Chapter 4
Treatment Strategies in Multiple Sclerosis

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4.1 Introduction

Multiple sclerosis (MS) is one of the leading causes of disability among young adults and presents a major health burden in the USA and other Western countries. Disease-modifying therapies (DMTs) for MS are primarily aimed at reducing relapse rate and disability accumulation over time, and have been shown to significantly decrease disease activity clinically as well as radiographically on MRI. In the past several years, the number of therapies for this debilitating disease has greatly increased, offering the ability to tailor treatment plans based on severity of disease, personal preference, risk tolerance, and comorbidities. However, new treatments also come with new safety concerns and monitoring requirements with which physicians must familiarize themselves. This chapter will review the data regarding the treatment options currently available. Finally, while the armamentarium of treatment options for relapsing forms of MS has expanded over the past few years, no currently available therapy has been efficacious in the treatment of (primary or secondary) progressive MS

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without relapses, and emerging treatment strategies are aimed at addressing this issue (see Chap. 5).

4.2 Initiating Therapy

Accurate diagnosis and early treatment with DMTs are imperative in the management of MS. The increased availability of MRI over the last decades has allowed for the diagnosis of MS earlier in the disease course (see McDonald Criteria in Chap. 3), often after only a single clinical attack. Moreover, even in patients with clinically isolated syndrome (CIS) who fall short of formal MRI criteria for the diagnosis of MS, the presence of characteristic brain MRI lesions portends a high risk of conversion to clinically definite MS (CDMS) [1]. Numerous studies have shown that early initiation of DMTs in these high-risk patients with CIS leads to a robust delay in conversion to CDMS, conversion to MS (via McDonald Criteria), and development of new MRI lesions [2–6]. Furthermore, earlier treatment with interferon (IFN) β-1b led to sustained benefit in cognitive performance [7]. Therefore, it is widely accepted that high-risk CIS patients should be treated early with a DMT.

Conversely, in the case of a patient with CIS and no lesions on MRI, the risk of CDMS is relatively low, and most providers would opt to forgo treatment in favor of close monitoring with serial exams and MRIs. However, because the presence of oligoclonal bands (OCBs) in the CSF, low serum vitamin D levels, and abnormalities on ocular coherence tomography (OCT) have all been shown to be predictors of conversion from CIS to MS independent of MRI lesion burden, some authors have more recently argued that these factors should also be used in stratifying risk of CDMS in CIS patients to inform the decision of whether to start a DMT [8–10]. Finally, as MRI utilization has increased, so, too, has the occurrence of incidentally discovered lesions suggestive of MS, termed radiologically isolated syndrome (RIS) (see Chaps. 1 and 3). There is a relative lack of data available to guide the management of

patients with RIS and, therefore, high variability in the viewpoint as to whether to begin a DMT in this population. Most clinicians opt for close monitoring of these patients for evidence of disease activity, while others use ancillary data, such as the presence of OCBs, to guide their decision.

Once the decision has been made to initiate therapy, DMT choice should be tailored to consider comorbidities, disease severity, risk tolerance, and the patient's personal preference. Available therapies have different risk profiles, monitoring requirements, and routes of administration. The clinician and patient should have a thorough discussion of the risks and benefits of each DMT prior to initiation.

4.3 Disease-Modifying Therapies

4.3.1 Interferons

IFN β-1b, approved by the US Food and Drug Administration in 1993, was the first injectable DMT available on the market. Currently, the IFN group includes two available subtypes: IFN β-1b and IFN β-1a, and each formulation has its own dosing frequency and route of administration (Table 4.1). Beta IFNs are cytokines that have both antiviral and anti-inflammatory effects, and their efficacy in MS is believed to be mediated by a reduction of T-cell activation and IFN-γ production, modulation of the blood–brain barrier, and promotion of an anti-inflammatory immune system profile [11].

Abundant data from multiple trials and almost two decades of clinical use are available regarding the efficacy and safety of the IFNs, and the major trials are listed in Table 4.1. These trials used annualized relapse rate (ARR) reduction, proportion of relapse-free patients, and sustained accumulation of disability (SAD) as the main outcomes. The IFN β Study Group Trial demonstrated that subcutaneous (SC) administration of 0.25 mg of IFN β-1b every other day (Betaseron®) decreased the ARR by 34 % compared to placebo, but a statistically significant effect on SAD was not

Table 4.1 FDA-approved disease-modifying therapies for relapsing-remitting multiple sclerosis

Disease-modifying agent		ROA and frequency	Mechanism of action	Major clinical trials	Major adverse events	Monitoring requirements
Interferons (IFN)	IFN β-1b (Betaseron®, Extavia®)	0.25 mg SC every other day	Immunomodulation, reduction of T-cell activation and IFN-γ production	IFN β Study Group	Injection site reactions; flu-like symptoms; depression; mild lymphopenia; transaminitis	CBC and LFT every 3 months
	IFN β-1a (Avonex®)	30 μg IM weekly		MS Collaborative Research Group		
	IFN β-1a (Rebif®)	44 μg SC three times a week		PRISMS		
	Peginterferon β-1a (Plegridy™)	125 μg SC every 14 days		ADVANCE		
Glatiramer Acetate (Copaxone®)		20 mg SC daily	Competition with myelin antigens, anergy of cytotoxic T cells	Copolymer 1 MS Study Group	Injection site reactions; immediate post-injection systemic reaction	No monitoring requirements
		40 mg SC three times a week		GALA		

Natalizumab (Tysabri®)	300 mg IV infusion every 28 days	Antibody to alpha4 integrin, inhibition of lymphocyte adhesion and transmigration to CNS	AFFIRM, SENTINEL	PML; possible disease rebound upon drug withdrawal; infusion reactions	JCV Ab every 6 months
Fingolimod (Gilenya®)	0.5 mg PO daily	Downregulation of $S1P_1$ receptor, sequestration of T cells in lymphatic tissues	FREEDOMS, TRANSFORMS	HTN; transient bradycardia; transient AV block; minimal increase in risk of skin cancers; PML; disseminated zoster	Varicella status prior to rx; cardiac monitoring at first dose; baseline and serial CBC, LFT, ophthalmological and dermatological exams

(continued)

Table 4.1 (continued)

Disease-modifying agent	ROA and frequency	Mechanism of action	Major clinical trials	Major adverse events	Monitoring requirements
Teriflunomide (Aubagio®)	14 mg PO daily	Inhibition of DHODH, reduction in pyrimidine synthesis, cytostatic effect on lymphocytes	TEMSO, TOWER, TENERE	Mild diarrhea and nausea; hair thinning; transaminitis; intestinal TB; teratogenicity	Baseline CBC, LFT, quantiferon gold; monthly LFT for 6 months; serial LFT and CBC during rx
Dimethyl fumarate (Tecfidera®)	240 mg PO twice daily	Activation of Nrf2 antioxidant pathway	DEFINE, CONFIRM	GI sx; flushing; lymphopenia; PML	CBC every 3 months

Alemtuzumab (Lemtrada™)	12 mg IV infusion daily × 5 days, then 12 mg IV infusion daily × 3 days 12 months after initial treatment	Antibody to CD52, pulsed administration leads to rapid long-lasting depletion of lymphocytes	CARE-MS I, CARE-MS II	Infusion-related reactions; infections: URIs, UTIs, HSV; autoimmune: thyroid disease, ITP, GN, AIHA; melanoma	Monthly CBC, Cr, UA, and TFTs at baseline and every 3 months until 48 months after last dose; baseline and yearly dermatological exams

AIHA autoimmune hemolytic anemia, *CBC* complete blood count, *Cr* creatinine, *DHODH* dihydroorotate dehydrogenase, *GN* glomerulonephritis, *HSV* herpes simplex virus, *IM* intramuscular, *ITP* idiopathic thrombocytopenic purpura, *IV* intravenous, *JCV Ab* John Cunningham virus antibodies, *LFT* liver function test, *PO* oral, *rx* treatment, *ROA* route of administration, *SC* subcutaneous, *sx* symptoms, *TFT* thyroid function test, *UA* urinalysis, *URI* upper respiratory infection, *UTI* urinary tract infection

seen [12]. The MS Collaborative Research Group Trial compared the efficacy of weekly intramuscular (IM) administration of 30 mcg IFN β-1a (Avonex®) with that of placebo, and showed an 18 % reduction in ARR and a 37 % reduction in SAD [13]. The PRISMS trial revealed that treatment with 44 mcg of IFN β-1a SC three times a week (Rebif®) led to a 32 % reduction in relapse rate, and a 78 % reduction in new T2 lesions on MRI, as well as a significant reduction in SAD [14]. The 22 mcg dose also significantly reduced the ARR and new lesions on MRI, albeit less robustly than the higher dose. More recently, a new pegylated IFN was developed, allowing for biweekly dosing. The recent ADVANCE trial showed a significant reduction in ARR with SC administration of 125 mcg of peg-IFN β-1a dosed every 2 weeks (Plegridy™) compared to placebo, as well as a reduction in SAD and new T2 hyperintense lesions on MRI [15]. While these findings are similar to those of other IFN studies, a direct comparison cannot be made as the study did not include an active comparator arm. Comparative studies have not provided conclusive evidence regarding possible differences in efficacy among the IFN formulations. Large retrospective studies (such as the Quality Assessment in Multiple Sclerosis Study) showed no difference between the IFN therapies, while some smaller prospective studies (EVIDENCE, INCOMIN) suggested improved efficacy with higher frequency IFN formulations such as INF β-1b every other day and SC INF β-1a three times a week, compared to weekly IM INF β-1a [16–18]. It is generally accepted that these higher-dose, higher-frequency IFNs are likely more effective than weekly intramuscular IFN β-1a, and it is unclear where pegylated IFN β-1a falls on that spectrum.

The IFNs have a favorable safety profile, but tolerability issues are common. The most frequent adverse events (AEs) are injection site reactions and influenza-like symptoms. Up to 60 % of patients in clinical trials reported injection site reactions including pain, bruising, and erythema. Flu-like symptoms consisted of fever, chills, headaches, and myalgias

and were reported by approximately 50 % of patients. In susceptible patients, IFNs may also worsen depression [19]. Side effects generally improve after the first 3 months but in some patients can be persistent. Injection site reactions are often ameliorated with nursing visits aimed at improving injection technique, and flu-like symptoms are often managed with acetaminophen or ibuprofen.

In clinical trials, mild and asymptomatic lymphopenia was present in 80 % of patients and mild neutropenia, anemia, thrombocytopenia, or transaminitis was present in 20 % [12–14]. It is rare for laboratory disturbances related to IFNs to reach clinical significance; however, it is recommended to monitor complete blood counts (CBCs) and hepatic function tests (LFTs) every 3 months. IFNs should be used with caution in patients with liver disease and the drug should be discontinued if liver enzymes reach five times the upper limit of normal or if clinical symptoms of liver dysfunction occur [20–22].

During treatment with IFNs, neutralizing antibodies (NAbs) can develop. NAbs usually appear between 6 and 18 months of treatment, and the incidence is variable, ranging from 2 to 45 % in clinical trials [23]. While the presence of NAbs is associated with decreased efficacy of IFNs, the clinical utility of testing for them is unclear because failure of an IFN would necessitate a change in DMT regardless of etiology.

4.3.2 Glatiramer Acetate

Glatiramer acetate (GA), a short polypeptide copolymer that is antigenically similar to myelin basic protein (MBP), is another commonly used injectable DMT. Its function in MS is thought to be mediated by its ability to bind to HLA-DR2 and compete with various myelin antigens for their presentation to T cells. GA causes anergy of MBP-reactive T cells and induction of anti-inflammatory T helper type 2 cells [11]. It is administered SC at a dose of 20 mg daily or at the more recently approved dosing of 40 mg three times a week.

The efficacy and safety of GA was evaluated in several placebo-controlled trials. The copolymer 1 MS Study Group trial showed that SC administration of 20 mg GA daily over 2 years led to a 29 % reduction in ARR [24], with an extension trial demonstrating sustained ARR reduction of 32 % over up to 35 months [25]. In addition, more patients in the placebo group had progression in disability as assessed by a standardized version of the neurological examination. Subsequently, a European/Canadian multicenter placebo-controlled study corroborated the beneficial effect of GA, showing a 33 % ARR reduction in GA-treated patients [26]. This study also demonstrated a statistically significant benefit with regard to MRI markers of disease activity, such as lesion volume and number of new T2 and enhancing lesions. More recently, a new dosing regimen of GA (40 mg SC three times a week) showed a comparable 34 % reduction in ARR compared to placebo [27] and was shown to reduce injection-related AEs when compared to the old regimen [28]. Finally, three trials have directly compared the efficacy of GA to that of IFN β-1a (REGARD) and IFN β-1b (BECOME, BEYOND), and found no statistically significant differences in ARR [29–31].

GA has the most favorable safety profile of all the DMTs. In clinical trials, the most common AEs were mild injection site reactions, consisting of pain and erythema, occurring in 90 % of patients. Focal lipoatrophy at injection sites occurs commonly after prolonged medication use but likely occurs less frequently with the new dosing schedule available [28]. The most notable AE in trials was a transient immediate post-injection reaction that was experienced at least once by 16 % of patients, occurring within minutes after an injection, and consisting of flushing, chest pressure, palpitations, shortness of breath, and anxiety. This reaction is of unknown etiology but is benign and resolves spontaneously within 30 min [32]. Finally, unique among all the DMTs, patients on GA are not required to undergo regular monitoring of laboratory values. No hematologic abnormalities have been encountered and drug-induced liver injury has only been reported in isolated cases as an idiosyncratic drug reaction and is exceedingly rare [33].

4.3.3 Natalizumab

Natalizumab is a humanized monoclonal antibody against α4 integrin, a glycoprotein expressed on the surface of lymphocytes that allows for adhesion to the endothelial vessel wall. By blocking adhesion and subsequent transmigration of lymphocytes into the central nervous system (CNS), natalizumab prevents CNS inflammation. It is administered as a 300 mg IV infusion every 28 days.

Natalizumab was approved for relapsing MS in 2004 on the basis of two Phase III trials. The randomized placebo-controlled AFFIRM study demonstrated a 68 % reduction in ARR and a 42 % reduction of SAD at 2 years in the treatment arm compared to placebo. It also showed a remarkable 83 % reduction in new/enlarging T2 lesions and a 92 % reduction in contrast-enhancing lesions [34]. An additional study, SENTINEL, enrolled patients who, despite treatment with weekly IFN β-1a, had experienced at least one relapse in the prior year. The study found that natalizumab added to INF β-1a 30 μg IM weekly was significantly more effective than IFN β-1a alone, with a 54 % reduction in ARR at 1 year and a 24 % decrease in the risk of SAD [35].

However, natalizumab was temporarily withdrawn from the market in 2005 after discovery of three cases of progressive multifocal leukoencephalopathy (PML), a potentially lethal opportunistic infection of CNS oligodendrocytes caused by reactivation of the John Cunningham polyomavirus (JCV). Natalizumab was reintroduced to the market in 2006 with the stipulation that it be only used as monotherapy and with the implementation of an extensive risk evaluation and monitoring program, Tysabri Outreach: Unified Commitment to Health (TOUCH). A better understanding of the risk factors for developing PML has emerged since re-introduction, and the drug is now FDA-approved as monotherapy for any patient with relapsing MS. The major risk factors include the presence of JCV antibodies (Ab) in the serum (which indicates prior exposure, essentially a prerequisite for developing PML), use of prior immunosuppressive therapy, and cumula-

tive duration of therapy [36]. The estimated probabilities of developing PML after accounting for known risk factors are detailed in Table 4.2. It is recommended to check JCV Ab prior to initiating therapy and at 6-month intervals during treatment because there is a seroconversion rate of 1–2 % per year [37]. Consideration of PML risk factors is useful for informing appropriate patient selection, and many practitioners feel comfortable prescribing natalizumab in Ab-negative patients. However, in the seropositive population, most clinicians will limit duration of exposure to the drug, or will restrict use of the drug to those who have failed other therapies or have especially active disease.

Another concern with natalizumab is that cessation of the medication has, in several studies, been associated with rebound inflammation [38]. However, other studies have failed to show that post-natalizumab inflammatory activity is higher than activity prior to treatment [39], arguing against a true rebound effect. Given the possibility of rebound inflammation after stopping natalizumab, long "washout periods" after discontinuation of the drug have fallen out of favor. Although there is no consensus regarding the optimal timing

Table 4.2 Estimated US incidence of PML stratified by risk factor

		Anti-JCV antibody positive	
Anti-JCV antibody negative	**TYSABRI exposure**	**No prior immunosuppressant use**	**Prior immunosuppressant use**
	49–72 months	**6/1000**	**13/1000**
<1/1000	1–24 months	<1/1000	1/1000
	25–48 months	3/1000	12/1000
	49–72 months	6/1000	13/1000

The risk estimates are based on post-marketing data in the USA from approximately 69,000 patients exposed to natalizumab (Tysabri; http://www.tysabri.com/about/safety)

for starting a DMT after natalizumab cessation, MS subspecialists increasingly recommend initiating alternative therapy by around 2 months after discontinuation of natalizumab.

Aside from PML, natalizumab is well tolerated and generally safe. In trials, there was no increased risk for other infections with natalizumab. However, the current prescribing information indicates an increased risk of encephalitis and meningitis caused by herpes simplex or varicella zoster virus. Allergic reactions occurred in 1–4 % of patients and were generally mild, and fatigue occurred more often than with placebo. A small number of patients (6 %) developed neutralizing Abs to natalizumab, which were associated with an increase in infusion-related AEs as well as a loss of efficacy [34].

4.3.4 Fingolimod

The first oral agent for relapsing forms of MS was approved by the FDA in 2010 [40]. Fingolimod is a nonselective sphingosine-1-phosphate (S1P) receptor modulator that is metabolized by sphingosine kinase to the active metabolite fingolimod-phosphate. The $S1P_1$ receptor on lymphocytes is responsible for T lymphocyte circulation, exit from lymph nodes, and differentiation. Fingolimod-phosphate causes internalization and degradation of this receptor, leading to sequestration of T cells in secondary lymphatic tissues, in turn bringing about a reduction of MS-related inflammation [41]. Fingolimod is administered as a once daily 0.5 mg capsule.

Several large Phase III trials have studied the efficacy and safety of fingolimod. The first trial, FREEDOMS, was a 24-month study that compared two doses of fingolimod (0.5 mg and 1.25 mg daily) with placebo. Patients receiving fingolimod showed a significantly decreased ARR compared to placebo (0.16 on 1.25 mg, 0.18 on 0.5 mg, 0.40 on placebo), and fingolimod use led to a reduction of the number of new/enlarged T2 lesions, T1-enhancing lesions, and brain-volume

loss on MRI. In this study, fingolimod significantly reduced SAD [42], and an extension of the trial showed sustained effect after 4 years [43]. The second trial, TRANSFORMS, was a 12-month long study comparing the same two doses of fingolimod (0.5 mg and 1.25 mg daily) to weekly intramuscular IFN β-1a (30 mcg). The two groups receiving fingolimod exhibited a lower ARR (0.20 on 1.25 mg, 0.16 on 0.5 mg, 0.33 on IFN) and had fewer new/enlarged T2 lesions and T1 enhancing lesions. Disability progression was infrequent in all three groups, and, unlike in FREEDOMS, there was no statistical difference in SAD [44]. The 1.25 mg dose of fingolimod failed to provide additional benefit compared to the 0.5 mg dose in both studies, leading to approval of only the 0.5 mg dose.

In both trials, AEs occurred at similar rates in all arms and were generally mild to moderate. The most common serious AEs were bradycardia and atrioventricular block after the initial dose, as well as macular edema. There were two deaths in the TRANSFORMS study, both in the group receiving 1.25 mg of fingolimod. One was due to disseminated primary zoster infection in a patient without history of chicken pox, while the other was secondary to herpes simplex encephalitis. However, infections as a whole occurred with similar rates in all arms. Cardiovascular side effects, such as hypertension, bradycardia, and AV block, were largely asymptomatic and are thought to be related to the presence of $S1P_1$ and $S1P_2$ receptors in the heart [45]. Hypertension occurred in 3 %–6 % of patients and was mild. Bradycardia was seen in 2–3 % of patients and was temporary, occurring within 1 h of initial fingolimod administration, and beginning to resolve within 6 h of administration. Heart block was infrequent, transient, and largely asymptomatic, occurring in 0.5 % of patients after initial administration. No further effects on heart rate or conduction were observed with continued administration of the drug during the clinical trials. Consistent with the drug's mechanism of action, peripheral lymphocyte counts decreased by 73–77 % over the first month of treatment with fingolimod in both

Phase III studies, and remained stable thereafter. Given an increased risk of skin cancers in the Phase II study of fingolimod [46], patients underwent close dermatological monitoring in Phase III trials. Five cases of basal cell carcinoma and three of melanoma occurred in the TRANSFORMS fingolimod treatment arms, and only one in the IFN group. FREEDOMS, on the other hand, showed a higher rate of malignancies in the placebo group. In a more recent Phase III trial, FREEDOMS II, there was a slight increase in incidence of basal cell carcinoma (3 % with 0.5 mg fingolimod vs. 1 % in placebo) [47]. Finally, while trials did not show any risk of PML in patients taking fingolimod, to date, there have been rare cases of PML in the absence of prior exposure to natalizumab among the >125,000 patients treated with fingolimod [48]. No PML risk stratification has been established for patients taking fingolimod, but currently the overall risk seems to be quite low.

Based on FDA recommendations, all patients should undergo evaluation with baseline ECG, blood pressure, complete blood count (CBC), liver function tests (LFTs), and ophthalmological and dermatological exams prior to starting fingolimod and regularly during treatment [49]. Varicella antibody should be tested in patients without a history of chicken pox or varicella immunization; those who are seronegative should be vaccinated before initiation of fingolimod, and treatment should be postponed for at least 30 days. Fingolimod is contraindicated in those with recent myocardial infarction, severe heart failure, unstable angina, prolonged QTc >500 ms, or history of Mobitz Type II 2nd or 3rd degree atrioventricular block or sick sinus syndrome unless a pacemaker is present. Patients should undergo observation and cardiac monitoring for at least 6 h after receiving the first dose of fingolimod, with a repeat electrocardiogram (ECG) at the end of observation. Those at higher risk of cardiac complications should be observed overnight. If treatment is interrupted for over 2 weeks, the observation and cardiac monitoring period has to be repeated upon restarting fingolimod [49].

4.3.5 Teriflunomide

The second oral agent for MS, teriflunomide, was approved by the FDA in the USA in 2012. Teriflunomide reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), leading to a decrease in de novo pyrimidine synthesis, a crucial step in DNA/RNA synthesis. In this manner, teriflunomide exerts a cytostatic effect on B and T cells [50]. The drug is administered as a once daily 7 mg or 14 mg dose.

Teriflunomide has been studied in several Phase III clinical trials in RRMS. TEMSO and TOWER both evaluated the efficacy and safety of the drug compared to placebo [51, 52]. Both trials included two treatment arms (7 mg and 14 mg doses) and used ARR as the primary outcome and SAD as a secondary outcome. In TEMSO, ARR was significantly reduced in both treatment arms when compared to placebo (ARR 0.37 for teriflunomide at either 7 mg or 14 mg vs. 0.54 for placebo). In TOWER, there was also reduction in ARR in both treatment arms (0.39 and 0.32 for teriflunomide at 7 mg and 14 mg, respectively, vs. 0.50 for placebo). The higher treatment dose in both trials reduced the risk of SAD (29.8 % reduction in TEMSO and 31.5 % in TOWER). MRI endpoints were also met. Based on these data, both the 7 and 14 mg doses were approved by the FDA; however, in practice, the 7 mg dose is rarely used and is not licensed in most countries outside of the USA. Finally, in another recent Phase III study, TENERE, teriflunomide was noninferior, but failed to show superiority, over three times weekly IFN β-1a in reducing risk of treatment failure [53].

In the Phase III trials, the most common AEs associated with teriflunomide were diarrhea, nausea, hair thinning, and transaminitis, each occurring in more than 10 % of patients. However, these were generally mild and rarely led to the discontinuation of the drug. Teriflunomide was not associated with an overall higher risk of infections; however, one case of intestinal tuberculosis occurred in the 14 mg treatment arm in the TOWER trial. Mean reductions in neutrophil and lym-

phocyte counts were generally mild and mostly occurred within 12 weeks of treatment. A small percentage of patients in the teriflunomide arms developed serious neutropenia, which was asymptomatic, and which resolved during continued treatment with the drug or after discontinuation [51, 52].

Based on FDA guidelines [54], patients should be evaluated with baseline CBC, LFTs, and TB testing prior to initiation of teriflunomide. LFTs should be monitored monthly for the first 6 months after starting the drug, and a CBC should be repeated regularly during treatment. Based on animal studies suggesting that use of teriflunomide can cause significant fetal malformations, it has been classified as pregnancy category X under the current FDA rating system. Women of childbearing age should be using reliable contraception and pregnancy should be ruled out prior to beginning treatment. In addition, since teriflunomide is present in low levels in semen, the FDA recommends that a man should not father a child while taking the drug, though this is not part of the European prescribing information. As teriflunomide is cleared slowly from plasma (an average of 8 months is necessary to achieve negligible drug levels), an accelerated elimination protocol consisting of either activated charcoal or cholestyramine followed by laboratory testing to ensure drug clearance should be implemented if reproduction is planned or if drug removal is necessary for another reason.

4.3.6 Dimethyl Fumarate

Dimethyl fumarate (DMF), the third oral agent for MS, was approved by the FDA in 2013 but related fumaric acid esters have been used in Europe since 1994 for treatment of psoriasis. Administered as a twice-daily 240 mg capsule, DMF is thought to function by reducing inflammation and neurodegeneration via activation of the nuclear factor-like 2 (Nrf2) antioxidant pathway.

Two Phase III trials have evaluated DMF in active RRMS. The DEFINE trial compared DMF 240 mg twice

daily, DMF 240 mg three times daily, and placebo, with the primary endpoint being the proportion of relapse-free patients at 2 years. The proportion of patients with relapses was lower in both treatment arms (27 % in the twice-daily group and 26 % in the thrice-daily group) when compared to the placebo group (46 %) [55]. In addition, DMF led to a reduction in ARR (by 53 % in the twice-daily group, 48 % in the thrice-daily group), SAD (by 38 % and 34 %, respectively), and the number of new/enlarging T2 lesions and T1-enhancing lesions [55]. The CONFIRM study also compared 240 mg DMF twice-daily and thrice-daily to placebo. However, this trial also included GA as an active comparator, though subjects in this group were not blinded and the study was not powered for a direct comparison of DMF with GA. The study demonstrated a reduction in ARR of 44 % with twice-daily DMF, 51 % with thrice-daily DMF compared to placebo, and 29 % compared to placebo. In addition, all treatment arms showed a favorable effect on MRI markers of disease. However, unlike the DEFINE study, CONFIRM did not demonstrate a statistically significant reduction in risk of SAD between treatment and placebo arms [56].

A mild decrease in total white blood cell (WBC) count and absolute lymphocyte count (ALC) can occur with DMF. In the trials above, WBC and ALC declined by an average of 11 % and 30 % within the first year and then stabilized. A WBC of less than 3.0×10^9/L or ALC of less than 0.5×10^9/L was infrequent, seen in under 5 % of patients. It is recommended to check a CBC prior to starting treatment, and many clinicians routinely check counts every 3 months during treatment as was done in the clinical trials.

While the initial trials showed no increased rate of infections with DMF, to date there have been four cases of PML reported among >155,000 patients treated with DMF. Three of these patients exhibited prolonged lymphopenia of less than 0.5×10^9/L [57] and the fourth patient showed a rapidly falling lymphocyte count. While prolonged severe lymphopenia might increase the risk of PML, a case has been reported with compounded DMF in the absence of this risk factor [58].

Nonetheless, discontinuation of DMF for persistently low ALC seems likely to be a reasonable strategy.

Finally, although they are not dangerous, gastrointestinal (GI) side effects (nausea, vomiting, diarrhea, or abdominal pain) and flushing (erythema of the upper body or face) can limit tolerability of DMF. In the clinical trials, 25 %–30 % of subjects experienced flushing and 20 %–25 % experienced GI side effects within the first month of treatment, though the majority of these AEs were mild to moderate and abated shortly thereafter. Flushing or GI upset rarely resulted in discontinuation of therapy during the clinical trial (in 2 %–4 % and 2 %–5 %, respectively). Post-marketing experience has shown that taking DMF with food can ameliorate side effects and aspirin prior to dosing may decrease flushing.

4.3.7 Alemtuzumab

Alemtuzumab, approved in the USA in 2014, is generally reserved for those patients who have failed two or more DMTs or have very aggressive MS because of its side effect profile and associated monitoring program. Alemtuzumab is a recombinant humanized monoclonal antibody to CD52, a cell-surface molecule present on T and B lymphocytes, natural killer cells, monocytes, and macrophages. Pulsed administration results in a rapid, long-lasting depletion of lymphocytes from the circulation via antibody- and complement-mediated cytolysis. Alemtuzumab is administered via an IV infusion consisting of 12 mg daily for five consecutive days (60 mg total) at the initiation of treatment, followed by 12 mg daily for three consecutive days (36 mg total) 12 months after the first treatment course [59]. Benefits may last for years, and patients are typically re-treated only if they exhibit new disease activity.

Two randomized Phase III trials, CARE-MS I and CARE-MS II, have evaluated treatment with alemtuzumab versus IFN β-1a 44 mcg three times weekly [60, 61]. CARE-MS I was a 2-year rater-blind trial that demonstrated a 54.9 % reduction in

ARR with alemtuzumab compared to IFN β-1a and showed a significant improvement in the percentage of patients who were relapse-free at the conclusion of the study. The study failed to show a significant improvement on the rate of SAD, possibly related to a lower than expected SAD rate in the IFN group. In contrast to CARE-MS I, which studied treatment-naive patients, CARE-MS II recruited only those who had exhibited a relapse on another MS therapy. Patients were once again randomized to either IFN β-1a or alemtuzumab. Alemtuzumab led to a 49.4 % reduction in ARR, as well as an increase in the percentage of patients who were relapse-free at the end of the trial (65 % vs. 47 %). In this trial, alemtuzumab also led to a significant decrease in the rate of SAD (13 % vs. 20 %).

The incidence of AEs was similar across both studies. Ninety percent of patients receiving alemtuzumab had infusion-related reactions, but only a small minority of reactions were serious. Infections occurred at a higher rate with alemtuzumab compared to IFN β-1a (67 % vs. 45 % in CARE-MS I, 77 % vs. 66 % in CARE-MS II), but the vast majority were mild to moderate. The most common infections in the alemtuzumab arms were URIs, UTIs, and herpesvirus infections. Herpes prophylaxis was subsequently added to the protocol and the incidence of these infections decreased.

Perhaps the biggest concern with alemtuzumab is the potential for emergent autoimmune disorders. Autoimmune AEs mostly consisted of mild to moderate autoimmune thyroid disease (16 %–18 %). In addition, immune thrombocytopenic purpura (ITP) occurred in 1.3 % of patients and autoimmune glomerulonephritis, hemolytic anemia, and pancytopenia were each observed in <1 % of patients. Two patients treated with alemtuzumab in CARE-MS I and one patient in CARE-MS II developed thyroid cancer. Finally, there have been case reports of melanoma in patients treated with alemtuzumab, with the manufacturer reporting that 0.3 % of alemtuzumab-treated patients developed melanoma in uncontrolled studies [59].

Despite the remarkable efficacy of alemtuzumab, its safety profile prevents the drug from being a first-line therapy for most patients. Prescribing information in the USA recom-

mends use only for those who have failed two or more agents, though this is not included on the European label. In the USA, treatment with alemtuzumab requires special registration through a restricted distribution program. To minimize the risk of infusion reactions, patients receiving alemtuzumab should be premedicated with corticosteroids prior to the infusion for the first 3 days of each course of treatment. Antihistamines and antipyretics may also be used. Herpetic prophylaxis with oral acyclovir 200 mg twice daily should be initiated on the first day of alemtuzumab dosing and continued for a minimum of 2 months after completion of the drug and until the CD4+ lymphocyte count is >200/mL. Regular monitoring includes monthly CBC, serum creatinine levels, and urinalysis for 48 months after the last dose. The possibility of secondary autoimmunity should be discussed with the patient. Thyroid function tests should be obtained at baseline and every 3 months until 48 months after the last infusion. Finally, patients should undergo baseline and yearly dermatological evaluation [59].

4.3.8 Mitoxantrone

Approved by the FDA in 2000, mitoxantrone is a second-line agent that is administered as an IV infusion of 12 mg/m^2 every 3 months, with a maximum dose of 140 mg/m^2. Due to cumulative dose-associated safety concerns (12 % incidence of systolic dysfunction, 0.4 % incidence of congestive heart failure, and 0.8 % of acute leukemia) and the growing availability of alternative agents, mitoxantrone has fallen out of favor as an MS treatment [62].

4.4 Switching Disease-Modifying Therapies

Evidence-based guidelines on criteria for switching DMTs in MS are limited, and decisions to change therapy are often based on observational reports and clinical judgment. Many

factors can motivate the decision to switch DMTs, from suboptimal efficacy, problems with tolerability, safety concerns, (as in a JCV Ab positive patient on natalizumab), and personal preference (as in a switch from an injectable to oral medication). Before treatment failure can be addressed, other possible reasons for a suboptimal response to therapy, such as poor compliance, should be investigated. The ultimate goal for therapy is the concept of "no evidence of disease activity" (NEDA), which refers to the absence of clinical relapses and disability worsening in combination with the absence of new/enlarging T2 lesions or contrast-enhancing lesions on MRI. However, in a recent cohort study, while 46 % of patients with MS met NEDA status after the first year, only 8 % maintained NEDA after 7 years [63]. Therefore, NEDA may not be a realistic goal with the current treatment options available. Because all DMTs are incompletely effective in reducing relapse rates and MRI activity, it is difficult to define treatment failure, and standardized definitions for suboptimal response still remain to be established. However, most clinicians would initiate a DMT switch in a patient with ongoing relapses, worsening disability, or significant MRI activity.

4.5 Acute Treatment of Relapses

While there has been considerable advancement made with regards to chronic treatment with DMTs, treatment of acute relapses has largely remained constant over the years. Acute exacerbations are typically treated with IV infusion of 1 g methylprednisolone daily for 3–5 days as this has been shown to hasten relapse recovery [64]. While a recent study demonstrated that high-dose oral methylprednisolone is not inferior to the IV form [65], use of oral steroids for relapses is not yet commonplace. If the symptoms are purely sensory and/or not impairing function, acute treatment may not be necessary. Practice differs on whether an oral prednisone taper should be included at the end of IV treatment, but there is no

evidence that this practice improves outcomes. ACTH or plasmapheresis can in some cases be used as a second-line treatment for severe attacks if steroids are contraindicated or response is suboptimal [66, 67]. While a short course of high-dose methylprednisolone is associated with few side effects in most patients, hyperglycemia, and dyspepsia can occur; therefore, glucose monitoring and gastrointestinal prophylaxis with H2 antagonists or proton pump inhibitors during treatment is common practice [68]. Avascular necrosis of the femoral head is a less common but severe potential complication of repeated short-course corticosteroid use in MS, and vigilance is key to preventing delayed diagnosis of this condition [69].

4.6 Treatment of Multiple Sclerosis During Pregnancy

As MS affects many women of childbearing age, management of MS during pregnancy is a crucial topic. Outcomes of pregnancy in patients with MS are usually no different than in the general population. Pregnancy is thought to be protective in terms of relapses and in the PRIMS study was associated with an increasingly robust reduction in relapse frequency, reaching 70 % in the third trimester [70]. However, the first 3 months postpartum are associated with a corresponding rebound increase in relapse risk. The etiology of this phenomenon is unclear.

The classical recommendation has been to stop any DMTs prior to conception. However, small pregnancy studies of exposure to GA and IFN in humans have shown no clear evidence of fetal harm [71, 72]. Many clinicians weigh the risk of relapse off DMTs while patients try to conceive with the purely theoretical risk of harm from GA or IFN exposure during early pregnancy. The risks and benefits of continuing GA or IFN therapy until conception should be discussed on a case-by-case basis between the clinician and patient [73]. The risk of the newer DMTs in pregnancy is even less well

elucidated, and current recommendation is to stop these medications prior to conception, the timing of which depends on the half-life of the individual agents. There are limited data on whether breastfeeding itself may be somewhat protective for MS, as well as on the safety of breastfeeding while on DMTs. Decisions regarding breastfeeding and the timing of DMT initiation should be discussed on a case-by-case basis, taking into account both individual preferences and MS disease severity.

4.7 Treatment of Pediatric Multiple Sclerosis

Management of MS in the pediatric population is an important issue and it is similar to that of adult patients. A detailed discussion is beyond the scope of this chapter, but a comprehensive review is available elsewhere [74].

4.8 Conclusion

In the past several years, the number of medications for the treatment of MS has grown significantly. With an increasing availability of choices comes an improved ability to tailor therapies to individual patient characteristics and preferences. This necessitates a thorough knowledge of each available DMT on the part of the clinician. While a large body of literature on the long-term safety and efficacy of the GA and IFN β preparations exists, relatively little is available on the long-term efficacy and potential complications of therapy with the newer agents. Vigilance is necessary with regard to existing and emerging safety issues. With an abundance of clinical trials currently underway, the treatment of MS will only become more complex in the coming years.

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