MILESTONE 6

More treatments create clinical dilemmas

With the introduction of several disease-modifying therapies (DMTs) for relapsing–remitting multiple sclerosis (MS), the decision of which treatment to use became increasingly complex. The choice between injectable therapies (MILESTONE 1), monoclonal antibodies (MILESTONES 2, 5) and oral drugs (MILESTONE 4) with different efficacies and risks meant clinicians had to start making decisions about which treatment is appropriate, when to commence treatment, and when and how to switch treatments if the clinical response is suboptimal. Each aspect has a dilemma to address for each patient.

Difficulty in selecting the initial therapy for a specific patient with MS comes from uncertainty about the relative efficacies of the DMTs and about how a patient will respond to a particular DMT. Trial results show that some DMTs have a higher efficacy than others; for example, natalizumab is more effective than interferon-β (IFNβ) (MILESTONE 2). However, few DMTs have been compared in head-to-head trials and the relative efficacies of DMTs remain controversial, posing a conundrum for clinicians. Analysis of real-world data can inform treatment decisions, but individual treatment responses cannot be accounted for.

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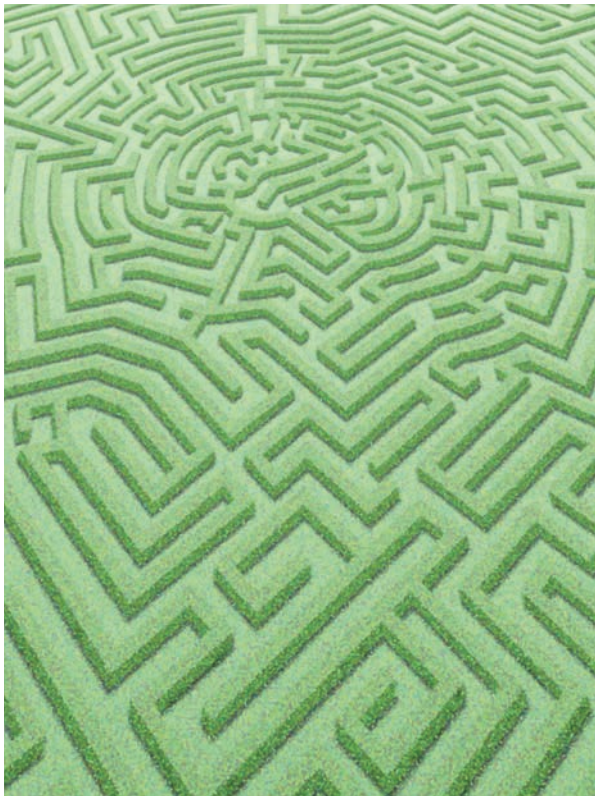

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Consensus has not been reached on how to identify patients who will benefit most from a particular DMT. Some patients respond well to the traditional first-line therapies (IFNβ-1a and glatiramer acetate; MILESTONE 1), whereas others do not and require more potent second-line treatments, such as natalizumab, fingolimod or alemtuzumab. However, these second-line DMTs are typically associated with severe adverse effects, which might preclude their use in some patients.

Consequently, the clinician is faced with a difficult choice. Initial therapy with first-line treatments with the option to escalate to second-line treatments is initially safer, but risks a suboptimal response that allows disease progression. By contrast, initial therapy with a second-line treatment is more likely to induce remission, but could have serious adverse consequences.

Guidelines recommend that the choice of initial therapy be based on a dialogue between patient and clinician and that it takes into account disease severity, patient lifestyle factors and the toxicity and efficacy of available drugs. These factors enable the risk–benefit ratio to be established before therapy is commenced.

Another difficulty that has arisen as a result of the approval of several DMTs is pressure on clinicians to make an early diagnosis. Studies of multiple DMTs have consistently shown that treatment of MS early in the disease course, and even in patients who do not fulfil the entire diagnostic criteria for MS (such as those with clinically isolated syndrome), is associated with better long-term outcomes than later treatment. This finding drives clinicians to make an early diagnosis. As a consequence, misdiagnosis of MS is a risk, occurs regularly and can lead to initiation of unnecessary or incorrect treatments that can have serious adverse effects and can be financially costly.

Finally, as the therapeutic armamentarium for MS has grown, treatment switching to improve a patient's clinical response or to improve tolerability has become an option, but is challenging in clinical practice. Switching therapies has been shown to reduce disease activity in patients with breakthrough disease, although precisely when a patient is deemed to be non-responsive to a particular DMT is a matter of debate. Indeed, even defining a lack of response to DMTs is difficult, as many patients receiving treatment for MS have some disease activity, and several different sets of criteria for a suboptimal treatment response — largely based around MRI activity or clinical findings — have been proposed. Moreover, selecting the appropriate treatment to switch to is complicated by the uncertainty over the relative efficacies of DMTs, and escalation to a treatment of higher efficacy is often associated with more-severe adverse effects.

These clinical dilemmas continue today, and their importance is reflected in the 2018 publication of the ECTRIMS/EAN and the AAN guidelines for the treatment of MS. With more experience, treatment strategies are likely to be refined, and such a range of treatment options presents an opportunity for personalized therapy.

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ORIGINAL ARTICLES Stuve, O. & Centonze, D. Treatment decisions for patients with active multiple sclerosis. *JAMA Neurol.* **72**, 387–389 (2015) | Montalban, X. et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Eur. J. Neurol.* **25**, 215–237 (2018) | Rae-Grant, A. et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* **90**, 777–788 (2018)

FURTHER READING Trojano, M. et al. Treatment decisions in multiple sclerosis — insights from real-world observational studies. *Nat. Rev. Neurol.* **13**, 105–118 (2017) | Solomon, A. J. & Corboy, J. R. The tension between early diagnosis and misdiagnosis of multiple sclerosis. *Nat. Rev. Neurol.* **13**, 567–572 (2017)