TABLE 458-6 TWO-YEAR OUTCOMES FOR FDA-APPROVED THERAPIES FOR MULTIPLE SCLEROSIS[a]

	Clinical Outcomes[b]		MRI Outcomes[c]	
Dose, Route, and Schedule	Attack Rate, Mean	Change in Disease Severity	New T2 Lesions[d]	Total Burden of Disease
IFN-β-1b, 250 μg SC qod	−34%[e]	−29% (NS)	−83%[f]	−17%[e]
IFN-β-1a, 30 μg IM qw	−18%[g]	−37%[g]	−36%[f]	−4% (NS)
IFN-β-1a, 44 μg SC tiw	−32%[e]	−30%[g]	−78%[e]	−15%[e]
GA, 20 mg SC qd	−29%[f]	−12% (NS)	−38%[f]	−8%[f]
MTX, 12 mg/m^2 IV q3mo	−66%[e]	−75%[g]	−79%[g]	NR
NTZ, 300 mg IV qmo	−68%[e]	−42%[e]	−83%[e]	−18%[e]
FGM, 0.5 mg PO qd	−55%[e]	−34%[f]	−74%[e]	−23%[e]
DMF, 240 mg PO bid	−52%[e]	−40%[f]	−71%[e]	NR
TF, 14 mg PO qd	−31%[e]	−26%[g]	−70%[e]	−20%[g]

[a]Percentage reductions (or increases) have been calculated by dividing the reported rates in the treated group by the comparable rates in the placebo group, except for magnetic resonance imaging (MRI) disease burden, which was calculated as the difference in the median percent change between the treated and placebo groups. [b]Severity = 1 point Expanded Disability Status Score progression, sustained for 3 months (in the IFN-β-1a 30 μg qw trial, this change was sustained for 6 months; in the IFN-β-1b trial, this was over 3 years). [c]Different studies measured these MRI measures differently, making comparisons difficult (numbers for new T2 represent the best case scenario for each trial). [d]New lesions seen on T2-weighted MRI. [e]$p = .001$. [f]$p = .01$. [g]$p = .05$.

Abbreviations: DMF, dimethyl fumarate; FDA, U.S. Food and Drug Administration; FGM, fingolimod; GA, glatiramer acetate; IFN-β, interferon β; IM, intramuscular; IV, intravenous; MTX, mitoxantrone; NR, not reported; NS, not significant; NTZ, natalizumab; PO, oral; q3mo, once every 3 months; qd, daily; qmo, once per month; qod, every other day; qw, once per week; qyr, once per year; SC, subcutaneous; TF, teriflunomide; tiw, three times per week.

the balance between proinflammatory and regulatory cytokines. Glatiramer acetate reduces the attack rate (whether measured clinically or by MRI) in RRMS. Glatiramer acetate also benefits disease severity measures, although, for clinical disability, this is less well established than for IFN-β. Nevertheless, two very large head-to-head trials demonstrated that the impact of glatiramer acetate on clinical relapse rates and disability was comparable to high-dose, high-frequency IFN-β. Therefore, glatiramer acetate should be considered as an equally effective alternative to IFN-β in RRMS patients. Its usefulness in progressive disease is unknown. Glatiramer acetate is administered by subcutaneous injection of either 20 mg every day or 40 mg thrice weekly. Injection-site reactions also occur with glatiramer acetate. Initially, these were thought to be less severe than with IFN-β, although two recent head-to-head comparisons of high-dose, high-frequency IFN-β to daily glatiramer acetate did not bear out this impression. In addition, approximately 15% of patients experience one or more episodes of flushing, chest tightness, dyspnea, palpitations, and anxiety after injection. This systemic reaction is unpredictable, brief (duration <1 h), and tends not to recur. Finally, some patients experience lipoatrophy, which, on occasion, can be disfiguring and require cessation of treatment.

Natalizumab Natalizumab is a humanized monoclonal antibody directed against the α_4 subunit of $\alpha_4\beta_1$ integrin, a cellular adhesion molecule expressed on the surface of lymphocytes. It prevents lymphocytes from binding to endothelial cells, thereby preventing lymphocytes from penetrating the BBB and entering the CNS. Natalizumab is highly effective in reducing the attack rate and significantly improves all measures of disease severity in MS (both clinical and MRI). Moreover, it is well-tolerated, and the dosing schedule of monthly intravenous infusions makes it very convenient for patients. However, progressive multifocal leukoencephalopathy (PML), a life-threatening condition resulting from infection by the John Cunningham (JC) virus, has occurred in approximately 0.3% of patients treated with natalizumab. The incidence of PML is very low in the first year of treatment but then rises by the second year to reach a level of about 2 cases per 1000 patients per year. Nevertheless, the measurement of antibodies against the JC virus in the serum can be used to stratify this risk. Thus, in patients who do not have these antibodies, the risk of PML is either minimal or nonexistent (as long as they remain JC antibody free). Conversely, in patients who have these antibodies (especially those who have them in high titer), the risk may be as high as 0.6% or greater. The risk is also high in patients who have previously received immunosuppressive therapy. Natalizumab is currently recommended only for JC antibody–negative patients, unless they have failed alternative therapies or if they have a particularly aggressive disease course. Head-to-head data show that natalizumab is superior to low-dose (weekly) IFN-β-1a in RRMS. However, its relative efficacy compared to other agents has not been established conclusively.

Natalizumab, 300 mg, is administered by IV infusion each month. Treatment with natalizumab is, in general, well tolerated. A small percentage (<10%) of patients experience hypersensitivity reactions (including anaphylaxis), and ~6% develop neutralizing antibodies to the molecule (only half of which persist).

The major concern with long-term treatment is the risk of PML. Approximately half of the adult population is JC antibody positive, indicating that they experienced an asymptomatic infection with the JC virus at some time in the past. Nevertheless, because the risk is extremely low during the first year of treatment with natalizumab (regardless of antibody status), natalizumab can still be used safely in JC antibody–positive patients for a period of 12 months. After this time, in antibody-positive patients, a change to another disease-modifying therapy should be strongly considered. By contrast, persistently antibody-negative patients can be continued on treatment indefinitely. Up to 2% of seronegative MS patients undergoing treatment with natalizumab seroconvert annually; thus it is recommended that JC antibody status be assessed at 6-month intervals in all patients receiving treatment with this agent.

Fingolimod Fingolimod is a sphingosine-1-phosphate (S1P) inhibitor that prevents the egress of lymphocytes from the secondary lymphoid organs such as the lymph nodes and spleen. Its mechanism of action is probably due, in part, to the trapping of lymphocytes in the periphery and inhibiting their trafficking to the CNS. Fingolimod reduces the attack rate and significantly improves all measures of disease severity in MS. It is well tolerated, and the daily oral dosing schedule makes it very convenient for patients. A large head-to-head phase 3 randomized study demonstrated the superiority of fingolimod over low-dose (weekly) IFN-β-1a. However, its relative efficacy compared to other agents has not been established conclusively.

Fingolimod, 0.5 mg, is administered orally each day. Treatment with fingolimod is also, in general, well tolerated. Mild abnormalities on routine laboratory evaluation (e.g., elevated liver function tests or lymphopenia) are more common than in controls, sometimes requiring discontinuation of the medication. First- and second-degree heart block and bradycardia can also occur when fingolimod therapy is initiated. A 6-h period of observation (including electrocardiogram monitoring) is recommended for all patients receiving their first dose, and individuals with preexisting cardiac disease should probably not be treated with this agent. Other side effects