include macular edema and, rarely, disseminated varicella-zoster virus (VZV) infection; prior to initiating therapy with fingolimod, an ophthalmic exam and VZV vaccination for seronegative individuals are indicated.

**Dimethyl Fumarate (DMF)** Although the precise mechanisms of action of DMF are not fully understood, it seems to have anti-inflammatory effects through its modulation of the expression of proinflammatory and anti-inflammatory cytokines. Also, DMF inhibits the ubiquitylation and degradation of nuclear factor E2-related factor 2 (Nrf2)—a transcription factor that binds to the antioxidant response elements (AREs) located on the DNA and thereby induces the transcription of several antioxidant proteins. DMF reduces the attack rate and significantly improves all measures of disease severity in MS patients. However, its twice-daily oral dosing schedule makes it somewhat less convenient for patients than daily oral therapies. In addition, compliance is likely to be less with a twice-daily dosing regimen—a factor that could be of concern given the observation (in a small clinical trial) that once-daily DMF lacks efficacy. A head-to-head trial provided evidence that DMF was superior to glatiramer acetate on some outcome measures.

DMF, 240 mg, is administered orally twice each day. Gastrointestinal side effects (abdominal discomfort, nausea, vomiting, flushing, and diarrhea) are common at the start of therapy but generally subside with continued administration. Other adverse events included mild decreases in neutrophil and lymphocyte counts and mild elevations in liver enzymes. Nevertheless, in general, treatment with DMF is well tolerated after an initial period of adjustment. Following the release of DMF, four cases of PML were reported in patients receiving other products (not Tecfidera) that contained DMF. Each of these patients was lymphocytopenic, and most had received previous immunosuppressant therapy so that the relationship of DMF to the PML (if any) in these cases is uncertain. Nevertheless, these reports underscore the fact, stated previously, that long-term safety can never be guaranteed by the results of short-term trials. In the case of DMF for MS, only time and experience will tell us whether or not there is any cause for concern.

**Teriflunomide** Teriflunomide inhibits the mitochondrial enzyme dihydro-orotate dehydrogenase, which is a key part of the pathway for de novo pyrimidine biosynthesis from carbamoyl phosphate and aspartate. It is the active metabolite of the drug leflunomide (FDA-approved for rheumatoid arthritis), and it exerts its anti-inflammatory effects by limiting the proliferation of rapidly dividing T and B cells. This enzyme is not involved in the so-called "salvage pathway," by which existing pyrimidine pools are recycled for DNA and RNA synthesis in resting and homeostatically proliferating cells. Consequently, teriflunomide is considered to be cytostatic rather than cytotoxic. Teriflunomide reduces the attack rate and significantly improves all measures of disease severity in MS patients. It is well tolerated, and its daily oral dosing schedule makes it very convenient for patients. A head-to-head trial suggested the equivalence, but not superiority, of teriflunomide and high-dose (thrice-weekly) IFN-β-1a. Teriflunomide, either 7 or 14 mg, is administered orally each day. In the pivotal clinical trials, mild hair thinning and gastrointestinal symptoms (nausea and diarrhea) were more common than in controls, but in general, treatment with teriflunomide was well tolerated. As with any new agent, the long-term safety is not guaranteed by the results of short-term trials. A major limitation, especially in women of childbearing age, is its possible teratogenicity (pregnancy category X); teriflunomide can remain in the bloodstream for 2 years, and it is recommended that exposed men and women who wish to conceive receive cholestyramine or activated charcoal to eliminate residual drug.

**Mitoxantrone Hydrochloride** Mitoxantrone, an anthracenedione, exerts its antineoplastic action by (1) intercalating into DNA and producing both strand breaks and interstrand cross-links, (2) interfering with RNA synthesis, and (3) inhibiting topoisomerase II (involved in DNA repair). The FDA approved mitoxantrone on the basis of a single (relatively small) phase 3 clinical trial in Europe, in addition to an even smaller phase 2 study completed earlier. Mitoxantrone received (from the FDA) the broadest indication of any current treatment for MS. Thus, mitoxantrone is indicated for use in SPMS, in PRMS, and in patients with worsening RRMS (defined as patients whose neurologic status remains significantly abnormal between MS attacks). Despite this broad indication, however, the data supporting its efficacy are weaker than for other approved therapies.

Mitoxantrone can be cardiotoxic (e.g., cardiomyopathy, reduced left ventricular ejection fraction, and irreversible congestive heart failure). As a result, a cumulative dose <140 mg/m$^2$ is not recommended. At currently approved doses (12 mg/m$^2$ every 3 months), the maximum duration of therapy can be only 2–3 years. Furthermore, >40% of women will experience amenorrhea, which may be permanent. Finally, there is risk of acute leukemia from mitoxantrone, estimated as at least a 1% lifetime risk, and this complication has been reported in several mitoxantrone-treated MS patients.

Because of these risks, and a growing list of alternative therapies, mitoxantrone is now only rarely used for MS. It should not be used as a first-line agent in either RRMS or relapsing SPMS, but might be considered in selected patients with a progressive course who have failed other therapies.

**Alemtuzumab** Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen, which is expressed on both monocytes and lymphocytes. It causes lymphocyte depletion (of both B and T cells) and a change in the composition of lymphocyte subsets. Both of these changes, particularly the impact on lymphocyte subsets, are long lasting. In preliminary trials, alemtuzumab markedly reduced the attack rate and significantly improved all measures of disease severity in MS patients. In two phase 3 trials, however, its impact on clinical disability was less convincing. Notably, both trials used the active comparator of thrice-weekly, high-dose IFN-β-1a. The European and Canadian drug agencies were the first to approve this agent for use in RRMS; the FDA has also approved alemtuzumab, but only after an appeal following initial disapproval. The reasons for the initial disapproval were based on a perceived lack of a convincing disability effect and concerns over potential toxicity. The toxicities of concern were the occurrence (during the trial or thereafter) of (1) autoimmune diseases including thyroiditis, Graves' disease, thrombocytopenia, hemolytic anemia, pancytopenia, antiglomerular basement membrane disease, and membranous glomerulonephritis; (2) malignancies including thyroid cancer, melanoma, breast cancer, and human papillomavirus (HPV)–related cancers; (3) serious infections; and (4) infusion reactions.

**Initiating and Changing Treatment** Previously, most patients with relapsing forms of MS received injectable agents (IFN-β or glatiramer acetate) as first-line therapy. However, with the introduction of effective and probably safe oral agents, including DMF, fingolimod, and teriflunomide, this has begun to change. In addition, the monthly infusion therapy natalizumab, which is highly effective, well tolerated, and apparently safe in JC antibody–negative patients, provides an attractive option in many cases. As noted above, with the exception of the first-generation injectable agents, long-term safety data are not available, and for the most part, comparative data are lacking. The value of combination therapy is also largely unknown, although a recent clinical trial demonstrated no added benefit to the combination of glatiramer acetate with low-dose, once-weekly IFN-β-1a.

Despite these unknowns, clinicians need to make decisions based on the best available evidence, coupled with practical considerations. One reasonable approach stratifies initial decision-making based on two levels of disease aggressiveness **(Fig. 458-4)**.

*MILD INITIAL COURSE* In the case of recent onset, normal exam or minimal impairment (EDSS ≤2.5 or less), or low disease activity, either an injectable (IFN-β or glatiramer acetate) or an oral (DMF,