Optimizing the initial choice and timing of therapy in relapsing-remitting multiple sclerosis

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Abstract: With 12 available US Food and Drug Administration approved medications for the treatment of relapsing multiple sclerosis (MS), choosing an initial therapy is no longer a straightforward task. Each disease-modifying therapy (DMT) has a distinct risk–benefit profile and each patient is an individual. Therefore, the development of a simple algorithm to apply in selecting initial therapy is not feasible. Instead, the prescribing physician must consider many factors related to the treatments themselves, such as efficacy, safety, and tolerability, while also taking into account a particular patient’s disease characteristics, personal preferences, comorbid illnesses and reproductive plans. The efficacy of each drug may be assessed through clinical trial data, although these data are limited by scarcity of direct comparisons among the different agents and lack of availability of biomarkers to predict an individual patient’s response. Differences in safety profiles help to distinguish the various DMTs and influence selection of agent; both the known safety concerns, which can be addressed with risk mitigation and monitoring strategies, and the potential for yet undiscovered safety issues must be assessed, and an individual patient’s comfort level with the risks and ability to comply with monitoring must be determined. Potential issues related to tolerability, which largely relate to matters of patient personal preference and lifestyle, should also be factored into the decision-making process. With regard to the timing of therapy initiation, it must be acknowledged that long-term benefits of early DMT have not yet been definitively demonstrated. Nonetheless, starting DMT early in the MS disease course has been shown to have a beneficial effect on relapse prevention, and appears to curtail the atrophy and neurodegenerative changes that are now known to begin at disease onset. Although under certain circumstances there are acceptable reasons for deferring treatment, it is generally recommended that DMT is initiated early in the disease course.

Keywords: multiple sclerosis, treatment, disease modifying therapy, timing, efficacy, safety, tolerability

Choice of agent

There are currently 12 disease-modifying therapies (DMTs) that are approved by the US Food and Drug Administration (FDA) for the treatment of relapsing multiple sclerosis (MS). Because each of these has a distinct risk–benefit profile and each patient is an individual, the development of a simple algorithm to apply in selecting initial therapy is not feasible. Instead, the prescribing physician must consider many factors related both to the treatments themselves, such as efficacy, safety, monitoring, and tolerability, as well as factors related to the patient, such as

comorbid illnesses, personal preferences and attitudes, and reproductive considerations. In weighing each consideration, it is necessary for the physician to understand not only the predicted severity of the patient’s disease (which itself is hard to ascertain) and the potential benefits and risks of the numerous agents themselves, but also to understand the patient’s priorities. The physician must assess the patient’s attitudes towards various risks, ability to comply with dosing and monitoring regimes, and lifestyle factors. One patient may prioritize long-term safety and prefer the drug that has been on the market the longest,

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while another may prioritize efficacy and feel comfortable with a higher degree of uncertainty regarding safety. Yet a third may prioritize ease of administration above all else. Because there is often no single 'best' choice, the decision must be made jointly by the patient and the physician after careful consideration of all of these factors.

Here we will discuss general issues related to efficacy, safety, and tolerability, and then review each of the various FDA-approved medications with regard to each of these factors. The discussion of each treatment option is not meant to be exhaustive, especially with regard to all potential adverse effects. Rather, the features essential for the consideration of each agent as an initial therapy are highlighted (and summarized in Table 1).

Efficacy

Efficacy of DMT naturally plays a significant role in the choice of initial DMT. From a purely medical perspective, it is not necessary to withhold a more efficacious drug from a patient with mild or moderate disease, but for a patient with more aggressive disease at onset efficacy is often a higher priority that trumps other factors. Unfortunately, there is no currently available biomarker to predict response to particular treatments at the individual patient level. Efficacy must therefore be discussed at the population level through clinical trial data. There are a number of large, well designed, double-blind, placebo-controlled studies evaluating the efficacy of the approved agents. However, considerations of efficacy are complicated by the fact that data directly comparing the different agents are scarce. Relatively few clinical trials have directly compared the various DMTs 'head to head' within the same trial; more often therapies were compared with placebo. Because of inter-trial differences, including differences in study populations and in outcome measures, it is not scientifically sound to compare agents across trials. Nonetheless, for practical purposes, physicians are sometimes pressed to do this in discussions with patients, and must make extrapolations.

In understanding the limitations of our efficacy data, it is also important to note that the data largely relate to prevention of clinical relapses and inflammatory magnetic resonance imaging (MRI) activity (new T2 lesions, gadolinium-enhancing lesions). The relationship between prevention of

inflammatory activity and the prevention of concurrent or subsequent neurodegeneration and disease progression with resulting disability remains unclear and somewhat controversial. Disability endpoints such as confirmed increase in disability at 6 months have been variably satisfied in clinical trials. Moreover, even when these endpoints are met it remains unclear whether these effects are achieved *via* relapse prevention or *via* progression and whether the benefits would be sustained long term regarding the transition to progressive disease. As the majority of MS-related disability is related to the progressive phase of the illness, discussions regarding efficacy of DMTs would ideally include the ability to prevent or mitigate progressive disease. Unfortunately these questions cannot be properly answered with current clinical trial design since most large clinical trials follow subjects rigorously for only 2 years. Currently available long-term data are riddled with biases and therefore nearly impossible to interpret. In addition, none of these agents has yet been found to be effective in the nonrelapsing MS patient population. Therefore, we must understand that the relationship between relapse prevention and long-term disability prevention is far from established.

Safety

All MS medications target the immune system and therefore have the theoretical potential to predispose patients to infection, reduce surveillance of neoplasms, or induce autoimmune disease, among other potential adverse effects. In general, there are two types of safety concerns related to MS medications: safety concerns of which the medical community is aware and those which have not yet arisen. The known risks can be mitigated through careful patient selection and close monitoring, however the latter, by definition, is harder to anticipate. The length of collective experience with interferon (IFN) and glatiramer acetate (GA) provides an increased comfort level regarding safety compared with the newer agents. Natalizumab's risk profile is fairly well established after 10 years of postmarketing experience. The newer oral agents carry known risks and overall have reasonable safety profiles, however it is possible that safety concerns will arise that were not exposed in clinical trials or early postmarketing data, either because exposure has not reached the required threshold of total patient years or because long-term data are insufficient.

Table 1. Disease Modifying Therapies Appropriate for Initial Therapy Choice.

Disease Modifying Therapy	Dose/ Route/ Frequency	Primary Mechanism of Action	Major Phase III Placebo Controlled Trials and Primary Outcomes*†	Key Potential Side Effects and Monitoring Requirements
IFN β -1a (Avonex)	30 μ g IM weekly	Suppresses Th1 cells, stimulates Treg cells, reduces antigen presentation	MSCRG- 18% reduction in ARR	Flu-like symptoms, LFT [†] abnormalities, leucopenia, depression, injection site reactions -check LFT s and WBCs [†]
IFN β -1a (Rebif)	22 or 44 μ g SC three times weekly		PRISMS- 29% reduction in ARR (22 μ g dose); 33% reduction in ARR (44 μ g dose)	
PegIFN β -1a (Plegridy)	125 μ g SC every 14 days		ADVANCE -36% reduction in ARR	
IFN β -1b (Betaseron/ Extavia)	0.25mg SC every other day		IFN beta MS study group- 34% reduction in ARR (8MIU dose)	
Glatiramer Acetate (Copaxone)	20mg SC daily or 40mg SC three times weekly	Induces Th1 to Th2 shift, MHC binding in periphery, inhibits myelin basic protein T cell response	The Copolymer 1 Multiple Sclerosis Study Group (20mg daily)- 29% reduction in ARR GALA (40mg TIW)- 34% reduction in ARR	Injection site reactions, post injection systemic reactions, lipoatrophy
Natalizumab (Tysabri)	300mg IV every 4 weeks	Monoclonal antibody against the alpha-4/ beta-1 integrin adhesion molecule, inhibits lymphocyte trafficking from blood to CNS	AFFIRM- 68% reduction in ARR; 42% reduction in sustained progression of disability at two years	Risk of PML [†] in JCV [†] Ab positive patients, allergic reactions -Assess for JCV Ab every 6 months -Consider periodic assessment of CBC and LFTs
Fingolimod (Gilenya)	0.5mg PO daily	Binds to sphingosine-1 phosphate receptors and inhibits lymphocyte egress from lymph nodes	FREEDOMS-54% reduction in ARR FREEDOMS II- 48% reduction in ARR	Bradycardia and AV block after first dose, macular edema, herpes virus infections, possibly basal cell carcinoma, one case of PML in patient without other risk factors -EKG prior to first dose and 6 hrs cardiac monitoring after first dose -ophthalmology evaluation prior to first dose and at 3-4 months -vaccinate for varicella if not previously exposed -lymphocyte count monitoring -consider dermatologic evaluations
Teriflunomide (Aubagio)	7mg (approved only in the US) or 14mg PO daily	Blocks denovo pyrimidine synthesis pathway exerting a cytostatic effect on peripheral B and T cells	TEMPO- 31%(7mg) and 32% (14mg) reduction in ARR TOWER- 22% (7mg) and 36% (14mg) reduction in ARR	Abnormal LFTs, tuberculosis reactivation, hair thinning, diarrhea, teratogenic in animals -LFTs prior to starting treatment and monthly for first 6 months then periodically -CBC prior to starting treatment and periodically

(Continued)

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Disease Modifying Therapy	Dose/ Route/ Frequency	Primary Mechanism of Action	Major Phase III Placebo Controlled Trials and Primary Outcomes*†	Key Potential Side Effects and Monitoring Requirements
Dimethyl Fumarate (Tecfidera)	240mg PO Twice daily	Exact mechanism unknown, may defend against oxidative stress by activating the nuclear 1 factor (erythroid-derived-2)-like 2 (Nrf2) pathway	DEFINE- 41% reduction in proportion of patients with relapses over 2 years CONFRIM- 44% reduction in ARR	Flushing, GI upset, leucopenia, one case of PML in patient with prolonged low lymphocyte count - CBC prior to starting treatment, 6 months after starting drug, and every 6-12 months thereafter -LFTs prior to starting treatment and periodically thereafter
*See main text for references. *Only placebo-controlled trials are included, see main text for trials with active comparators. †Ab, antibody; ARR, annualized relapse rate ; CBC, complete blood count; CONFIRM, Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis; DEFINE, Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; GI, gastrointestinal; IFN, interferon; JCV, John Cunningham virus; LFT, liver function test; MHC, major histocompatibility complex; MS, multiple sclerosis; MSCRG, Multiple Sclerosis Collaborative Research Group; PEG, pegylated; PML, progressive multifocal leukoencephalopathy; PRISMS, Prevention of Relapses and Disability by IFN β -1a Subcutaneously in Multiple Sclerosis; TEMSO, Teriflunomide Multiple Sclerosis Oral trial; Th1, T helper 1; TOWER, Teriflunomide Oral in People With Relapsing Remitting Multiple Sclerosis; WBC, white blood cell.				

The MS community became painfully aware of this lesson of ‘unknown unknowns’ when unexpected cases of progressive multifocal leukoencephalopathy (PML), an opportunistic, potentially fatal brain infection first emerged in patients with MS on natalizumab. These cases emerged during the open-label extension phase of the SENTINEL study that compared natalizumab plus weekly intramuscular IFN β -1a with IFN alone [Rudick *et al.* 2006]. The drug was withdrawn from the market in 2005 and subsequently reintroduced with a risk mitigation strategy that has evolved over the years as risk stratification and monitoring plans developed. Similarly, a case of PML emerged in a dimethyl fumarate patient only in an extension phase of the study (<http://www.fda.gov/Drugs/DrugSafety/ucm424625.htm>) despite no evidence of PML occurring in initial phase III clinical trials. This, however, was not completely unexpected given that the disease had been known to occur rarely in patients with psoriasis taking related fumarate preparations in the setting of lymphopenia [Ermis *et al.* 2013; Van Oosten *et al.* 2013a, 2013b].

Given that MS is frequently diagnosed in women in their childbearing years, reproductive safety of DMT is of particular concern when selecting

initial therapy. Due to the rarity of clinical trials in pregnant women, there is a paucity of conclusive data related to the safety of DMTs during pregnancy as well as breastfeeding. The FDA currently assigns pregnancy categories A, B, C, D, and X based on animal data, as well as small case studies, and registries (though the FDA plans on moving to a more qualitative, descriptive way of evaluating medications by the Spring of 2015: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm425317.htm>). GA is the only DMT with a pregnancy category rating of B; the others have pregnancy category ratings of C with the exception of teriflunomide which has a rating of X due to teratogenic potential. This is an extremely important part of the initial discussion. The approach to a patient who intends to try to conceive in the next few months is very different from the approach to a patient who does not intend to have children.

Physicians and patients must be aware of the known risks involved with each medication, the availability and limitations of strategies used to mitigate those risks, and the potential for unknown long-term risks with the newer medications. Each physician and each patient may have a different standard for what constitutes an acceptable level of risk in a given situation.

Tolerability

Tolerability relates to issues such as side effects, route and schedule of administration, and burden of monitoring requirements. It is perhaps the most individualized issue with regard to medication choice, and relates strongly to matters of patient personal preference and lifestyle. Potential side effect profiles may be more or less acceptable to different patients and each patient will have different experiences with side effects which cannot be anticipated. A patient whose daily schedule is erratic may find it overly burdensome to remember to take a capsule twice daily and prefer a monthly infusion, whereas someone who travels frequently may not be able to commit to going to the same infusion center every four weeks but is easily able to take a pill twice a day. Some patients are extremely averse to injections, some to the point that when these were the only available options they chose to go untreated. Others barely mind injections at all. From the physician's perspective finding a medication that is tolerable is important not only for maintaining the best possible quality of life for the patient but for maximizing patient adherence to medication.

IFN β (IFN β -1a: Rebif, Avonex, Plegridy; IFN β -1b: Betaseron, Extavia)

IFNs, which are cytokines with immunomodulatory properties, have been on the market since 1993 when Betaseron became the first FDA approved MS therapy (Bayer AG, Leverkusen, Germany). There are two types of IFN β : IFN β -1a whose formulations include Rebif, Avonex, and Plegridy, (Biogen, Cambridge, United States) and IFN β -1b, whose formulations include Betaseron (sold in Europe under the trade name betaferon) and Extavia (Bayer AG, Leverkusen, Germany; Novartis, Basel, Switzerland). Both forms are produced by recombinant technologies: IFN β -1a is produced in the bacterial cell (*Escherichia coli*) whereas IFN β -1b is produced in mammalian cells. All formulations are injections, either subcutaneous or intramuscular and have different dosages and frequency of administration. The most recently approved IFN, Plegridy, takes advantage of the pegylation process (attachment of polyethylene glycol chain) to prolong the duration of time within the circulation and reduce the frequency of administration to once every 2 weeks.

Efficacy

IFNs such as IFN β -1a 44 μ g subcutaneously three times weekly (Rebif) and IFN β -1b 250 μ g

subcutaneously every other day (Betaseron, Extavia) have all been found to reduce relapses by approximately one-third compared with placebo. IFN β -1b, administered at 250 μ g subcutaneously every other day was approved as the result of a phase III clinical trial published in 1993 by the IFNB MS Study Group. In this multicenter, randomized, placebo-controlled, 2-year trial, two doses of IFN β -1b, 1.6 MIU (0.05 mg) and 8 MIU (0.25 mg), injected subcutaneously every other day were compared with placebo in 372 patients. Both IFN dosages reduced relapse rates and increased the proportion of patients remaining relapse free compared with placebo. The annualized relapse rate (ARR) in the 1.6 MIU group was 0.84 compared with 1.17 in the 8 MIU group, and 1.27 in the placebo group. In the higher dose IFN group severity of relapses as well as evidence of MRI activity were also reduced. However, there was no statistically significant difference in terms of 3-month sustained Expanded Disability Status Scale (EDSS) progression between the groups [IFNB MS Study Group, 1993]. Follow-up data on these patients demonstrated prolonged efficacy in terms of relapse reduction; after 5 years on the study drug, IFN β -1b continued to reduce ARR by one-third compared with placebo in each of the 5 years studied [IFNB MS Study Group and University of British Columbia MS/MRI Analysis Group, 1995].

High-dose formulations of IFN β -1a have also been shown to reduce relapse rates in the range of one-third. The PRISMS (Prevention of Relapses and Disability by IFN β -1a Subcutaneously in MS) Study Group randomized 560 patients with relapsing–remitting MS (RRMS) to 2 years of either 22 or 44 μ g subcutaneous injections three times weekly or to placebo. Relapse rates were decreased in both groups; in the 44 μ g group relapses were reduced by 33%. It also prolonged time to first relapse by 5 months and delayed mean sustained accumulation of disability from 12 to 22 months [PRISMS Study Group, 1998].

Three large trials directly compared the efficacy of IFN β formulations with that of GA, the only other standard treatment option at the time, and found the efficacy to be comparable. The Rebif *versus* GA in Relapsing MS Disease (REGARD) study randomized 764 treatment-naïve RRMS participants to either IFN β -1a 44 μ g subcutaneously three times weekly or GA 20 mg subcutaneously daily and found no significant difference in time to first relapse or in MRI parameters, except that the IFN group had significantly

fewer enhancing lesions [Mikol *et al.* 2008]. The Betaseron *versus* Copaxone in MS with Triple-Dose Gadolinium and 3-tesla MRI Endpoints (BECOME) study randomized 75 RRMS or clinically isolated syndrome (CIS) participants to IFN β -1b 250 μ g subcutaneously every other day or GA 20 mg subcutaneously daily and found no difference between the groups in combined active lesions (the primary outcome) or clinical relapses [Cadavid *et al.* 2009]. The Betaferon Efficacy Yielding Outcomes of a New Dose (BEYOND) trial randomized RRMS participants in a 2:2:1 fashion to IFN β -1b 250 μ g subcutaneously every other day, IFN β -1b 500 μ g subcutaneously every other day, or GA 20 mg subcutaneously daily, and found no significant difference in relapse risk between the groups [O'Connor *et al.* 2009].

The most recently approved IFN formulation, 125 μ g of pegylated IFN β -1a dosed subcutaneously every 2 weeks (Plegridy), appears to have an efficacy comparable to that of the other high-dose IFNs, though it has never been directly compared. In year one of the ADVANCE trial, 125 μ g of pegylated IFN β -1a was dosed either every 2 or 4 weeks and compared with placebo. Both treatment arms showed a reduction in ARR compared with placebo: 35.7% reduction in the every 2-week dosage group and 27.5% in the every 4-week dosage group. Both groups also showed a reduction in the proportion of subjects with disability progression [Calabresi *et al.* 2014a]. In year two of the trial, this efficacy was maintained [Kieseier *et al.* 2014].

Lower dose IFNs such as IFN β -1a 30 μ g intramuscularly weekly (Avonex) have shown a lower rate of relapse reduction. Jacobs and colleagues compared IFN β -1a 30 μ g administered intramuscularly once weekly with placebo and found an ARR reduction of 18.3% in IFN-treated patients. They also reported significantly fewer patients with sustained disability progression, their primary outcome (21.9% *versus* 34.9%), which had not been shown to be the case for IFNs in other trials [Jacobs *et al.* 1996]. However, multiple methodological concerns were raised regarding these disability claims [Rice and Ebers, 1998].

The open-label INCOMIN (Independent Comparison of IFN) study randomized 188 patients to either IFN β -1b 250 μ g subcutaneously every other day or IFN β -1a 30 μ g intramuscularly once weekly for a 2-year period. Over

2 years, 51% of patients given IFN β -1b remained relapse free whereas only 33% of patients given IFN β -1a remained relapse free, a relative relapse risk reduction of 0.76. The group given IFN β -1b also performed better in terms of proportion of patients free from new lesions, with a relative risk reduction of 0.6 [Durelli *et al.* 2002]. The EVIDENCE trial compared two IFN β dosing regimens: subcutaneous IFN β -1a 44 μ g three times weekly and intramuscular IFN β -1a 30 μ g once weekly. Patients and treating physicians were not blinded to the treatment arm, though the assessor was blinded. The high-dose, high-frequency IFN was found to be superior to the low-dose, low-frequency IFN in terms of primary endpoint, proportion of relapse-free patients at 24 weeks (75% *versus* 63%), and the difference was maintained throughout the remainder of the trial, in which patients were followed for a minimum of 1 year [Schwid and Panitch, 2007]. These trials do have some methodologic limitations, including lack of blinding, and in the case of the INCOMIN trial, differences in baseline characteristics between the two groups [Vartanian, 2003].

The Combi-Rx trial provided data comparing low-dose IFN with GA. This 3-year double-blind, double-dummy trial designed to assess the safety and efficacy of combined IFN and GA treatment randomized 1008 patients to three arms: a GA arm, a weekly IFN β -1a 30 μ g intramuscularly arm, and a combination arm. The GA arm reduced the relapse risk by 31% compared with the IFN arm, and the combination of the two agents provided no advantage over GA alone in relapse reduction [Lublin *et al.* 2013].

Safety

IFNs have been used for over 20 years, and at this point potential safety issues are well established. It is theoretically possible that pegylated versions of IFNs, which have only recently come to the market, will be shown to have additional safety issues, though based on experience with other pegylated products there is no particular reason to suspect this.

All IFN formulations have similar safety issues. Compared with placebo, each has been shown to be associated with asymptomatic decreases in total white blood cell (WBC) count, lymphocyte count, granulocyte count, as well as increases in liver function tests (LFTs) including aspartate aminotransferase or alanine aminotransferase

(ALT) in a minority of patients. These laboratory abnormalities were most likely to occur relatively early and only very rarely necessitated drug discontinuation in clinical studies [IFNB MS Study Group, 1993; IFNB MS Study Group and University of British Columbia MS/MRI Analysis Group, 1995; PRISMS Study Group, 1998; Durelli *et al.* 2002; Calabresi *et al.* 2014a]. It is recommended that blood counts and hepatic function are checked periodically; the authors of this article typically check them every 3 months.

IFNs may lead to or worsen depression, with some studies showing increased rates of depression in IFN-treated patients [IFNB MS Study Group and University of British Columbia MS/MRI Analysis Group, 1995], though others found no difference compared with placebo [PRISMS Study Group, 1998] or GA [Mikol *et al.* 2008; O'Connor *et al.* 2009; Lublin *et al.* 2013]. Nonetheless, IFNs should be used with caution in patients with a history of existing depression.

There have been rare incidences of cutaneous necrosis of IFN injection sites [Balak *et al.* 2012].

IFNs are rated as pregnancy category C. In doses higher than those used in humans, IFNs have been shown to have an abortifacient effect in animals. Studies have shown mixed results in humans. Based on a review of the literature, Lu and colleagues concluded that the available higher-quality studies showed no increased rate of spontaneous abortion. However, neonates who were exposed to IFNs *in utero* did show lower mean birth weight, lower mean gestational age, and an increased incidence of preterm birth [Calabresi *et al.* 2007; Lu *et al.* 2012]. Analysis of a global database of 425 pregnancies exposed to IFN β -1a followed prospectively determined that there was no increased risk of either spontaneous abortions or congenital anomalies [Sandberg-Wollheim *et al.* 2011]. Many practitioners recommend discontinuing IFN prior to attempts at conception, though in certain cases, there are those who argue it may be acceptable to continue IFNs up to conception, or even throughout pregnancy [Coyle *et al.* 2004; Fragoso, 2013; Ghezzi *et al.* 2013].

Tolerability

Tolerability to IFNs can be limited by injection-site reactions and flu-like symptoms. All IFNs are administered *via* injection: Avonex *via* intramuscular injection, the others *via* subcutaneous

injection, which range in frequency from once every other day (Betaseron, Extavia) to once every 2 weeks (Plegridy). Injection site reactions, including pain, pruritus, induration, and swelling, can occur with IFNs, though they are less frequent than with GA [Mikol *et al.* 2008; O'Connor *et al.* 2009; Calabresi *et al.* 2014a; IFNB MS Study Group and University of British Columbia MS/MRI Analysis Group, 1995]. Each manufacturer provides complimentary nursing services to train patients regarding injections and troubleshoot any injection-related issues.

Flu-like symptoms, including myalgias, arthralgias, headache, pyrexia, and fatigue, typically occur within 24 h postinjection and occur in up to 50% of patients [Mikol *et al.* 2008; O'Connor *et al.* 2009; Calabresi *et al.* 2014a; IFNB MS Study Group and University of British Columbia MS/MRI Analysis Group, 1995] though in clinical trials discontinuations of the drug for this reason were rare. In general, flu-like reactions decrease significantly within the first few months of treatment. It is unclear whether the decrease is as robust when administration is less frequent, as in the case of pegylated IFNs, though naturally the decreased frequency of administration means fewer opportunities for flu-like symptoms. When necessary, flu-like symptoms can be mitigated by premedicating with nonsteroidal anti-inflammatory drugs or acetaminophen.

Glatiramer acetate

GA (Copaxone (Teva Pharmaceutical Industries, Petah Tikva, Israel)) is an immunomodulator consisting of random polymers of four amino acids designed to be similar to myelin basic protein. The 20 mg subcutaneous daily formulation was approved by the FDA in 1997 and the 40 mg subcutaneous three times weekly formulation was approved in 2014.

Efficacy

Similar to high-dose IFN, GA reduced relapses by approximately one-third in clinical trials [Johnson *et al.* 1995, 1998; Martinelli Boneschi *et al.* 2003]. A multicenter, phase III, 2-year study of 251 patients with RRMS found a mean ARR of 0.59 for GA compared with 0.84 for placebo, a 29% reduction [Johnson *et al.* 1995]. A total of 203 of these patients enrolled in an extension study in which blinding was continued for up to a total of 35 months. After including the extended period data, the mean ARR was 0.58 for patients

receiving GA *versus* 0.81 for patients receiving placebo, a 29% reduction in relapse rates [Johnson *et al.* 1998]. There was no statistically significant difference in sustained progression of disability, despite trends in this direction. When directly compared with IFN, GA has been shown to be equally as effective as high-dose IFN β -1a and IFN β -1b [Mikol *et al.* 2008; O'Connor *et al.* 2009] and more efficacious than low-dose IFN β -1a [Lublin *et al.* 2013]. Although not compared directly with the 20 mg daily formulation, the 40mg three times a week formulation appears to be roughly comparable to the 20mg daily formulation when measured against placebo. In a randomized, double-blind trial in 1404 patients, GA 40 mg three times a week was associated with an ARR of 0.331 compared with 0.505 in the placebo-controlled group, a 34% reduction [Khan *et al.* 2013].

Safety

GA seems to be the safest of the MS medications; there have been no significant safety issues reported in any clinical trials or in the almost 20 years of postmarketing experience. GA is the only medication for which no regular laboratory monitoring is required. However, there have been rare reports of acute hepatotoxicity in patients receiving GA [Subramaniam *et al.* 2012; Makhani *et al.* 2013; Antezana *et al.* 2014; La Gioia *et al.* 2014]. In each of these cases, liver function normalized upon drug withdrawal. Given the infrequency of these cases, it is not the authors' practice to routinely check labs in patients with no systemic complaints.

It is important to note that while no DMT is approved for women who are attempting to conceive, are pregnant, or are breastfeeding, GA is the only DMT with a pregnancy category rating of B. The others have pregnancy category ratings of C, with the exception of teriflunomide which has a rating of X. There are no adverse effects of GA on fetal organogenesis in animals, and observational studies in patients with MS have failed to identify any adverse pregnancy outcomes such as lower birth weights, congenital defects, miscarriages, or prematurity [Lu *et al.* 2012; Fragoso *et al.* 2010; Giannini *et al.* 2012]. Some practitioners do in fact recommend continuing pregnant patients on GA throughout the course of pregnancy [Fragoso, 2014].

There is not much known about the use of GA during lactation, but pharmacokinetic information

indicates that GA is rapidly degraded after administration, and therefore would not be expected to be present in breast milk. Even if GA did appear in breast milk, it would likely be degraded in the infant's gastrointestinal (GI) tract. There are some small studies that show no adverse effect of maternal GA on breastfed babies [Fragoso, 2014]. Some physicians therefore feel comfortable with patients breastfeeding while on GA.

Tolerability

Injection site reactions and lipoatrophy are the most common adverse effects with GA [Johnson *et al.* 1995, 1998; Khan *et al.* 2013]. Local injection site reactions may include erythema, induration, and pain, and are relatively common, occurring in up to two-thirds of patients, though usually they are mild to moderate in severity, and are typically short lived [Johnson *et al.* 1995, 1998; Khan *et al.* 2013].

Lipoatrophy, small divets in the fatty tissue that occur with years of repeated subcutaneous injection, may be a cosmetic issue for some patients. It is conceivable that the three times a week formulation, which contains twice the dosage in the same volume of liquid as the daily formulation, will result in a decreased rate of associated lipoatrophy compared with the daily formulation but this has not been formally studied.

An immediate, systemic postinjection reaction can occur sporadically with GA, and has been reported to occur after 2% of injections [Mikol *et al.* 2008]. Such systemic reactions can consist of chest tightness, palpitations, anxiety, or dyspnea, and can be mistaken for a myocardial infarction or other emergency in a patient who is not forewarned. Though frightening, it is benign and self limited, usually resolving in 30 s to 30 min.

Natalizumab

Natalizumab (Tysabri (Biogen, Cambridge, United States)) is a humanized monoclonal antibody that inhibits α -4 integrin, a transmembrane leukocyte receptor. It thereby prevents leukocyte adhesion to vessel walls and subsequent migration across the blood-brain barrier. It is administered *via* intravenous infusion once every 4 weeks. The European Medicines Agency licensed natalizumab as a first-line agent only for patients with high levels of disease activity, although FDA licensing has not included these stipulations.

Efficacy

Natalizumab is widely considered to be the most efficacious of the approved agents in terms of relapse prevention. A randomized, placebo-controlled study comparing 300 mg intravenous natalizumab every 4 weeks with placebo (AFFIRM) met both of its primary endpoints, significantly reducing the rate of clinical relapse by 68% as well as reducing the risk of sustained progression of disability at 2 years by 42%. New MRI activity was dramatically decreased; there was an 82% reduction in new T2 lesions and a 93% reduction in gadolinium-enhancing lesions at 2 years [Polman *et al.* 2006]. An additional study (SENTINEL) showed that natalizumab in combination with IFN β -1a was significantly more effective than IFN alone with a 54% reduction in relapses at 1 year and a 24% decrease in the risk of sustained disability progression [Rudick *et al.* 2006]. Although lack of head-to-head trials with other agents makes direct comparison impossible, the fact that the reduction in ARR compared with placebo approaches twice that of many other agents (approximately two-thirds *versus* one-third for the injectables and teriflunomide), as well as anecdotal clinical experience over the last 10 years, has led to the general consensus that this is likely the most effective of the approved agents. The one exception may be the newly approved alemtuzumab, though at the moment this medication is not being recommended as initial therapy due to safety concerns (see below).

Safety

The primary safety concern with natalizumab is the associated risk of PML, a serious, potentially fatal brain infection caused by the John Cunningham (JC) polyoma virus that had previously been known to affect only those who were severely immunosuppressed, such as patients with late-stage acquired immunodeficiency syndrome; 50–60% of the population have been exposed to the virus as evidenced by positive antibodies. Symptomatology of initial JC virus exposure is unknown. Following primary exposure the virus resides dormant in the kidneys and possibly the lymphoid organs. However, in the setting of immunologic alterations the virus can infect glial cells with devastating consequences. After approval of the drug in 2004, two cases of PML occurred in patients with MS receiving both natalizumab and IFN β -1a in the open-label phase of the SENTINEL trial. This led to the

withdrawal of natalizumab from the market in 2005. The drug was reintroduced in the USA in 2006 with the caveat that it was to be used only as monotherapy and with the instatement of a risk mitigation and monitoring program. Since reintroduction, a number of cases of PML have been revealed in patients on monotherapy (464 as of May 2014) [Chahin and Berger, 2014] and an overall incidence of 2 in 1000 patients has been estimated.

Over the years there has also been a better understanding of risk factors for developing PML. Three major risk factors have emerged: presence of serum antibodies to the JC virus (JCV ab), history of prior immunosuppression, and length of natalizumab exposure greater than 2 years [Bloomgren *et al.* 2012; Sorensen *et al.* 2012]. Rates of PML are estimated to climb from under 0.1/1000 in patients who are seronegative for the JCV ab, to 0.5/1000 for JCV positive patients without prior immunosuppressants in the first 2 years, to 4.6/1000 for JCV ab positive patients without prior immunosuppressants after 2 years, to 11.1/1000 for JCV ab positive patients with a history of immunosuppression who have been exposed to natalizumab for over 2 years [Bloomgren *et al.* 2012]. Prior to starting therapy with natalizumab, patients must be risk stratified for the presence of serum JCV ab. In JCV ab negative patients, the authors believe natalizumab can be safely used as an initial therapy. The risk–benefit ratio is certainly favorable in patients with aggressive disease onset, but also reasonable for those with seemingly mild disease onset who are JCV ab negative. After starting therapy, it is recommended JCV ab status is checked at least every 6 months as patients can be subsequently exposed to the virus. There is a negative to positive seroconversion rate of the two-step enzyme-linked immunosorbent assay (ELISA) assay of 1–2% per year [Gorelik *et al.* 2010].

The authors of this review would generally not recommend using natalizumab as initial therapy in a JCV ab positive patient, especially in a patient with seemingly mild disease at onset. Some may feel it would be reasonable to use natalizumab as the initial therapy despite JCV ab positivity for a patient with aggressive onset of MS with the plan to limit the length of therapy to less than 2 years. However, of potential concern is that withdrawal of natalizumab has, in some studies, been reported to precipitate increased inflammation [Tubridy *et al.* 1999]. However, other studies have not

shown inflammatory activity post-natalizumab to be higher than that pre natalizumab or in patients on placebo [O'Connor *et al.* 2011a; Sorensen *et al.* 2014], arguing against a true rebound effect. Choosing natalizumab as the initial agent in a JCV ab positive patient necessitates at a minimum discussing what agent will be used next and how the transition will be managed.

Natalizumab may cause an allergic reaction, which has been reported to occur in 1–4% of patients [Polman *et al.* 2006; O'Connor *et al.* 2014], with serious allergic reactions occurring in a fraction of these cases. It appears that hypersensitivity reactions are sometimes linked to the presence of anti-natalizumab antibodies that occur in approximately 6% of patients [Calabresi *et al.* 2007]. These antibodies develop postexposure and therefore are not useful for risk stratification prior to therapy initiation. Allergic reactions necessitate permanent discontinuation of natalizumab.

Tolerability

Natalizumab is generally very well tolerated. In clinical trials, the only other adverse event occurring more often in patients treated with natalizumab compared with placebo was fatigue [Polman *et al.* 2006]. However, some postmarketing studies have in fact reported decreases in self-reported measures of fatigue in patients on natalizumab [Wilken *et al.* 2013]. Occasionally there can be infusion-related reactions other than allergic reactions, including headache.

Fingolimod

Fingolimod (Gilenya (Novartis, Basel, Switzerland)), the first oral medication to receive FDA approval in 2010, is a sphingosine-1-phosphate receptor modulator. It functionally antagonizes the receptor, preventing the egress of lymphocytes from secondary lymphatic tissue into the peripheral circulation and thereby restricting them from entering the central nervous system (CNS). Although not the case in the USA, many European countries have restricted use of fingolimod as a first-line therapy to those patients with highly active disease.

Efficacy

The FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis) and TRANSFORMS (Trial Assessing Injectable IFN *versus* FTY 720 in Relapsing

Relapsing Multiple Sclerosis) studies evaluated the effect of fingolimod on relapse reduction and led to the approval of Gilenya as the first oral medication for MS. In FREEDOMS, two doses of fingolimod (1.25 and 0.5 mg daily) were compared with placebo in a 2-year trial involving 1272 patients. The ARR was 0.18 in those assigned to 0.5 mg of fingolimod, the dose ultimately approved, compared with 0.40 in those assigned to placebo, translating into a relative risk reduction of 54%. This dose of fingolimod was found to reduce the probability of disability progression sustained over 3 months to 17.7% compared with 24.1% in the placebo group [Kappos *et al.* 2010]. FREEDOMS II, a second randomized, double-blinded, placebo-controlled, 2-year study of fingolimod that involved 1083 patients, similarly found a 48% reduction in the 0.5 mg fingolimod group compared with the placebo group, though failed to find a difference in disability progression [Calabresi *et al.* 2014b].

TRANSFORMS directly compared the same two doses of fingolimod with intramuscular IFN β -1a at a weekly dose of 30 μ g in a year-long double dummy study. The ARR was found to be lower in both fingolimod groups than the IFN group. The group that received the 0.5 mg daily dose had a relapse rate of 0.16 compared with 0.33 in the IFN group, a 52% reduction in ARR. There was no significant difference between the three arms with regards to disability progression [Cohen *et al.* 2010].

Safety

Fingolimod has several potential safety concerns. These include infectious concerns that stem from the sequestration of lymphocytes within the lymph nodes. They also include first-dose bradycardia, hypertension, and macular edema that result from the fact that the drug's targets, sphingosine-1-phosphate receptors, are ubiquitous throughout the body.

Due to the decreased lymphocyte count in the systemic circulation, there is a theoretical increased risk for infection with fingolimod. A slight increase in herpes infections was documented in the 1.25 mg group in the TRANSFORMS study, though this was not noted in FREEDOMS. Although most infections were considered mild, two TRANSFORMS patients receiving the 1.25 mg dose died of herpes-related infections: one from disseminated zoster and one from herpes simplex encephalitis. As a result, the FDA advises checking

antibody titers in patients who do not have a clear history of varicella zoster infection or vaccination. If patients do not have antibodies, they should be vaccinated with two doses of Varivax/Varilix (Merck & Co., Kenilworth, United States; GlaxoSmithKline, Brentford, England) separated by 4 weeks, and treatment with fingolimod should begin no sooner than 1 month after the second dose [Arvin *et al.* 2015]. This can significantly delay DMT initiation. Though not seen in clinical trials, one case of PML in a patient who had no prior natalizumab exposure was reported by the manufacturer in February 2015 (<http://www.fda.gov/Drugs/DrugSafety/ucm456919.htm>). This diagnosis was suspected based on MRI findings and confirmed *via* positive JC virus PCR in the cerebrospinal fluid (CSF) in an asymptomatic patient.

In clinical studies, the absolute lymphocyte count (ALC) dropped by 73% to a mean of 0.5×10^9 /liter and fingolimod was discontinued if it dropped below 0.2×10^9 /liter. As a result, lymphocyte counts must be monitored regularly. It is routine practice to discontinue the medication if ALC drops below 0.2×10^9 /liter as was done in the clinical trials [Francis *et al.* 2014]. Using these parameters, studies have not noted a generalized increase in infection rate. Although the lymphocyte count may appear low, it is important to remember that lymphocytes are able to perform some immune surveillance while sequestered in the lymph nodes and therefore infectious risk is much less than in truly immunosuppressed patients with similar counts. The maintained ability to fight infections may also result from the differential effects on lymphocyte subsets with naïve and central memory T cells relatively reduced compared with peripheral effector memory T cells [Mehling *et al.* 2008].

Based on phase II trial data suggesting an increased rate of basal cell cancer, yearly dermatologic checks were implemented in phase III trials. Although TRANSFORMS found a slightly increased incidence of basal cell carcinoma, FREEDOMS found a decreased incidence. Though not specifically recommended by regulatory agencies, the authors of this article encourage yearly dermatologic checks. There was no overall increased rate of neoplasm with fingolimod.

Because sphingosine-1-phosphate receptors are present throughout the body, including on cardiac myocytes, there is a well established slowing of the heart rate and, less often, a delay in atrioventricular

(AV) node transmission that occurs following the first dose, peaking at 4–5 h. Bradycardia is generally asymptomatic and self limited. Clinical trials have shown that 6% of patients have a recorded heart rate of less than 50 beats per minute (bpm), with 0.4–0.5% of patients experiencing transient first- or second-degree heart block [Cohen *et al.* 2010; Kappos *et al.* 2010]. As a result, the first dose of fingolimod must be administered at a monitoring center where the patient's heart rate, electrocardiogram (EKG), and blood pressure can be monitored. In rare cases, such as when the patient's heart rate reaches its nadir or below 45 bpm at hour 6 postdosing, when the patient has symptomatic bradycardia, or when the patient has certain risk factors for cardiac arrhythmia, longer monitoring is indicated. There are rare reports of sudden cardiac arrest and death in patients taking fingolimod, though this seems to be a concern only in patients with other cardiac risk factors [Lindsey *et al.* 2012; Espinosa and Berger, 2011]. Because of these effects on cardiac conduction, EKG abnormalities such as baseline bradycardia or delayed QT interval, or prior history of cardiac disease would preclude use of fingolimod as first-line treatment (or at all).

Because sphingosine-1 phosphate signaling also plays a role in endothelial and vascular smooth muscle cells, fingolimod can lead to a slight sustained increase in blood pressure. Small mean increases in systolic/diastolic blood pressure (approximately 3/approximately 1 mmHg) became evident after 2 months of fingolimod treatment in clinical trials [Cohen *et al.* 2010; Kappos *et al.* 2010; Camm *et al.* 2014].

A low incidence of macular edema is also associated with fingolimod treatment, possibly as a result of sphingosine-1 phosphate's role in regulating vascular permeability [Camm *et al.* 2014]. In clinical trials, macular edema has been found to occur in less than 1% of patients. Patients with diabetes or a prior history of uveitis may be at increased risk. Macular edema may present as a decrease in visual acuity, pain, or may be asymptomatic, and typically develops within the first 3–4 months of treatment. In most cases, the edema resolves after discontinuation of the drug [Cohen *et al.* 2010; Kappos *et al.* 2010; Zarbin *et al.* 2013]. As a result, an ophthalmic examination is recommended prior to drug initiation and again at 3–4 months, with subsequent follow up if patients develop symptoms. The authors recommend ophthalmologic screening at baseline, 3

months after initiation of fingolimod, 6 months, and then yearly thereafter. If there is a history of diabetes or uveitis, patients may require more intensive ophthalmologic care.

Tolerability

Aside from the extensive monitoring requirements as detailed above, fingolimod is easy to administer (once daily capsule) and well tolerated. FREEDOMS showed no increase in any tolerability-related side effects compared with placebo. In young patients without medical comorbidities who are concerned about potential daily side effects from other agents, fingolimod may therefore be a good initial option.

Teriflunomide

Teriflunomide (Aubagio (Genzyme Corporation, Cambridge, United States)) is an inhibitor of the mitochondrial enzyme dihydro-orotate dehydrogenase. It blocks *de novo* pyrimidine synthesis, limiting DNA and RNA synthesis in rapidly dividing cells, and thereby decreasing the production of overactive lymphocytes. In 2012 it became the second oral agent to receive FDA approval. It is the active metabolite of leflunomide (Arava (Sanofi, Paris, France)) which has been approved to treat rheumatoid arthritis since 1998.

Efficacy

TEMSo (Teriflunomide Multiple Sclerosis Oral trial) and TOWER (Teriflunomide Oral in People With Relapsing Remitting Multiple Sclerosis) were the two phase III clinical trials that demonstrated the efficacy of teriflunomide. They were both multicenter, randomized, placebo-controlled, double-blind studies with ARR as the primary outcome measure. In TEMSo, teriflunomide 7 mg and 14 mg were found to reduce ARRs by 31% and 32%, respectively, compared with placebo. In addition, both treatment arms had diminished proportions of patients with 12-week confirmed disability progression compared with the placebo arm [O'Connor *et al.* 2011b]. In TOWER, ARR was reduced by 22% and 36% in the 7 mg and 14 mg treatment arms, respectively. In the 14 mg treatment arm, there was a 31.5% reduction in the risk of 12-week sustained disability accumulation compared with placebo, while there was no statistically significant difference in the 7 mg treatment arm [Confavreux *et al.* 2014].

Other evidence for teriflunomide's effectiveness comes from the TENERE study, which directly compared the two doses of teriflunomide with IFN β -1a 44 μ g subcutaneously three times weekly. In this study, the primary outcome measure was a composite measure of 'treatment failure' defined as the first occurrence of confirmed relapse or permanent treatment discontinuation for any cause. At 48 weeks, there was no statistical superiority of either dose of teriflunomide over IFN with regards to treatment. Analysis of a secondary outcome, ARR, found similar ARRs in teriflunomide 14 mg and IFN β -1a (0.259 and 0.216, respectively), while the 7 mg teriflunomide group had a higher ARR (0.410) [Vermersch *et al.* 2014].

From these studies, the general consensus is that teriflunomide's efficacy (at least that of the 14 mg dosage) is comparable to that of high-dose IFN and by extrapolation, GA.

Safety

In TEMSo and TOWER, the most common laboratory abnormality seen with teriflunomide was mildly elevated ALT levels, though levels greater than three times the upper limit of normal occurred with a frequency equal to that of those in the placebo group, and there were no between-group differences in the numbers of patients who discontinued the drug due to liver abnormalities. It is recommended that baseline LFTs be obtained prior to starting therapy, monthly for 6 months after starting therapy, and then periodically afterwards. Teriflunomide is not recommended as first-line therapy for those patients with baseline liver dysfunction, and is contraindicated in those with severe hepatic injury.

In clinical trials, patients on teriflunomide had a mild reduction in WBC count, including lymphocyte and neutrophil count, of approximately 15% from baseline, with cell counts that stabilized after the first several months. Several cases of significant neutropenia were reported in trials; in TEMSo only one patient had to discontinue the drug due to a neutrophil count below $0.9 \times 10^9/\text{liter}$, however in TOWER 12 patients (1% of the 7 mg group, 2% of the 14 mg group) had to discontinue the drug due to counts below $1 \times 10^9/\text{liter}$. A complete blood count should be tested prior to treatment and periodically afterwards.

There was no increase in the incidence of overall or serious infections, although four cases of tuberculosis (TB) in patients with MS taking teriflunomide were observed in clinical trials: one case in each of the TEMSO, TOWER, TENERE, and TOPIC trials. Baseline testing for latent TB is recommended, and if positive, patients should be treated with standard medical therapy for TB prior to starting teriflunomide. Teriflunomide may therefore not be an ideal first-line therapy for those with positive TB screening.

The potential for pregnancy, planned or otherwise, should be taken into consideration before starting individuals of childbearing age on this medication. Teriflunomide is contraindicated in pregnancy; it carries a pregnancy category X rating based on multiple studies demonstrating teratogenicity in animals with clinically relevant plasma drug levels. Recently reported data regarding the teratogenicity of teriflunomide in humans was somewhat more reassuring: of the 70 pregnant women exposed to teriflunomide in phase II or III trials, the rates of spontaneous abortion were comparable to those of the general population, and none of the 26 babies born had structural defects [Papadopoulou *et al.* 2015]. Nonetheless, all women of childbearing potential should be tested for pregnancy prior to beginning therapy, and advised to use a reliable form of contraception. If patients taking teriflunomide do become pregnant or wish to become pregnant, an accelerated elimination procedure with cholestyramine or activated charcoal is indicated. In men taking teriflunomide, the drug can be detected in semen, although data from the clinical trials showed no increased rate of spontaneous abortions and no birth defects in the children of 19 men exposed to teriflunomide [Papadopoulou *et al.* 2015]. As a precaution, the US prescribing information recommends that men do not father children while on teriflunomide, although the European prescribing information does not include this recommendation. Teriflunomide is therefore not an optimal first-line therapy for patients who plan to conceive in the near future or for those in whom the provider is concerned about compliance with contraception.

Though teriflunomide has only been on the market since 2012, it is the active metabolite of leflunomide which has been approved since 1998 to treat rheumatoid arthritis, providing some supportive evidence of the long-term safety of the drug.

Tolerability

In phase III trials, the most common adverse effects in patients taking teriflunomide included diarrhea, nausea, and hair thinning. These only rarely necessitated drug discontinuation. Hair thinning occurred in 10–20% of patients and in the majority of patients was graded as mild in severity. Hair thinning typically resolves within 3–6 months despite treatment continuation [Sartori *et al.* 2014].

Teriflunomide is eliminated slowly from plasma; clinically negligible levels are typically not reached until an average of 8 months, but in some individuals may take as long as 2 years. Therefore, should rapid elimination become necessary either for pregnancy or a serious adverse event, an elimination procedure involving ingestion of cholestyramine or activated charcoal for 11 days is needed, followed by laboratory testing to confirm success.

Dimethyl fumarate

Dimethyl fumarate (Tecfidera (Biogen, Cambridge, United State)), the newest oral agent available for the treatment of MS, was approved in 2013. It is purported to work *via* its effects on the nuclear factor erythroid 2 related factor, which ultimately decrease inflammation. A related fumarate preparation containing both monomethyl and dimethyl esters has been used in Germany for many years for the treatment of psoriasis, providing some element of long-term safety information.

Efficacy

DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting MS) and CONFIRM (Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis) were the two pivotal trials establishing the efficacy of dimethyl fumarate and leading to FDA approval. The DEFINE trial was a randomized, double-blind study that compared dimethyl fumarate 240 mg twice daily (the dose ultimately approved by the FDA), 240 mg three times daily, and placebo in 1237 patients with active RRMS. The proportion of patients with relapses over 2 years was lower in both treatment groups (27% in the twice daily group; 26% in the three times daily group) compared with the placebo group (46%). The study drug also met several secondary endpoints; in the 240 mg twice daily group there was a reduction in ARR of 53% and a reduction in confirmed

progression of disability of 38%, as well as a reduction in the number of new or enlarging T2 lesions and gadolinium-enhanced lesions [Gold *et al.* 2012].

Similarly, CONFIRM was a randomized, double-blind trial comparing 240 mg dimethyl fumarate twice daily and three times daily with placebo. This trial also included GA as a reference comparator, though subjects in this group were not blinded to their treatment arm, and the study was not powered to directly compare dimethyl fumarate with GA. Compared with placebo, the relative risk reduction for twice daily dimethyl fumarate was 44%, three times daily dimethyl fumarate was 51%, and GA was 29% (all were statistically significant). In addition, all treatment arms reduced the number of new or enlarging T2 lesions compared with placebo. However, unlike in the DEFINE study, there was no statistically significant reduction in disability progression between the treatment arms and the placebo arm [Fox *et al.* 2012].

Safety

A mild decrease in WBC count and lymphocyte count is expected with dimethyl fumarate. In clinical trials, white cell and lymphocyte counts decreased from baseline values by 10–12% and 28–32%, respectively, though mean levels of each remained within normal limits. WBC counts of less than $3.0 \times 10^9/\text{liter}$ or lymphocyte counts of less than $0.5 \times 10^9/\text{liter}$ were seen in 4–5% of the patients on dimethyl fumarate. Elevations in aminotransferase levels occurred in 6% in patients receiving dimethyl fumarate as opposed to 3% of patients on placebo. Prescribing information recommends checking CBC prior to starting treatment, 6 months after starting the drug, and every 6–12 months thereafter; the authors of this article typically check CBC and LFTs before treatment and every 3–6 months after treatment initiation.

Phase III pivotal trials showed no increase in infections or serious infections with dimethyl fumarate and no evidence of opportunistic infections. However, in October 2014 a case of PML was reported in a patient enrolled in an extension phase study, ENDORSE, who had been taking dimethyl fumarate for 4.5 years, with prolonged (3.5 years) lymphopenia with ALC in the range of $0.29\text{--}0.58 \times 10^9/\text{liter}$ (<http://www.fda.gov/Drugs/DrugSafety/ucm424625.htm>).

It does not currently seem necessary to consider JCV ab status in choosing whether or not to initiate dimethyl fumarate as a first-line therapy given the overall very low incidence of PML (one case in over 135,000 patients on the drug) and its occurrence solely in the setting of a prolonged low lymphocyte count. However, the authors do recommend discontinuing the drug if ALC is sustained at $0.5 \times 10^9/\text{liter}$ or less in any patient due to potential infectious risks. Patients with sustained lymphocyte counts at this level have not been adequately studied, and potential for opportunistic infection is certainly a theoretical possibility in this group.

Tolerability

GI side effects (including nausea, vomiting, diarrhea, abdominal pain), and flushing (warmth, redness, or pruritus to the face or upper body) have been the major tolerability issues with dimethyl fumarate. In clinical trials, 20–25% of subjects experienced GI discomfort and 25–30% reported flushing initially; however, after the first month the occurrence of these side effects dropped dramatically. Only 2–4% discontinued dimethyl fumarate due to flushing, and 2–5% for GI upset. Experience has shown that administration of the medication with food can abate GI side effects and flushing; aspirin can also be used prior to medication administration to reduce flushing and antihistamines can be used if there is a pruritic component. Whether GI side effects occur with greater incidence or severity in patients with baseline GI issues related to inflammatory bowel disease, gastroesophageal reflux disease, irritable bowel syndrome, or other conditions is unknown. However, these patients may be wary about choosing dimethyl fumarate as initial therapy given the potential for further GI issues.

Agents not typically appropriate for initial DMT

There are several other agents approved for disease modification in MS, but these are generally not appropriate choices for initial treatment due to safety concerns. Alemtuzumab, a monoclonal antibody against the CD52 protein present on mature lymphocytes, received FDA approval for MS in 2014. Given the potential for the development of secondary autoimmune disorders, including a small risk of idiopathic thrombocytopenic purpura, the FDA recommended this drug only for patients with MS whose condition has

failed to respond to two other agents. European regulatory agencies have been less stringent regarding the indication for alemtuzumab and have licensed it for active disease, defined by clinical or imaging features, without reference to prior failed therapy. The authors of this article believe there are potential situations in which alemtuzumab may be considered as initial therapy, such as in a patient with highly aggressive disease onset who is positive for JCV ab; however, they recommend this strategy only in consultation with an MS specialist. Rituximab, a monoclonal antibody against the CD20 protein on B cells, may also be considered in this scenario, though it is not currently FDA approved for the treatment of MS. Mitoxantrone, FDA approved for MS in 2000, is a topoisomerase inhibitor that disrupts DNA synthesis and repair. Its usage is limited by dose-dependent cardiomyopathy and risk of myelogenous leukemias, and it is therefore not appropriate as an initial therapy for MS. A complete discussion of the indications for these medications is beyond the scope of this review.

Timing of therapy

The stated goal and indication for all currently available MS DMTs relates to the prevention of acute inflammation and relapse, including the prevention of the development of new lesions on MRI. Ultimately the true goal is to prevent the development of disability, including long-term disability related to progressive disease as described above. All currently available agents work by modulating the immune system to prevent CNS inflammation that is thought to be the initial event in the pathological cascade leading to neurological disability. There is evidence that axonal damage appears early in the MS disease course and that this axonal damage depends, at least in part, on the inflammatory process [Trapp *et al.* 1998; Kuhlmann *et al.* 2002; De Stefano *et al.* 2001; Paolillo *et al.* 2004]. Brain atrophy [Calabrese *et al.* 2007; Audoin *et al.* 2007, 2010; Bergsland *et al.* 2012; Rojas *et al.* 2015], spinal cord atrophy [Biberacher *et al.* 2015], and cognitive changes [Glanz *et al.* 2007, 2012; Rieckmann 2005; Feuillel *et al.* 2007; Reuter *et al.* 2011] can be quite common even in the early stages of MS. Moreover, early changes such as lesion burden and atrophy on MRI have been found to be predictive of later, long-term disability [Filippi *et al.* 2013; Di Filippo *et al.* 2010; Popescu *et al.* 2013]. The logical extension of this is that the best stage

in which to intervene is as early as possible, before disability accrues.

Studies have illustrated that DMTs can have a beneficial effect on relapse prevention even before a formal MS diagnosis can be made. Patients with an initial clinical event suggestive of demyelinating disease, termed CIS, and imaging that is consistent with MS have a high likelihood of going on to develop a second, disease-defining, MS relapse in the near future [Optic Neuritis Study Group, 1997; Fisniku *et al.* 2008; Galetta 2001; Kappos *et al.* 2006a, 2006b; Comi *et al.* 2001, 2009; Miller *et al.* 2014]. There are several randomized controlled multisite studies providing evidence that intervention with various DMTs at the CIS stage prolongs time to second clinical event. The Controlled High Risk Avonex Multiple Sclerosis Study (CHAMPS) showed that among patients with a first clinical event and at least two clinically silent MRI lesions, the use of IFN β -1a 30 μ g administered intramuscularly once weekly reduced the 3-year probability of developing a second clinical event by 44% and additionally reduced the accrual of silent MRI lesions [Galetta, 2001]. The Early Treatment of MS (ETOMS) Study Group found that 22 μ g IFN β -1a administered subcutaneously once weekly decreased the risk of conversion to clinically definite MS (CDMS) by 25% over 2 years [Comi *et al.* 2001]. The Rebif Flexible dosing in early MS (REFLEX) trial found that 44 μ g IFN β -1a administered subcutaneously either once or three times weekly was superior to placebo at decreasing conversion rates by 47% and 52%, respectively [Comi *et al.* 2012]. The Betaferon in Newly Emerging MS for Initial Treatment (BENEFIT) trial found 250 μ g IFN β -1b administered subcutaneously every other day decreased conversion to CDMS by 50% over the 2-year trial period [Kappos *et al.* 2006a]. In PreCISE, GA was found to decrease the risk of developing CDMS by 45% over the 3-year trial period [Comi *et al.* 2009]. More recently, in TOPIC (Teriflunomide in Patients with Early Multiple Sclerosis), the oral medication teriflunomide was shown to have a similar effect on delaying new onset clinical activity; over the 108-week trial period, teriflunomide reduced the rate of conversion to clinically definite MS by 37% and 43% in the 7 mg and 14 mg arms, respectively [Miller *et al.* 2014].

These studies provide ample evidence that DMTs help delay conversion from CIS to clinically definite MS. They suggest that DMT should be

initiated for all patients with a clinically isolated event and an MRI consistent with MS, defined in trials as two or more brain lesions greater than or equal to 3 mm at least one of which is periventricular, ovoid, or infratentorial, regardless of whether a patient meets full McDonald 2010 criteria for time and space for a formal MS diagnosis. Currently, Avonex, Betaseron, Extavia, and Copaxone are the only agents FDA approved for CIS (Rebif is also approved in Europe) but most clinicians extrapolate that any agent approved for relapse reduction in RRMS would likewise be effective in CIS.

More recently, physicians have contemplated pushing the start of therapy even earlier, in what is considered the preclinical phase of the disease. As the use of MRI in patients with headache, trauma, and other issues has increased, lesions suggestive of MS have been noted in patients who lack clinical symptomatology of MS, a phenomenon termed radiologically isolated syndrome (RIS). A proportion of these patients will ultimately go on to develop clinical disease [Moore and Okuda, 2009; Okuda *et al.* 2014]. Identified risk factors for the development of clinical disease include a younger age at RIS identification, male sex, and spinal cord involvement [Okuda *et al.* 2014]. Trials of DMTs have not yet been conducted in patients with RIS, however some clinicians consider starting such patients on DMTs, especially if there are spinal cord lesions, if the MRI is changing, or if there is other paraclinical evidence of MS (i.e. CSF positive for oligoclonal bands or elevated immunoglobulin G index). A full review of this topic is beyond the scope of this review.

Despite recommendations for early treatment, and the scientific reasoning behind this, it must be noted the effects of early intervention on the accrual of long-term disability have not yet been definitively established. Long-term trials assessing delayed effects of initial treatment are relatively rare and have had mixed results. When comparing early treatment with IFN β -1b with delayed treatment, the open-label follow up of the BENEFIT trial found that those who were started on medication upon CIS diagnosis were 40% less likely to have had progression in their EDSS scores at 3 years compared with those who delayed IFN initiation until after the diagnosis of clinically definite MS [Kappos *et al.* 2007], although this benefit did not appear to be sustained after a 5-year period on open-label therapy [Kappos *et al.* 2009]. After an 8-year observational period, there were no

significant differences found in EDSS or Multiple Sclerosis Functional Composite (MSFC) scores between the two groups [Edan *et al.* 2014]. Subjects in PRISMS initially assigned to IFN β -1a had less EDSS progression and a lower T2 lesion burden 8 years later compared with patients initially assigned to placebo and transitioned to therapy 2 years later [Kappos *et al.* 2006b]. However, a retrospective follow up of the pivotal IFN β -1b study could not find an effect on initial treatment assignment on disability 16 years later [Ebers *et al.* 2010]. Methodologic limitations, including lack of blinding and randomization following the initial placebo-controlled phase and differential follow up, have made the results of these studies even harder to interpret. Long-term studies of the newer, potentially more effective therapies will take many years to complete and will likely be riddled with similar issues and biases.

There may occasionally be situations in which deferring therapy after an initial diagnosis of MS is reasonable. Perhaps the most frequent example is when a patient is either pregnant or hoping to conceive in the near future. If the disease does not appear to be highly active, it may be reasonable to defer therapy until after delivery, or even after breastfeeding is completed, depending on which agent is planned. As relapse rates are decreased during pregnancy, particularly during the third trimester [Confavreux *et al.* 1998], this strategy may be safe in select patients. Some level of risk of delaying DMT initiation will be present, particularly if the patient does not conceive quickly. The postpartum period, which comes with increased risk of relapse, may be more difficult to manage and data regarding potential reduction in relapse rates with breastfeeding have not been conclusive [Confavreux *et al.* 1998; Langer-Gould *et al.* 2009; Hellwig *et al.* 2012; Portaccio *et al.* 2011]. In a patient with aggressive MS onset, it may be more appropriate to promptly initiate DMT and control disease activity prior to attempting conception.

Other potential scenarios may delay DMT initiation, such as another medical condition that takes precedence over the MS diagnosis. These are rare and the benefits and risks of DMT initiation should be considered on a case-by-case basis. However, in the majority of cases, early initiation of DMT for MS is recommended. The choice of initial agent is impacted by factors relating to the agents themselves, the severity of the onset of the patient's disease, and patient-specific factors such as a medical

comorbidities, reproductive status, and tolerance for risk. The decision must be based on careful consideration by the physician and discussion with the patient, taking many potential issues into account and realizing in some cases there is no clear 'best' choice. Though the long-term benefits have not been definitively demonstrated due to difficulties with design and relatively recent introduction of several agents, available evidence and collective anecdotal experience demonstrate that early initiation of an effective DMT can positively impact a patient's life for many years to come.

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