated in patients with a hypersensitivity to mannitol, as it is used in the injectable solution.

Fingolimod is contraindicated in patients who what have experienced a myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure within the past six months. Additionally, it should not be used in patients with a history of Mobitz Type II second- or third-degree atrioventricular block unless the patient has a functioning pacemaker, in patients with a baseline QTc interval of 500 ms or greater or in patients concurrently using Class Ia or III anti-arrhythmic drugs.

Teriflunomide is contraindicated in patients with severe hepatic impairment, during pregnancy, and in patients concurrently receiving leflunomide.

Black Box Warning for Teriflunomide

WARNING
Hepatotoxicity • Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide. Obtain transaminase and bilirubin levels within 6 months before initiation of Aubagio® and monitor alanine aminotransferase levels at least monthly for six months. If drug induced liver injury is suspected, discontinue Aubagio® and start accelerated elimination procedure. Risk of Teratogenicity • Based on animal data, Aubagio® may cause major birth defects if used during pregnancy. Aubagio® is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during Aubagio® treatment.

Warnings and Precautions

Table 7. Warnings and Precautions[1-8]

Warnings and Precautions	Dimethyl fumarate	Fingolimod	Glatiramer Acetate	Interferon β-1b*	Interferon β-1a†	Interferon β-1a‡	Teriflunomide
A recent complete blood count (within six months) should be available before initiating therapy and be obtained annually.	✔	✔	-	-	-	-	-
An accelerated elimination procedure using either cholestyramine or charcoal may be necessary in patients requiring rapid elimination.	-	-	-	-	-	-	✔
An increase in the incidence of seizures was observed.	-	-	-	✔	✔	✔	-
An ophthalmologic evaluation should be performed at baseline and three to four months after fingolimod treatment is started in order to evaluate the presence of macular edema which can occur with or without visual symptoms.	-	✔	-	-	-	-	-
Anaphylaxis and other allergic reactions have been reported as a rare complication and medication should be discontinued if it occurs.	-	-	-	✔	✔	✔	-
Associated with a decrease in pulmonary function tests; evaluation of respiratory function and diffusion lung capacity for carbon monoxide should be performed when indicated.	-	✔	-	-	-	-	-
Associated with an increased risk of depression and suicide in patients with multiple sclerosis.	-	-	-	✔	✔	✔	-
Associated with post-injection reactions consisting of flushing, chest pain, palpitations, anxiety, dyspnea and constriction of the throat or urticaria, however symptoms are generally transient and self-limiting.	-	-	✔	-	-	-	-
Associated with rare cases of severe hepatic injury. The potential risk of these products in combination with other hepatotoxic drugs or other products (e.g. alcohol) should be considered prior to administration.	-	-	-	✔	✔	✔	-
Blood pressure should be checked and managed before initiating treatment and periodically thereafter.	-	-	-	-	-	-	✔
Congestive heart failure (CHF) and cardiomyopathy (with or without CHF) have been reported in patients without known predisposition to these events.	-	-	-	✔	-	-	-
Flu-like symptom complex; analgesics and/or antipyretics on injection days should be considered.	-	-	-	✔	-	-	-

Warnings and Precautions	Dimethyl fumarate	Fingolimod	Glatiramer Acetate	Interferon β-1b*	Interferon β-1a†	Interferon β-1a‡	Teriflunomide
Heart rate and blood pressure should be monitored during treatment initiation because of risk of bradyarrhythmia and atrioventricular block.	-	✔	-	-	-	-	-
If patient develops peripheral neuropathy symptoms, evaluate patient and consider discontinuing drug.	-	-	-	-	-	-	✔
Increased risk of interstitial lung disease.	-	-	-	-	-	-	✔
Increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis.	-	-	-	-	-	-	✔
Increased risk of severe liver injury and/or hepatotoxicity.	-	-	-	-	-	-	✔
Injection site necrosis has been reported.	-	-	-	✔	-	-	-
Leukopenia; complete blood count should be monitored.	-	-	-	✔	-	-	-
Lipoatrophy may occur up to several months after treatment initiation and is thought to be permanent.	-	-	✔	-	-	-	-
May cause flushing; administration with food may decrease it.	✔	-	-	-	-	-	-
May decrease lymphocyte counts.	✔	✔	-	-	-	-	-
May increase liver transaminases. Recent liver enzyme results should be available before starting therapy.	-	✔	-	-	-	-	-
May modify immune response and interfere with immune function.	-	-	✔	-	-	-	-
Monitor renal function and potassium in patients with symptoms of renal failure or hyperkalemia.	-	-	-	-	-	-	✔
Patients should be monitored for decreased peripheral blood counts, cardiomyopathy, congestive heart failure and development of autoimmune disorders, as all have been reported in post-marketing studies with the intramuscular IFNβ-1a formulation.	-	-	-	-	-	✔	-
Withholding treatment should be considered in patients with serious infections.	✔	✔	-	-	-	-	-
Women of childbearing potential should not be started on therapy until pregnancy is excluded and it has been confirmed they are using reliable contraception.	-	-	-	-	-	-	✔
Women of childbearing potential should use effective contraception during and for two months after stopping therapy.	-	✔	-	-	-	-	-

* Betaseron®, Extavia®
†Rebif®
‡ Avonex®

Drug Interactions

Due to their potential to cause hepatic injury, patients must be monitored when interferon β (IFNβ) is administered in combination with another agent that can cause hepatic injury, or when new agents are added to a regimen of a patient already receiving IFNβ.[3-7]

Due to its potential to cause neutropenia and lymphopenia, patients must be monitored when IFNβ-1a (Rebif®) is given in combination with another agent that can cause myelosuppression or when new agents are added to a regimen of a patient already receiving subcutaneous IFNβ-1a.[3-7]

Table 8. Drug Interactions[1-8]

Generic Name	Interacting Medication or Disease	Potential Result
Biological response modifiers (interferon β, fingolimod, teriflunomide)	Live vaccines	Interferon β can decrease the immune response, resulting in an increased risk of infection by live vaccines.
Fingolimod	Class Ia antiarrhythmic agents (flecainide, mexiletine, procainamide)	Concurrent use of fingolimod and Class Ia antiarrhythmic agents may result in increased risk of developing bradycardia or heart block.
Fingolimod	Class III antiarrhythmic agents (amiodarone, dronedarone, sotalol)	Concurrent use of fingolimod and Class III antiarrhythmic agents may result in increased risk of developing bradycardia or heart block.
Fingolimod	Ketoconazole	Concomitant administration may result in an increase in fingolimod exposure and a greater risk of adverse events.
Teriflunomide	Breast Cancer Resistant Protein (BCRP) inhibitors (cyclosporine, eltrombopag, gefitinib)	BCPR inhibitors may increase exposure to teriflunomide and increase risk of adverse events.
Teriflunomide	CYP2C8 substrates (repaglinide, paclitaxel, pioglitazone)	Teriflunomide may be an inhibitor of CYP2C8, resulting in increased exposure of CYP2C8 substrates. Patient monitoring is recommended.
Teriflunomide	CYP1A2 substrates (duloxetine, alosetron, theophylline, tizanidine)	Teriflunomide may be a weak inducer of CYP1A2, resulting in reduced exposure of CYP1A2 substrates. Monitor for decreased efficacy of CYP1A2 substrates.
Teriflunomide	Oral contraceptives	Teriflunomide may increase exposure and risk of estrogen and progestin-related adverse effects. Consider type and dose of oral contraceptive.

Dosage and Administration

Table 9. Dosing and Administration[1-8]

Generic Name (Trade name)	Adult Dose	Pediatric Dose	Availability
Dimethyl fumarate (Tecfidera®)	Treatment of patients with relapsing forms of multiple sclerosis: Delayed-release capsule: initial, 120 mg BID for seven days; maintenance, 240 mg BID	Safety and efficacy in children <18 years of age have not been established.	Delayed-release capsule: 120 mg 240 mg
Fingolimod	Treatment of patients with relapsing forms of	Safety and	Capsule:

Generic Name (Trade name)	Adult Dose	Pediatric Dose	Availability
(Gilenya®)	multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability: Capsule: 0.5 mg orally once daily	efficacy in children <18 years of age have not been established.	0.5 mg This medication is initially administered under the care of a medical professional. This medication is available only after enrollment in the medication-specific safety program.
Glatiramer acetate (Copaxone®)	Reduction of the frequency of relapses in patients with relapsing-remitting multiple sclerosis: Prefilled syringe: 20 mg SC once daily Patients who have experienced a first clinical episode and have magnetic resonance imaging features consistent with multiple sclerosis: Prefilled syringe: 20 mg SC once daily	Safety and efficacy in children <18 years of age have not been established.	Prefilled syringe: 20 mg This injectable medication is self-administered.
Interferon β-1b (Betaseron®, Extavia®)	Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations: Single use vial: initial, 0.0625 mg SC every other day; maintenance, 0.25 mg SC every other day Patients who have experienced a first clinical episode and have magnetic resonance imaging features consistent with multiple sclerosis: Single use vial: initial, 0.0625 mg SC every other day; maintenance, 0.25 mg SC every other day	Safety and efficacy in children <18 years of age have not been established.	Single use vial: 0.3 mg lyophilized powder This injectable medication is self-administered.
Interferon β-1a (Rebif®)	Treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability: Prefilled syringe: initial, 20% of maintenance dose; maintenance, 22 to 44 µg SC three times a week	Safety and efficacy in children <18 years of age have not been established.	Prefilled syringe: 8.8 µg 22 µg 44 µg This injectable medication is self-administered.
Interferon β-1a (Avonex®, Avonex	Treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency	Safety and efficacy in children <18	Prefilled syringe: 30 µg

Generic Name (Trade name)	Adult Dose	Pediatric Dose	Availability
Administration Pack®)	of clinical exacerbations: Prefilled syringe and single use vial: 30 µg IM once a week Patients who have experienced a first clinical episode and have magnetic resonance imaging features consistent with multiple sclerosis: Prefilled syringe and single use vial: 30 µg IM once a week	years of age have not been established.	Single use vial: 30 µg lyophilized powder This injectable medication is self-administered.
Teriflunomide (Aubagio®)	Treatment of patients with relapsing forms of multiple sclerosis: Tablet: 7 mg or 14 mg QD	Safety and efficacy in children <18 years of age have not been established.	Tablet: 7 mg 14 mg

BID=twice daily, IM=intramuscular, SC=subcutaneous, QD=once daily

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the Multiple Sclerosis Council for Clinical Practice Guidelines: **Disease Modifying Therapies in Multiple Sclerosis (2002)**[15]	• No one agent is recommended over another, but glucocorticoids, interferon beta and glatiramer acetate have the strongest recommendations for use in relapsing forms of multiple sclerosis (MS). Glucocorticoids • Glucocorticoids have been demonstrated to provide short-term benefits on the speed of functional recovery in patients with acute attacks of MS. Consider glucocorticoids for treatment of any patient with an acute attack of MS (Type A recommendation). • There are no apparent long-term benefits of glucocorticoids on MS (Type B recommendation). • Clinical benefits of glucocorticoids are not influenced by particular glucocorticoid, route of administration or dosage (Type C recommendation). • Regular pulse glucocorticoids may be useful in the long-term management of relapsing-remitting MS (RRMS) (Type C recommendation). Interferon beta (IFNβ) • IFNβ has been shown to reduce the attack rate in patients with MS or with clinically isolated syndromes at high risk for developing MS (Type A recommendation). • IFNβ treatment produces a beneficial effect on MRI measures of disease severity and probably also slows disability progression (Type B recommendation). • Consider IFNβ treatment for any patient at high risk of developing MS or any patient with RRMS or secondary-progressive MS (SPMS) still experiencing relapses (Type A recommendation). • It is probable that there is a dose-response curve associated with the

Clinical Guideline	Recommendations
	use of IFNβ for MS (Type B recommendation). • The route of administration of IFNβ is probably not of clinical importance with regard to efficacy, although the side-effect profile does differ (Type B recommendation). • IFNβ treatment is associated with the production of neutralizing antibodies, but the rate of production is probably less with IFNβ-1a than IFNβ-1b (Type B recommendation). Their presence may be associated with a reduction in clinical effectiveness of IFNβ treatment (Type C recommendation). Glatiramer acetate • Glatiramer acetate has been shown to reduce attack rates, produce a beneficial effect on MRI measures of disease severity and possibly slow disability progression in RRMS. • Consider glatiramer acetate in any patient with RRMS (Type A recommendation). Cyclophosphamide • Pulse cyclophosphamide treatment does not alter the course of progressive MS (Type B recommendation). • It is possible that younger patients with progressive MS may derive some benefit from pulse plus booster cyclophosphamide (Type U recommendation). Methotrexate • It is possible that methotrexate favorably alters disease course in progressive MS (Type C recommendation). Azathioprine • Azathioprine may reduce relapse rate in MS (Type C recommendation). Cladribine • Cladribine reduces gadolinium enhancement in relapsing and progressive MS, but does not favorably alter disease course (Type C recommendation). Cyclosporine • It is possible that cyclosporine provides some therapeutic benefits in progressive MS (Type C recommendation). • Cyclosporine is not recommended due to frequency of adverse events and small magnitude of potential benefit (Type B recommendation). Mitoxantrone • Mitoxantrone probably reduces attack rate in relapsing MS, but its potential toxicity may outweigh benefits early in disease course (Type B recommendation). Intravenous immunoglobulin • It is only possible that intravenous immunoglobulin reduces attack rate in RRMS (Type C recommendation).

Clinical Guideline	Recommendations
	• Intravenous immunoglobulin is of little benefit in slowing disease progression (Type C recommendation). Plasma exchange • Plasma exchange may be helpful in the treatment of severe acute episodes of demyelination in previously nondisabled individuals (Type C recommendation).
Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology: **Neutralizing Antibody to Interferon β: Assessment of Their Clinical and Radiographic Impact: an Evidence Report (2007)**[19]	• It is probable that the presence of neutralizing antibodies (NAbs), especially in persistently high titers, is associated with a reduction in the radiographic and clinical effectiveness of interferon β (IFNβ) treatment. • It is probable that the rate of NAb production is less with IFNβ-1a treatment compared to IFNβ-1b treatment. However, the magnitude and persistence of any difference in between these forms of IFNβ is difficult to determine. • It is probable that the prevalence of NAbs to IFNβ is affected by ≥1 of the following: formulation, route of administration, dose and/or frequency of administration.
National Clinical Advisory Board of the National Multiple Sclerosis Society: **Multiple Sclerosis Disease Management Consensus Statement (2008)**[88]	• Initiation of treatment with an interferon β (IFNβ) product or glatiramer acetate (GA) should be considered as soon as possible following a definite diagnosis of multiple sclerosis (MS) with active, relapsing disease. • Initiation of treatment with an IFNβ product or GA may also be considered for select patients with a first attack who are at high risk of MS. • Natalizumab is generally recommended by the Food and Drug Administration (FDA) for patients who have had an inadequate response to, or are unable to tolerate, other MS therapies. • Mitoxantrone may be considered for selected relapsing patients with worsening disease or patients with secondary progressive multiple sclerosis (SPMS) who are worsening, whether or not relapses are occurring. • Access to medication should not be limited by the frequency of relapses, age or level of disability. • Treatment should not to be discontinued while insurers evaluate for continuing coverage of treatment. • Therapy should be continued indefinitely, except for the following circumstances: clear lack of benefit, intolerable side effects or availability of better therapy. • The most appropriate agent should be selected on an individual basis. • All FDA-approved agents should be included in formularies and covered so that the most appropriate agent for an individual can be utilized; failure to do so is unethical and discriminatory. • Transition from one disease-modifying agent to another should occur only for medically appropriate reasons. • No therapy has been approved for use by women who are trying to become pregnant, are pregnant or are nursing mothers.
National Institute for Clinical Excellence:	Making the diagnosis of MS • For a patient who presents with a first episode of neurological

Clinical Guideline	Recommendations
Multiple Sclerosis: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care (2003)[89]	symptoms, or signs suggestive of demyelination, a diagnosis of multiple sclerosis (MS) should be considered. A second episode of neurological symptoms calls for a referral to an appropriate expert for investigation. • A diagnosis of MS is clinical by a doctor with specialist neurological experience, on the basis of evidence of central nervous system lesions scattered in space in time and primarily on the basis of the history and examination. • A patient should be informed of the potential diagnosis of MS as soon as the diagnosis is considered reasonably likely. Diagnosis of an acute episode • If a person with MS has a relatively sudden increase in neurological symptoms or disability, or develops new neurological symptoms, a formal assessment should be made to determine the diagnosis. • Assessment should be undertaken within an appropriate time based on clinical presentation, consider the presence of an acute infective cause and should involve a general practitioner or acute medical/neurological services. • The two specific types of acute clinical syndromes that are recognized include optic neuritis and transverse myelitis. Treatment of acute episodes • A patient experiencing an acute episode that causes distressing symptoms or an increased limitation on activities should be offered a course of intravenous (500 to 1,000 mg) or oral (500 to 2,000 mg) methylprednisolone daily for three to five days. • Frequent or prolonged use of corticosteroids should be avoided. • Other medications for the treatment of acute relapse should not be used unless as part of a formal research protocol. Interventions affecting disease progression • Linoleic acid 17 to 23 g/day may reduce progression of disability. • Azathioprine, mitoxantrone, intravenous immunoglobulin, plasma exchange and intermittent short courses of high-dose methylprednisolone should not be used except in these specific circumstances: after full discussion and consideration of all the risks; with formal evaluation, preferably in a randomized or other prospective trial by an expert in the use of these medicines in MS with close monitoring for adverse events. • Cyclophosphamide, antiviral agents, cladribine, long-term treatment with corticosteroids, hyperbaric oxygen, linomide, whole-body irradiation and myelin basic protein should not be used due to the lack of evidence for beneficial effects on the course of the condition. Diagnosis and treatment of specific impairments • If a patient is diagnosed with significant depression it should be treated appropriately. • At present none of the medications targeted at treating fatigue should be used routinely. Patients should be informed that a small clinical benefit may be gained with amantadine 200 mg/day. • Urgency or urge incontinence should be treated by providing advice

Clinical Guideline	Recommendations
	on changes to clothing and/or toilet arrangements, intermittent self-catheterization if there is high residual volume, an anticholinergic medication (oxybutynin or tolterodine) and checking for an increased post-voiding residual volume if symptoms recur. • Nocturia should be treated with desmopressin (100 to 400 µg orally or 10 to 40 µg intranasally, at night). • Patients who wish to control urinary frequency during the day, and who have failed with other measures, should be offered desmopressin. Patients should be instructed to never use desmopressin more than once in a 24 hour period. • Patients at risk of urinary tract infections should not be recommended prophylactic use of antibiotics or cranberry juice. • Urinary tract infections should be treated with antibiotics appropriately. If more than three infections occur in one year, the patient should be referred to a specialist. • Patients who are constipated should be advised on fluid intake and dietary changes that may improve their condition, and then be considered for oral laxatives. • If a patient has apparent constipation despite treatment with oral laxatives he or she should be considered for the routine use of suppositories or enemas. • Motor weaknesses should be managed via exercises and techniques that maximize strength and endurance appropriate to their circumstances. In some patients, equipment may be helpful. • If spasticity or spasms are present, simple causative or aggravating factors such as pain and infection should be sought and treated. • Baclofen or gabapentin should be used initially for bothersome regional or global spasticity or spasms. • Clonazepam, dantrolene, diazepam or tizanidine should be used if baclofen and gabapentin provided no benefit or was associated with intolerable side effects. • Combination of medications, and other medications such as anticonvulsants, should only be used after seeking further specialist advice. • Intramuscular botulinum toxin should not be used routinely for the treatment of spasticity or spasm. It can be considered for relatively localized hypertonia or spasticity that is not responding to other treatments. • Patients who are at risk of developing contractures should consider prolonged stretching using serial plaster casts and other similar methods, such as standing in a standing frame and removable splints. In addition these modalities are usually combined with local botulinum toxin injections and surgery, when necessary. • Patients who experience limitations due to tremor should be assessed by a specialist. • Patients who experience a limitation of activities not otherwise explained should be assessed for sensory losses. • Patients who experience reduced visual acuity, despite using suitable glasses, should be assessed by a specialist. • Patients with nystagmus that causes reduced visual acuity or other visual symptoms should be treated with a time-limited trial of gabapentin. This should be initiated and monitored by a specialist.

Clinical Guideline	Recommendations
	• Musculoskeletal pain should be managed initially with exercise, passive movement, better seating or other procedures. If these modalities do not provide relief, appropriate analgesic medications should be offered to the patient. • Patients with continued, unresolved, secondary musculoskeletal pain should consider transcutaneous nerve stimulation or antidepressant medications. • Ultrasound, low-grade laser treatment, and anticonvulsants should not be routinely used for the treatment of musculoskeletal pain. • Neuropathic pain should be treated using anticonvulsants or antidepressants. If no benefit is achieved, patients should be assessed by a specialist. • If emotionalism is sufficient to cause concern or distress, a tricyclic antidepressant should be offered to the patient. A selective serotonin reuptake inhibitor may also be used. • Pharmacologic treatment of anxiety should be with antidepressants or benzodiazepines. • Men with persisting erectile dysfunction and who do not have contraindications should be offered sildenafil 25 to 100 mg. Other specific treatments that can be considered include alprostadil or intracavernosal papaverine. • Pressure ulcers should be dressed according to appropriate local guidelines. • There is some evidence to suggest that the following items might be of benefit; however, due to the lack of evidence there are no strong recommendations made regarding their use: reflexology and massage, fish oils, magnetic field therapy, neural therapy, massage plus body work, t'ai chi and multi-modal therapy.
National Institute for Clinical Excellence: **β Interferon and Glatiramer Acetate for the Treatment of Multiple Sclerosis (Appraisal) (2002)**[90]	• Four general approaches to the treatment of multiple sclerosis (MS), which may be undertaken separately or in combination, include management of symptoms and disability with speech, physio- and occupational therapy and pharmacological or other therapeutic agents; management of emotional and social consequences of relapses and disability; treatment of acute relapses with corticosteroids; and disease modifying treatment targeted at reducing the frequency and/or severity of relapses and/or slowing the progression of the disease. • Interferon β (IFNβ) and glatiramer acetate (GA) are the only disease modifying agents currently available (Note: this statement is no longer true). • Clinical trials have shown that all three IFNβ products reduce relapse frequency and severity in patients with relapse-remitting multiple sclerosis (RRMS) and may also influence duration of relapse. The reduction is on average 30%, which is equivalent to approximately one relapse avoided every two and a half years, and has been adequately demonstrated for the first two years of therapy. • The IFNβ products also delay disability progression, but the effects of treatment on disability in the long term, following cessation of therapy, cannot be predicted reliably on the basis of the short-term evidence from clinical trials currently available. • The proposition that the IFNβ products have a positive effect beyond two years is supported by open-label trials.

Clinical Guideline	Recommendations
	• IFNβ has also been shown to reduce relapse frequency and severity in secondary progressive multiple sclerosis (SPMS). • Clinical trials have shown that GA reduced relapse frequency in patients with RRMS. The reduction is on average 30%, which is equivalent to approximately one relapse avoided every two and a half years, and has been adequately demonstrated for the first two years of therapy. • Data from an open-label, follow-up trial (N=73) of RRMS patients showed that 75% of them were unchanged or improved in terms of accumulation of disability after eight years of treatment with GA.
National Institute for Health and Clinical Excellence: **Natalizumab for the Treatment of Adults With High Active Relapsing-Remitting Multiple Sclerosis (Appraisal) (2007)**[91]	• Natalizumab is recommended as an option for the treatment only of rapidly evolving severe relapse-remitting multiple sclerosis (RRMS), defined as two or more disabling relapses in one year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared to a previous MRI. • Patients currently receiving natalizumab, but for whom treatment would not have been recommended based on the above bullet, should have the option to continue therapy until they and their clinicians consider it appropriate to stop. • Natalizumab also has marketing authorization as a single disease modifying therapy in highly active RRMS for patients with high disease activity despite treatment with interferon β (IFNβ). This group of patients is defined as patients who have failed to respond to a full and adequate course of IFNβ. These patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintensive lesions in cranial MRI or at least one gadolinium-enhancing lesion. This group of patients is referred to as the “suboptimal therapy group.” • Natalizumab has been associated with an increased risk of progressive multifocal leukoencephalopathy. Use may also be associated with infections, urticaria, headache, dizziness, vomiting, nausea, arthralgia, infusion reactions and hypersensitivity reactions.
Association of British Neurologists: **Guidelines for Prescribing in Multiple Sclerosis (2009)**[92]	• In patients with relapse-remitting multiple sclerosis (RRMS), and SPMS with superimposed relapses, Interferon β (IFNβ) has a consistent effect in reducing relapses (by about one third over two years). • This may apply to patients with a clinically isolated syndrome in whom an abnormal magnetic resonance imaging (MRI) indicates a high probability of future conversion to clinically definite MS and patients subsequently meeting the revised McDonald criteria for MS. • In patients with RRMS, glatiramer acetate (GA) reduces relapse rate by about one third over two years. • The IFNβ products and GA may reduce the development of disability through prevention of relapses that would otherwise result in residual dysfunction, although the benefit appears modest at best, and some trials have not shown any benefit. • IFNβ and GA do not appear to modify disability progression that is unrelated to relapses. When patients with RRMS are treated with IFNβ and GA, it is not known whether the long term course of multiple sclerosis (beyond five years), is altered. Specifically, it is not established reliably that long-term IFN reduces the accumulation of

Clinical Guideline	Recommendations
	disability by whatever mechanism or prevents or slows entry to the secondary progressive stage of the disease. • In clinically isolated syndromes, IFNβ reduces the conversion rate to MS from 45 to 50% in untreated patients to 28 to 35% over two to three years and GA probably has a similar effect. However, at best, only a marginally significant gain in terms of disability with IFNβ treatment has been demonstrated over three to five years. • In patients with rapidly evolving aggressive RRMS, consideration should be given to the use of natalizumab in accordance with National Institute for Clinical Excellence guidelines. In expert centers, various other treatments may also be considered, including mitoxantrone. • No treatments have been approved that convincingly alter the course of progressive MS in the absence of relapses after reaching this stage of the disease. • As newer treatments emerge and clinical equipoise is agreed between the clinician and patient, participation should be encouraged in clinical trials, rather than open label prescribing.
National Institute for Clinical Excellence: **Fingolimod for the Treatment Highly Active Relapsing-Remitting Multiple Sclerosis (2012)**[16]	• Fingolimod is recommended as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults, only if: o They have an unchanged or increased relapse rate or ongoing severe relapses compared to the precious year despite treatment with beta interferon, and o The manufacturer provides fingolimod with the discount agreed as a part of the patient access scheme • People currently receiving fingolimod whose disease does not meet the above criteria should continue treatment unless they or their clinician feels it is appropriate to stop

Conclusions

The agents currently Food and Drug Administration (FDA)-approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) include dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®), glatiramer acetate (Copaxone®), interferon β (IFNβ)-1b (Betaseron®, Extavia®), intramuscular (IM) IFNβ-1a (Avonex®), subcutaneous (SC) IFNβ-1a (Rebif®), and teriflunomide (Aubagio®).[1-8] In addition, glatiramer acetate, IFNβ-1b, and IM IFNβ-1a are FDA-approved for the treatment of patients with a first clinical episode and magnetic resonance imaging (MRI) evidence of multiple sclerosis (MS).[3-7] Dimethyl fumarate, fingolimod, and teriflunomide are the only oral agents available to treat MS.

All available agents have been shown to decrease MRI lesion activity, prevent relapses, delay disease progression, and ultimately reduce disability from MS.[26-76] Fingolimod was shown to reduce the annualized relapse rate (ARR) in patients with MS by up to 60% in placebo-controlled trials, and up to 52% when compared to IM IFNβ-1a. Dimethyl fumarate and teriflunomide have been shown to reduce ARR by 44% to 53% and by 31%, respectively, compared to placebo.[13] Teriflunomide did not show a significant efficacy benefit when compared to SC IFNβ-1a (Rebif®).[48] Sustained reductions in ARR were reported in an extension study for patients continuing fingolimod treatment and patients switched from IM IFNβ-1a to fingolimod.[27,32,33] In general, patients treated with IFNβ or glatiramer acetate can expect a 30% reduction in ARR during a two-year period following treatment initiation with IFNβ or glatiramer acetate.[13,90] Head-to-head clinical trials have found IFNβ and glatiramer acetate to be comparable in terms of efficacy.[35-83] Several studies have demonstrated an improved tolerability at the cost of a decreased therapeutic response with the low dose IM IFNβ-1a compared to the higher dose SC IFNβ-1a.[66-69]

The American Academy of Neurology, the National MS Society, and the National Institute for Health and Care Excellence (NICE) recommend treatment with glatiramer acetate or IFNβ in MS patients.[15,88,90] The best evidence for effectiveness has been in patients with RRMS, but therapy may also be considered in certain patients with clinically isolated syndrome and progressive forms of the disease.[11,13,15,17] To date, neither organization has updated its guidelines to reflect the use of the oral agents. However, NICE has recommended that due to its adverse effect profile, fingolimod be reserved as an option for highly active RRMS in adults, only if patients have an unchanged or increased relapse rate or ongoing severe relapses compared to the precious year despite treatment with beta interferon.[16] Pediatric MS is rare and understudied. In general, treatment recommendations for adults are adapted to children with MS.[93] Additional studies are needed to establish the role of biologic response modifiers in patients with progressive MS and in children with MS.

Despite advancements in treatment, many patients fail initial biologic response modifier therapy with glatiramer acetate or IFNβ, primarily due to intolerable adverse effects or perceived inadequate efficacy.[20,21] Clinical trials have shown that patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor response, achieve a significant reduction in relapse rates and a delay in disease and disability progression.[20-23] The guidelines suggest that all first-line MS biologic response modifiers should be made accessible, and the choice of initial treatment should be based on patient-specific factors.[15,88] Premature discontinuation rate is high among patients with MS; therefore factors that will maximize adherence should be considered when initiating therapy. Failure with one first-line agent does not necessitate failure to another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different biologic response modifier.[20,21] With regard to the oral agents, fingolimod has been associated with post-marketing cases of cardiac-related death and thus requires substantial cardiac monitoring and is contraindicated in patients with pre-existing cardiovascular conditions.[2] Teriflunomide has two black box warnings regarding hepatotoxicity and its risk of teratogenicity.[8] Dimethyl fumarate, although it has limited post-marketing data, appears to have the most mild side effect profile with its most common adverse events being flushing and gastrointestinal effects.[1] Future head-to-head trials and guideline recommendations are necessary to confidently determine the place in therapy of each agent.

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