Multiple sclerosis therapeutic strategies

Use second-line agents as first-line agents when time is of the essence

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Multiple sclerosis (MS) is a damaging CNS disease. Because the CNS has inherent properties that prevent the damage from manifesting readily (e.g., redundancy, plasticity, repair), often irreversible damage is not appreciated until very late. Pathologically it is apparent that permanent and irreversible damage occurs very early in MS plaque formation.[1] Treatment of the disease course can therefore be viewed as having 3 goals:

1. Damage control to prevent or limit further damage
2. To protect injured axons and neurons from further injury
3. To encourage repair of reversibly damaged tissue

It is clear that once patients are diagnosed with MS, or at high risk of developing MS (clinically isolated syndrome), they have already sustained damage to their CNS. How much damage it takes before patients actually present is variable: it is astounding at times to see patients even after one attack who have accumulated substantial disease loads on their MRI scans or already demonstrate symptoms and signs of chronic disease, such as cognitive or even physical impairment. It can be argued that current therapies are inadequate for some of these patients, though the goals of therapy are still probably reasonable but more difficult to realize. Once a patient enters the progressive phase of illness, with few relapses and minimal activity on MRI, it may be too late with our current armamentarium of agents to attain any of the stated goals of treatment.

The exact etiopathogenesis of damage in MS is still not certain, but autoimmune mechanisms seem to prevail in terms of being the most likely means of CNS injury, at least early in the course of disease. Current disease-modifying agents are directed at controlling this type of immune-mediated damage, but are not all equal in terms of their ability to do so in any given individual. Theoretically, there may be different mechanisms operating at a given time or in a given individual,[2] but there is really no way of knowing what this is in order to choose the most effective treatment. Treatment therefore becomes more empiric: more "hit and miss." Typically the choice of therapy is based on several factors such as perceived efficacy, safety, mode of administration, cost, and others, but the main goals of therapy must be kept in mind. For a patient who is deemed early in their course of disease and has not yet sustained much accumulated damage or a very active disease course (i.e., numerous relapses or active lesion formation), the main goal might be to protect the CNS from further damage. Alternatively, some patients may present rather late in their disease course, having already sustained considerable damage, and one can imagine that "one more hit" will tip that individual over into a more progressive course, where few if any of our current therapies have shown convincing

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Figure   Window for treatment
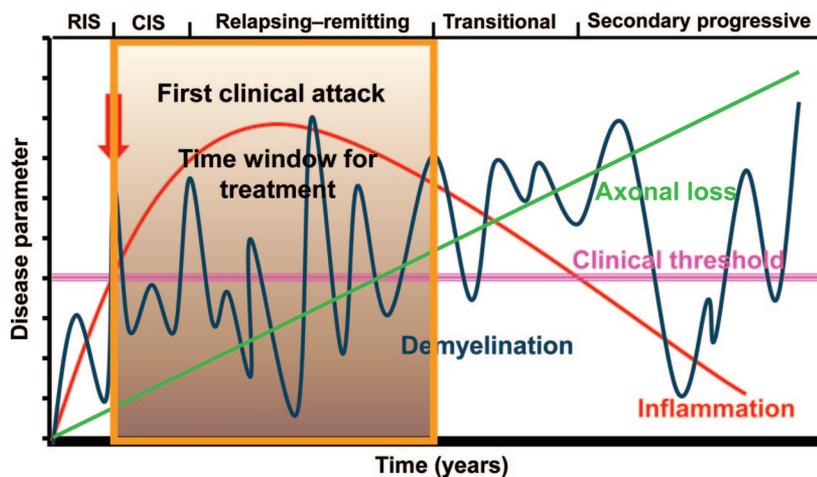
The "window for treatment" probably opens when patients first present clinically with their condition and might be considered to close once it is clear that they are in the progressive phase of illness with waning inflammation and growing axonal damage. CIS = clinically isolated syndrome; RIS = radiologically isolated syndrome.

efficacy. We must keep in mind that our tiered therapies (first, second, et cetera) are based on their benefit to risk ratio, with the perception that more effective therapies may also buy into a higher risk of toxicity. Should treatment therefore always begin with the safest of agents, and only when they demonstrate an inability to adequately contain the disease should second- or third-line agents be called into play? For the last patient described who is apt to enter a progressive phase with "one more hit," it may be too late to try and fail with a first-line agent. For such an individual, time is of the essence and one might consider using a highly efficacious but potentially toxic agent first in an effort to quickly shut down any active inflammation.

So what is the evidence that second-line or greater agents can accomplish better disease control compared with first-line agents? There are 2 lines of studies to guide us in this direction. First there are comparator studies such as SENTINEL, which compared natalizumab and weekly interferon-β1a IM with weekly interferon-β1a IM alone,[3] and the TRANSFORMS study, comparing the same interferon with fingolimod,[4] both showing that either natalizumab or fingolimod were superior to the interferon in terms of continued disease control. In SENTINEL, patients had to demonstrate continued activity while on interferon prior to being randomized, whereas in TRANSFORMS, nearly 60% of patients had been on first-line treatments prior to coming into the study. An extension of TRANSFORMS[5] also was able to demonstrate that switching from the interferon to fingolimod led to enhanced efficacy. Both studies therefore show that either natalizumab or fingolimod might be superior to first-line agents in terms of disease control. The second line of evidence comes from the assessment of newer therapies in terms of patients whose baseline characteristics would characterize them as being more advanced with higher disease burdens and reanalyzing efficacy outcomes. Despite being post hoc, such analyses would indicate that older patients, those with higher relapse rates, those who had accumulated disease burden by Expanded

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Disability Status Scale >3, or those who had very active MRI studies with enhancing lesions or greater T2 burden of disease all fared just as well or better on the newer agents.[6] It is hard to say how first-line therapies would have done with this subgroup of patients, since such data are not readily available from what are now nearly decades-old studies, and the population today has clearly changed.

Choice of therapy boils down to "where" in the "window of treatment opportunity" (figure) a patient lies when being assessed, what if anything has already been tried in terms of treatment, and what is available for use in any given part of the world. A patient with high level disease activity or someone approaching the "end of the window" might be willing to accept a higher risk in return for a more rapid induction of disease control.

Clearly not all MS cases present the same or follow similar courses and it is imperative that we have available all possible therapies so effective disease control can be attained for as many patients as possible, because "time is brain" even when it comes to MS.[7]

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