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Letter to Editor

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Escalation or high-efficacy disease-modifying therapies in multiple sclerosis

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Dear Editor,

Question

Considering safety and future disability, which approach (high-efficacy disease-modifying therapy OR escalation) is preferable in multiple sclerosis (MS) patients?

Search strategy

The search was performed in PubMed and Cochrane databases using the keywords "multiple sclerosis" AND "escalation" OR "early intense therapy" OR "high efficacy therapy" OR "high efficacy disease-modifying therapy".

Cochrane Results: not matched

Search outcome

Forty articles were found. Title and abstracts of all articles were evaluated. 14 relevant studies were found: 3 cohorts, 6 reviews, 3 cross-sectional retrospectives, 1 clinical trial, and 1 editorial. Three recent and most relevant articles were selected.

Comments

The treatment strategy for MS is a highly controversial debate. Disease-modifying therapies for MS are divided into escalation therapies and high-efficacy therapies. Escalating treatment means starting with the safest disease-modifying therapies with moderate effect. High-efficacy therapies mean starting with a strong immune intervention.

The majority of studies agree on this issue that the advantage of the escalation scheme is to allow many patients to have satisfying control of the disease while receiving relatively safe drugs and never escalating to more aggressive therapy (Table 1). But the disadvantage is exposing some patients to the risk of losing precious years spent receiving a treatment that was not potent enough and potentially leading to sustained accumulation of disability. The advantage of high-efficacy disease-modifying therapies is to facilitate an earlier achievement of "no evidence of disease activity", and the disadvantage is the risk to expose some patients needlessly to serious side effects.

Clinical bottom line

The current challenge in therapeutic strategy is to identify the most effective drug and strategy during a specific phase of the disease of every single patient. Sex, age, and presenting symptoms might predict increased disease severity in MS patients. With present markers, such as volumetric MRI and emerging markets such as serum neurofilament light chain, early and accurate prognostication in individual patients will become possible. New MRI techniques (brain and spinal cord imaging) should help us to identify those MS patients, especially individuals without any real disability, who are more at risk of developing destructive CNS lesions with or without first-line therapy and who are therefore more eligible for an early and more aggressive treatment strategy (6).

The higher costs of high-efficacy therapies can present challenges, particularly for patients without comprehensive insurance coverage or those residing in regions with limited access to healthcare resources. Escalation therapies, on the other hand, may be more cost-effective initially, but they might not provide the same level of disease control as high-

Table 1. Results of the included studies

Harding *et al. (1)*	
Patients	A total of 592 MS patients (104 received early intense therapy and 488 received escalation therapy)
Study type	A population-based cohort of patients with MS
Outcome	Five-year change in Expanded Disability Status Scale (EDSS) score, and time to sustained accumulation of disability (SAD)
Key results	Those who received high-efficacy treatment initially had a smaller increase in EDSS score at 5 years vs those who first received moderate-efficacy disease-modifying therapy. There was no difference in hazard of SAD between the groups
Study weakness	A lack of uniformly acquired imaging or adverse event data compared with clinical trials
Prosperini *et al. (2)*	
Patients	3851 patients in the escalation group and 132 in the induction group who started treatment from 1998 to 2009, successfully matched 150 MS patients (75 early intense therapy and 75 escalation therapy) were included
Study type	Retrospective, independent, multicenter, post-marketing study
Outcome	Serious adverse events, risk of reaching the disability milestone
Key results	Lower proportion of patients reached the milestone of EDSS 6 at 10 years, in patients with poor prognostic factors, induction was more effective than escalation in reducing the risk of reaching the disability milestone, albeit with a worse safety profile
Study weakness	Retrospective design, small sample size (especially for induction group), and comparison of patients in different treatment eras (MTX and CYC are no longer prescribed given the increased availability of newer drugs)
Due Buron *et al. (3)*	
Patients	388 MS patients, 194 starting initial therapy with high-efficacy disease-modifying therapies matched to 194 patients starting medium-efficacy disease-modifying therapies.
Study type	A cohort study
Outcome	The probabilities of a 6-month confirmed EDSS score worsening, probability of a first relapse
Key results	Lower probability of 6-month confirmed EDSS score worsening and lower probability of a first relapse in patients starting a medium-efficacy disease-modifying therapies as first
Study weakness	They were not compared the characteristics and severity of adverse events between the study groups.
Simonsen *et al. (4)*	
Patients	694 patients diagnosed with MS who had been treated with either moderate efficacy disease modifying therapies or high efficacy DMTs for at least 12 months
Study type	A cohort study
Outcome	the impact of initial treatment choice in achieving no evidence of disease activity (NEDA) at year 1 and 2.
Key results	Patients treated with high-efficacy disease modifying therapies have a notably higher likelihood of achieving NEDA at year 1 and 2 compared to those on moderate efficacy therapies, and the initial treatment selection plays a crucial role
Study weakness	Some patients were excluded from the study due to missing or incomplete information
Rojas *et al. (5)*	
Patients	patients with relapsing-remitting multiple sclerosis in Argentina
Study type	retrospective multicenter cohort study
Outcome	confirmed disability progression (Expanded Disability Status Scale [EDSS] increase); the proportion of patients and time to: EDSS 6; new relapses; new T2–magnetic resonance imaging (MRI) lesions; no evidence of disease activity; and specific adverse events
Key results	study shows that early high-efficacy therapies prevent disease progression, relapses, and new MRI lesions and demonstrated no increased risk of specific adverse events when compared with Escalation therapy
Study weakness	the study did not include a direct comparison of the cost-effectiveness of the two treatment approaches

efficacy options (5).

High-efficacy disease-modifying therapies (DMTs) in the context of MS can provide potent control over the disease, but they are also accompanied by potential adverse effects (7). These may encompass immunosuppression, reactions during infusion or injection, potential harm to the liver, cardiac complications, an elevated risk of developing certain cancers, blood-related disorders, headaches, flu-like symptoms, gastrointestinal disturbances, and alterations in mood. Patients considering the use of high-efficacy DMTs should be well-informed about these potential side effects and engage in

comprehensive discussions with their healthcare providers to carefully assess the risks and benefits of these treatment options tailored to their individual MS management plan (8). Regular monitoring and open communication with healthcare providers are fundamental to effectively manage any possible side effects and maximize the benefits of these therapies (1).

Considering lifestyle modifications, especially exercise and diet, alongside disease-modifying therapies is crucial in managing MS. Lifestyle factors can significantly impact the disease's progression and should be a part of the overall treatment strategy. Regular exercise offers numerous benefits for individuals with MS, including improved muscle strength, balance, mobility, reduced fatigue, and enhanced mood and well-being (9). A well-balanced diet, rich in nutrients, antioxidants, and omega-3 fatty acids, can help reduce inflammation and support brain health in MS patients. Including information about lifestyle modifications in treatment discussions would lead to a more comprehensive approach to MS management, empowering patients to actively participate in their care and enhance their overall health and quality of life (10).

Keywords: Escalation, high-efficacy, Multiple Sclerosis

Declaration

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Conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

Ethical approval

No need

Consent for publication

This manuscript has been approved for publication by all authors.

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