TABLE 120-4 DISEASE MODIFYING MEDICATIONS FOR MS

DRUG (BRAND NAME), DOSING	APPROVED	MS INDICATION	MECHANISM OF ACTION
Interferon beta 1b (Betaseron, Extavia), 250ug SQ qod	1993, 2009	RRMS, CIS	Inhibits "pro-inflammatory" cytokines, such as interferon (IFN)-gamma, tumor necrosis factor alpha, and lymphotoxin. Increases IL-10.
Interferon beta 1a (Avonex) 30ug IM weekly	1996	RRMS, CIS	
Interferon beta 1a (Rebif) 22 or 44ug SQ 3x /wk.	2002	RRMS	
Interferon beta 1a (Plegridy) 125ug SQ every 14 days	2014	Relapsing forms of MS	Adhesion molecule and class II MHC induction reduced.
Glatiramer acetate (Copaxone) 20mg SQ daily, or 40mg SQ 3x/wk	1996 2014	RRMS, CIS	Alters T cell cytokine profile toward that of Th2 immunomodulatory cells.
Mitoxantrone (Novantrone) 12mg/m^2 IV q 3 months	2000	Worsening RRMS, relapsing SPMS PRMS	Anthracenedione chemotherapeutic agent
Natalizumab (Tysabri) 300mg IV q 4 weeks	2004/2006	Relapsing MS*	Monoclonal antibody targeting the alpha-4-integrins, part of the VLA-4 adhesion molecule.
Fingolimod (Gilenya) 0.5mg po daily	2010	Relapsing MS, approved for treatment naïve patients	Down-modulates sphingosine-1-phosphate receptors, lymphocytes unable to migrate out of lymphoid tissue. May have direct effects in CNS
Teriflunomide (Aubagio) 7mg or 14mg po daily	2012	Relapsing MS, approved for treatment naïve patient	Inhibits dihydroorotate dehydrogenase, thus inhibiting proliferation of activated lymphocytes
Dimethyl fumarate (Tecfidera) 240mg po BID	2013	Relapsing MS, approved for treatment naïve patients	Activates nuclear factor erythroid 2-related factor 2 (Nrf2) pathway which enhances response to oxidative stress
Alemtuzumab (Lemtrada) IV infusion, SQ in development	2014	Relapsing forms of MS	Monoclonal antibody that lyses cells expressing CD52

considered the safest MS disease modifying therapy to use in women who may become pregnant.

Mitoxantrone is an anthracenedione chemotherapeutic agent that is FDA approved for secondary progressive MS, progressive relapsing MS, or worsening relapsing-remitting MS. It is administered by IV infusion every 3 months and has a lifetime dose limit due to dose-related cardiotoxicity. In a prospective randomized 2-year study enrolling worsening relapsing-remitting or secondary progressive MS patients, those that received mitoxantrone had longer time to first treated relapse and improved level of disability compared with those randomized to placebo (level A). Beneficial effects were still measurable 12 months after treatment discontinuation. In addition to dose-limiting cardiotoxicity, mitoxantrone is associated with leukemia in approximately 1% of MS patients. Because of these risks and with the advent of more targeted medications, mitoxantrone is not commonly used in the United States.

Natalizumab is a humanized monoclonal antibody targeting the α-4-integrins, part of the VLA-4 adhesion-related heterodimer. The dose is 300 mg given intravenously every 4 weeks. A 2-year phase 3 trial of natalizumab showed 68% reduction in annualized relapse rate, 42% reduction in sustained disability, and over 90% reduction in gadolinium-enhancing lesions compared with placebo (level A). Natalizumab was temporarily removed from the market in 2005 due to an association with progressive multifocal leukoencephalopathy, a severe viral disorder caused by the JC virus. Because of its association with progressive multifocal leukoencephalopathy, this drug is generally recommended in cases of an inadequate response or intolerance of an alternate MS therapy. Patients receiving it must take part in a risk-mitigation program and can only be infused at certified infusion centers. Natalizumab is pregnancy category C.

Fingolimod was the first oral disease modifying therapy to be approved for relapse rate reduction in MS. This once daily 0.5 mg capsule reduces annualized relapse rate by about 50% and disability progression by about 25% versus placebo (level A). Fingolimod has several risks, including macular edema, pulmonary dysfunction, bradycardia, and herpetic infections. It is contraindicated in some settings, such as recent myocardial infarction or uncontrolled heart failure, and with certain medications (such as class IA and class III anti-arrhythmic drugs). Medical monitoring for potential bradycardia for at least 6 hours is necessary for the first dose. Fingolimod is pregnancy category C.

Teriflunomide is a once daily oral tablet of 7 mg/day or 14 mg/day. Two phase 3 studies in relapsing patients with relapsing forms of MS found that the 14 mg/day dose significantly reduced annualized relapse rate by over 30% and disability progression by around 30% (level A). The 7 mg dose had a lesser beneficial effect. Thus, the 14 mg daily dose is favored by many clinicians. Teriflunomide can cause hepatotoxicity, and it is contraindicated in pregnancy (pregnancy category X). If necessary, teriflunomide can be rapidly eliminated from the body using cholestyramine, otherwise it persists for long periods. Teriflunomide is closely related to the drug leflunomide, approved for rheumatoid arthritis in 1998.

Dimethyl fumarate is a capsule taken orally twice daily. In phase 3 trials, it reduced MS relapse rates by 44 to 53% and also improved MRI outcomes (level A). The white blood cell count may drop and should be monitored. As of late 2014, one fatal case of PML in a person taking the medication and with persistent low lymphocyte counts has occurred. Adverse effects include flushing, gastrointestinal side effects, and rash. Dimethyl fumarate is pregnancy category C.

Alemtuzumab is a monoclonal antibody targeting cells expressing CD52, which includes T and B lymphocytes, monocytes, and other mononuclear white blood cells. In the CARE-MS I and II studies in RRMS patients, alemtuzumab was compared not to placebo, but instead to 44 μg BIFN-1a given subcutaneously three times per week. Patients treated with alemtuzumab had lower annualized relapse rate (by 49% and 53.8%) and disability progression (by 28% and 42%). Alemtuzumab leads to a profound drop in the white blood cell count, which may last for months or even years. In trials, secondary autoimmune diseases developed in a sizeable proportion of alemtuzumab-treated subjects, with autoimmune thyroid disease being most common.