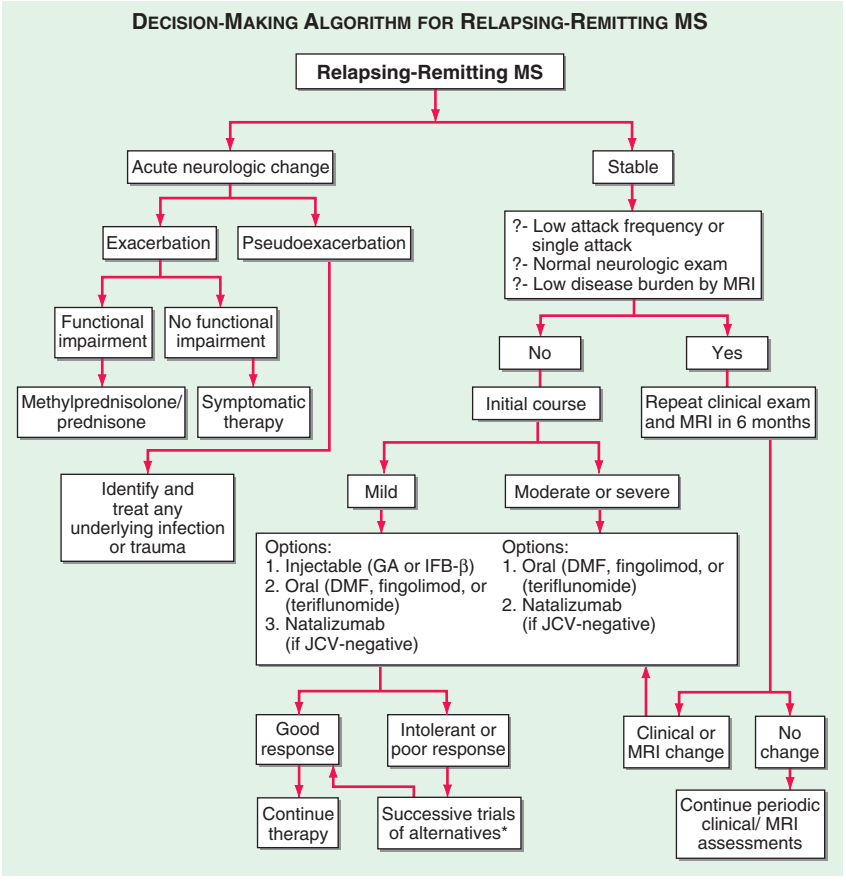

FIGURE 458-4 Therapeutic decision-making for multiple sclerosis (MS). *Can include trials of different preparations of interferon β (IFN-β, particularly advancing from once-weekly (Avonex) to a more frequent (e.g., Rebif, Betaseron/Extavia) dosing regimen. Options also include use of natalizumab in JC virus–positive patients. MRI, magnetic resonance imaging.

fingolimod, or teriflunomide) agent is reasonable. Although head-to-head comparisons are not available, natalizumab is thought to be more effective than these other agents, and therefore, this therapy can be considered even in minimally affected, JCV antibody–seronegative patients. The injectable agents (IFN-β and glatiramer acetate) have a superb track record for safety but have a high nuisance factor due to the need for frequent injections, as well as bothersome side effects that contribute to noncompliance. Some of the oral agents (DMF and fingolimod) are probably more effective than the injectables, but long-term risks are mostly unknown; DMF produces bothersome gastrointestinal symptoms in many patients at least initially (can be mitigated by beginning at one-quarter strength and gradually advancing to full dose), and fingolimod can lead to bradycardia and other cardiac disturbances of unclear clinical significance. Teriflunomide may be less effective than the other oral agents, and there are concerns about its possible long-lasting pregnancy risks. Nevertheless, its long-term safety has likely been established because of its extensive human exposure as the active metabolite of leflunomide—a drug long approved by the FDA.

MODERATE OR SEVERE INITIAL COURSE In highly active disease or moderate impairment (EDSS >2.5), either a highly effective oral agent (DMF or fingolimod) or, if the patient is JC virus antibody seronegative, infusion therapy with natalizumab is recommended.

Regardless of which agent is chosen first, treatment should probably be changed in patients who continue to have relapses, progressive neurologic impairment or, arguably, ongoing evidence of subclinical MRI activity (Fig. 458-4).

The long-term impact of these treatments on the disease course remains controversial, although several recent studies have shown that these agents improve the long-term outcome of MS including a prolongation of the time to reach certain disability outcomes (e.g., SPMS and requiring assistance to ambulate) and reduction in MS-related mortality. These benefits seem most conspicuous when treatment begins early in the RRMS stage of the illness. Unfortunately, however, already established progressive symptoms do not respond well to treatment with these disease-modifying therapies. Because progressive symptoms are likely to result from accumulated axonal and neuronal loss, many experts now believe that very early treatment with a disease-modifying drug is appropriate for most MS patients. It may also be reasonable to delay initiating treatment in patients with (1) normal neurologic exams, (2) a single attack or a low attack frequency, and (3) a low burden of disease as assessed by brain MRI. Untreated patients, however, should be followed closely with periodic brain MRI scans; the need for therapy is reassessed if scans reveal evidence of ongoing, subclinical disease. Finally, vitamin D deficiency should be corrected in all patients with MS, and generally this requires oral supplementation with vitamin D_3, 4000 to 5000 IU daily.

DISEASE-MODIFYING THERAPIES FOR PROGRESSIVE MS

SPMS High-dose IFN-β probably has a beneficial effect in patients with SPMS who are still experiencing acute relapses. IFN-β is probably ineffective in patients with SPMS who are not having acute attacks. All of the other agents have not yet been studied in this patient population. Although mitoxantrone has been approved for patients with progressive MS, this is not the population studied in the pivotal trial. Therefore no evidence-based recommendation can be made with regard to its use in this setting.

PPMS No therapies have been convincingly shown to modify the course of PPMS. A phase 3 clinical trial of glatiramer acetate in PPMS was stopped because of lack of efficacy. A phase 2/3 trial of the monoclonal antibody rituximab (anti-CD20) in PPMS was