

## Escalation or induction?

# Treatment of relapsing-remitting multiple sclerosis

Marie Théaudin<sup>a</sup>, Gilles Edan<sup>b</sup>

<sup>a</sup> Department of Neurology, CHUV, Lausanne, Switzerland

<sup>b</sup> Department of Neurology, CHRU Pontchaillou, Rennes, France

## Summary

Standard therapy for the majority of multiple sclerosis patients is escalation therapy. Induction therapy may be indicated for severe and active multiple sclerosis. The only two pharmacological agents that can be used for an induction approach are alemtuzumab and mitoxantrone because of their prolonged residual effect. Brain magnetic resonance imaging is a key examination for monitoring patients with relapsing-remitting multiple sclerosis.

Key words: escalation; induction; multiple sclerosis; treatment



## Introduction

Extensive advances in multiple sclerosis treatment options have revolutionised multiple sclerosis treatment approaches. After a period when escalation therapy was considered the main option for relapsing-remitting multiple sclerosis, there is now increasing interest in using induction therapy in selected patients.

## Escalation therapy

### Definition

The escalation therapy strategy starts with a first-line medication with fewest side effects, with a switch to more effective, but usually more toxic, treatment when the response to first-line treatment becomes suboptimal. This approach has the advantage of working in most patients, who will have relatively low risk therapy, but the downside is that some patients may lose several years as a result of receiving one or more ineffective treatments, leading to permanent disability. The main challenge with this approach is defining up-front, with the patient, the point at which his or her first-line treatment response is no longer adequate, justifying the switch to more intensive treatment.

### Defining treatment failure

The Sormani criteria [1] can be useful for defining treatment failure (fig. 1). This combination of clinical and radiological criteria makes it possible to identify patients at risk of an unfavourable disease course. However,

these measures were validated for the evaluation of response to interferon therapy 1 year after treatment initiation. Can we extrapolate them to all treatment regimens, regardless of the duration of the on-going treatment? Should all patients have brain magnetic resonance imaging (MRI) every year, or just during the first years of treatment? Some would say that the appearance of one or two new lesions a year is not a critical factor for a no-response-to-treatment decision, and that no evidence of disease activity (NEDA) is more appropriate [2]. What is certain is that any criteria used to define inadequate response to current treatment and to prompt a switch to a new treatment stage must take into account previous disease history (disease course length, previous disease activity, severity of attacks, treatments already tried) and, most likely, the present lesion load. Simple decision-making algorithms can be proposed, but the choice to change to the next line of treatment because of current treatment “failure” must be made on an individual basis, which is often complex with additional factors to take into account, such as JC virus serology, desire for pregnancy in the short or medium term, the psychosocial profile of the patient and treatment acceptability.

### Practical scenarios (figures 1 and 2)

The prioritisation of pharmacological agents according to their efficacy is rarely based on head-to-head randomised comparison studies. Propensity score studies have provided some answers [3, 4], but with limitations related to their methodology.

Please note that the proposed algorithms are based on available scientific data and personal experience of the author and in no way constitute proven “standard of care”.

## Induction therapy (fig. 2)

### Definition

The induction therapy strategy entails use of a powerful treatment right from the start, which generally allows NEDA to be reached quickly. This is followed by either no treatment, treatment as needed, or main-

tenance therapy with a better-tolerated drug. The risk with this approach is “overtreatment” of patients thereby exposing them to potentially serious side-effects.

*What type of patient?*

There is no international consensus on the profile of patients for induction therapy. In 2013, Edan et al. [5] proposed the following selection criteria: recurrent relapsing multiple sclerosis, age <50 years, very active multiple sclerosis with at least two relapses in the last year, at least one severe relapse with an Expanded Disability Status Scale (EDSS) score >4, progression of the EDSS score due to relapse (by at least 2 EDSS points in the last 12 months), and at least two gadolinium-enhanced lesions on recent MRI. However, these criteria are not exclusive and decisions about induction therapy should currently be made on a case-by-case basis.

*What types of drugs?*

The only two drugs available with proven ability to act as therapeutic inducers are mitoxantrone and alemtuzumab [6, 7]. Cladribine has a prolonged residual effect and may also fall into this use category when it becomes available [8]. Autologous haematopoietic stem cell transplantation [9] has an efficacy profile that would allow its use in this indication, although currently it is essentially proposed as part of a therapeutic protocol and only in experienced centres. There are no data in the literature suggesting a long-term effect on disease control after ocrelizumab discontinuation and thus we would not recommend it for induction therapy.

**Conclusion**

Widening of the therapeutic arsenal in multiple sclerosis opens up new perspectives bringing greater opportunity for personalised therapy. However, detailed guidelines, based on general consensus, that define treatment efficacy at the individual level have yet to be published. Randomised trials testing the benefit and safety of early induction therapy, and comparing escalation with induction therapy are warranted. Finally, the neurologist today faces new problems, including management of short- to long-term side effects, of treatment switches, and of pregnancy in patient of childbearing potential.

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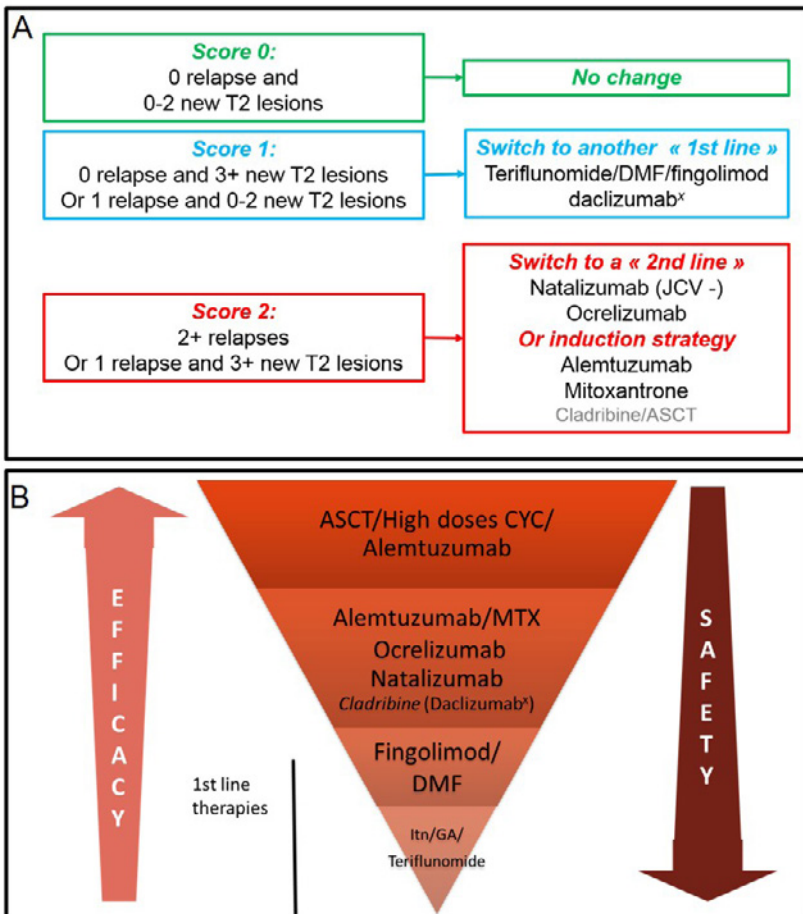
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**References**

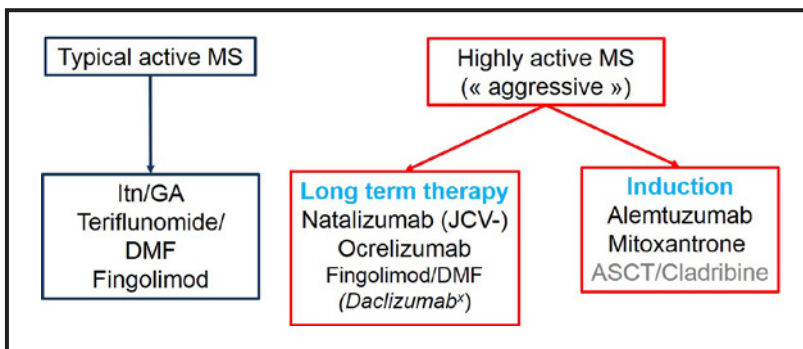
The full list of references can be found in the online version of this article: 10.4414/sanp.2018.00552.

**Correspondence:**

Marie Théaudin, MD PhD  
Department of Neurology, CHUV, avenue du Bugnon 46, CH1011 Lausanne  
marie.theaudin[at]chuv.ch



**Figure 1:** A. Proposed criteria for switching therapy based on clinical and radiological activity under treatment and after 1 year of treatment. The baseline MRI for follow-up should be within 3 to 6 months of initiation of treatment. B. Proposal to prioritise the available treatments based on effectiveness and side effects. GA: glatiramer acetate; DMF: dimethyl fumarate; Itr: interferon; ASCT: autologous stem cell transplantation.



**Figure 2:** First-line treatment initiation algorithm for relapsing-remitting multiple sclerosis (MS), depending on the initial disease activity. GC: glatiramer acetate; JCV: JC virus serology; DMF: dimethyl fumarate; Itr: interferon; ASCT: autologous stem cell transplantation. \* Owing to risk of serious liver damage, EMA has restricted the use of daclizumab to patients who have had an inadequate response to at least two disease modifying therapies (DMTs) and cannot be treated with other DMTs.