Neurotherapeutics (2020) 17:971–972
https://doi.org/10.1007/s13311-020-00869-8

COMMENTARY

Commentary: The Multiple Sclerosis Controversy: Is It Escalation or Induction High Efficacy?

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Published online: 2 June 2020

Multiple sclerosis (MS) is the major acquired central nervous system (CNS) disease of young adults [1, 2]. It causes organ-specific immune-mediated pathology characterized by inflammation, demyelination, and neurodegeneration. MS shows a 3:1 female predominance and great variability in disease expression. Particularly in untreated individuals, there are ongoing accumulating macroscopic and microscopic damages to the CNS.

MS is a poster child for a success story in the clinical neurosciences. This major disease has moved from untreatable to quite manageable, with a wide array of disease-modifying therapies (DMTs) [3]. In the USA, the FDA has approved 23 distinct agents covering 10 mechanisms of action, all focused on manipulating the immune system.

One of the major current debates in MS involves the optimal choice of the very first DMT. This treatment debate is couched in terms of taking an escalation approach or a high-efficacy induction approach [4]. Should a very safe but modestly effective DMT be chosen routinely, or would most patients do better if they were started on a high-efficacy agent from the beginning, even if it carried more risk? Induction, also referred to as immune reconstitution therapy, involves using a potent immunosuppressive for a limited time, because it produces a long-lasting effect on the host immune system [5]. Its use may be followed by a prolonged drug-free period or the institution of a milder maintenance agent.

Because MS is so variable and most people present with relatively mild disease, high-efficacy, higher-risk DMTs are generally reserved for very active MS individuals with a poor prognostic profile. The MS DMTs can be divided into injectable immunomodulators, oral agents, and high-efficacy monoclonal or infusible agents. There is accumulating data for a therapeutic window of opportunity early on in MS, to maximize long-term therapeutic benefits [6]. The argument has been that a highly effective agent will quickly shut down the immune attack against the CNS, perhaps resetting the severity of the disease and minimizing epitope spread.

Virtually, every study has noted MS patients treated early do better than those in whom treatment is delayed. But does the potency of the DMT truly matter? In a recent retrospective observational study from the Global MSBase Registry and the Swedish MS Registry, relapsing patients, who started a high-efficacy DMT (rituximab, ocrelizumab, mitoxantrone, alemtuzumab, natalizumab) within 2 years of disease onset (early treatment; $N = 213$), were matched to those who started these therapies after 4 to 6 years (late treatment; $N = 253$) [7]. The outcome was development of long-term disability, 6–10 years later. MS patients who received early high-efficacy treatment showed significantly less long-term disability (their mean Expanded Disability Status Scale (EDSS) was 2.3 *vs* 3.5, $p < 0.001$). But, this is a single study suggesting high-efficacy DMTs are more effective when used early. It does not truly address the escalation *versus* high-efficacy induction debate.

Two recent studies, from Cardiff Wales and from a global study including the MSBase Registry, both reported that MS individuals given early high-efficacy *versus* escalation therapy had less late disability, measured respectively by EDSS change at 5 years, and lower rates of conversion to secondary progressive MS [8, 9]. Such studies favor high efficacy.

In this issue of *Neurotherapeutics*, the study by Prosperini et al. [10], from 5 MS centers in Central Italy, adds to the accumulating data on this therapeutic controversy. They looked at untreated relapsing patients within 5 years of disease onset. Most ($N = 738$) were started on a moderately effective escalation DMT, interferon beta. A minority ($N = 75$) was started on high-efficacy cyclophosphamide or mitoxantrone. Both of these therapies would qualify as long-lasting induction immune reconstitution therapy. The MS group who started on induction therapy was older and more disabled.

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To try to make up for the lack of randomization, propensity score matching was carried out to whittle the escalation group down to 75 well-matched patients. Both groups were followed for 10 years, to determine time to a hard disability marker of EDSS ≥ 6, sustained to the end of the study. EDSS 6 means requiring a cane to walk 100 m. In this independent multicenter, post-marketing study, the induction therapy group was less likely to reach this disability marker over the next 10 years (28% *vs* 38.7%, $p = 0.024$). Considering the entire group, the induction therapy cohort did experience more serious adverse events (10.7% *vs* 2.4%, $p = 0.001$). There is always a risk–benefit analysis that goes into choosing an MS DMT. This study of course was not randomized. It also employed two high-efficacy agents that are now rarely used in MS (cyclophosphamide and mitoxantrone). The ultimate answer to this controversy cries out for randomized trials.

The Patient-Centered Outcomes Research Institute has funded two ongoing studies: DELIVER-MS [11] and TREAT-MS [12]. They are randomizing relapsing MS individuals to receive either escalation or high-efficacy DMT. The primary outcomes are brain volume loss at 3 years and time to sustained clinical disability up to 4.5 years. We look forward to seeing results from these prospective trials. They may finally answer the controversy surrounding escalation *versus* induction high-efficacy therapy for MS.

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