Multiple sclerosis
therapeutic strategies
Start safe and effective, reassess early, and escalate if necessary

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Multiple sclerosis (MS) is a serious disease that, if left untreated, often leads to disability and reduced quality of life. Some of the newer and emerging MS therapies (e.g., natalizumab, fingolimod) hold potential for enhanced efficacy in comparison to more established treatments (i.e., interferon and glatiramer acetate). However, the increased efficacy appears to sometimes come at the costs of safety and monitoring. In assessing the risk/benefit ratio for the individual patient, clinicians must synthesize many factors to decide upon an ideal treatment strategy. Acknowledging that there may be the rare patient with fulminant and rapidly disabling early MS who may need a highly effective treatment at the beginning, agents with considerable safety concerns should generally be used as “second line.” The initiation of a safe and effective first-line agent should include a comprehensive plan for monitoring disease activity, with potential for rapid changes in therapy if necessary.

Rationale for a stepped approach to treat patients with MS

1. New agents will require several years and tens of thousands of patients before we understand their full safety profile. While recent phase III MS clinical trials are relatively large and reasonably long, important adverse events may be discovered only after the approved medicine is launched. Serious safety concerns may be missed if they are uncommon or associated with a long latency. For example, the multistep process of neoplastic growth and metastasis may take many years to realize. Slow viral infections (e.g., progressive multifocal leukoencephalopathy) may peak after the second year of treatment. In addition,
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clinical trials recruit relatively young and healthy patients, reducing the generalizability of safety to all our patients with MS. Phase III trials cannot provide all the data on safety to offer full counseling to our patients.

2. Patients with MS with aggressive early disease may still respond optimally to a safe, first-line agent. A dramatic initial presentation does not always portend an uncontrollable future disease course. Such patients need to be diligently monitored, but a significant number will respond favorably to a “first-line” agent when provided the chance.

3. MS is a disease of years to decades, not weeks to months. The first-line agents are well-established to reduce relapse rates and severity and MRI lesions. The overwhelming majority of patients will have time to try one first-line medication for 3–12 months to determine whether the initial response is optimal. Malignant and fulminant MS, which may result in sustained disability over a short interval, is uncommon. Continued disease activity despite this first treatment can provide strong rationale for a switch, and would be reassuring to both clinician and patient that a more aggressive approach is warranted.

4. “Induction” strategies remain unproven in MS. While some have advocated for brief and early intervention with a immunosuppressive agent, no evidence supports the concept that we can “reset” this disease to make it more manageable and easier to treat. In addition, even brief treatment with an immunosuppressive agent may carry significant risks for complications due to idiosyncratic and nondose related toxicities.

5. The target population for early and aggressive therapies remains undefined. Properly designed studies are needed to establish who would benefit the most. We do not yet know the number needed to treat nor the number needed to harm. Head-to-head comparisons are lacking between newer and more established medications with regards to reduction in disability progression. Consensus and evidence-based practice guidelines will need to be developed to assist clinicians in these decisions. Should we be attempting to treat the worst 5% of MS, the worst 20%, or the worst 50% with these second-line agents?
Recommendations for newly diagnosed patients with MS

1. At the earliest opportunity after the MS diagnosis, begin a long-established safe and effective agent, along with an individualized plan to monitor response.

2. Utilize early prognostic factors to determine when to make an initial reassessment of treatment response. Those with the most concerning prognostic factors should return early (i.e., 3–6 months) to assess compliance, clinical response, and to obtain imaging studies to assess disease activity on treatment. Concerning prognostic factors might include short interval between first and second relapse, early motor or cerebellar involvement, incomplete relapse recovery, large burden of cerebral T2 lesions, numerous contrast-enhancing lesions at baseline, older age, male gender, and African American ethnicity.

3. Those with less concerning prognostic factors should return for an assessment of medication efficacy at approximately 6 to 12 months. This will allow time for dose titration and full therapeutic effect.

4. One does not need to try all available first-line agents before moving to second line. Some patients cannot wait several years for multiple therapies to fail before switching to what would hopefully be a more definitive treatment.

MS therapeutic research is evolving rapidly. Our level of comfort for an agent will become refined with time and experience, and in the context of other available therapeutics. Additional tools will be integrated into our decision algorithm. For example, the JC virus antibody assay may provide an effective means to help stratify patients into high or low risk for PML.5 Biomarkers for disease prognosis and treatment response are being vigorously pursued. The safety of sequential therapy remains an important consideration (e.g., PML risk with natalizumab and prior immunosuppression). Head-to-head studies are needed which demonstrate improvement in disability with newer agents. Whether other future agents should be used as first line would depend upon mechanism of action, the initial safety signal from phase III study, prior experience in other diseases with similar compounds, and the therapeutic half-life.

Over the past 2 decades, early treatment of relapsing MS has led to improved outcomes. Considerable numbers of patients have had excellent control of their disease for many years. However, patients can still become disabled despite effective therapies and our best efforts. The next generation of medications holds promise for improving outcomes even further. With increasing options, vigilance in monitoring disease activity will be an increasing part of our clinical practice.

REFERENCES


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