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Multiple sclerosis on behalf SFSEP

Induction or escalation therapy for patients with multiple sclerosis?

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ABSTRACT

The concept of induction followed by a long-term maintenance treatment has attracted much attention for the treatment of multiple sclerosis over the 30 past years. It was first demonstrated by the combination of induction therapy with mitoxantrone (six-monthly courses) followed by maintenance therapy with an immunomodulatory treatment such as an interferon-β or glatiramer acetate. Long-term observational studies confirmed that this therapeutic regimen provides a rapid reduction in disease activity and sustained disease control up to at least five years in 60% of patients. A better treatment response was observed in patients with early signs of aggressive disease, as shown in randomised studies (using six-monthly 12 mg/m^2 of mitoxantrone intravenously at a cumulative dose of 72 mg/m^2, followed by an interferon-β) as well as in long-term observational studies. But the safety profile of mitoxantrone make it more particularly suitable for young patients with frequent early relapses with incomplete recovery and multiple gadolinium-enhancing T1 lesions or spinal cord lesions on magnetic resonance imaging. More recently approved, the second candidate for an induction strategy is alemtuzumab: phases II and III randomised studies showed the superiority of alemtuzumab 12 mg per day given intravenously for only five days and repeated for 3 days one year later, compared with interferon-β three times a week. Like with mitoxantrone, results supported the concept of long-term benefit after a short induction rather than escalation, in a subset of patients with early very active MS, with a sustained control of the disease for up to 7 years in 60% of patients in the phase III extension studies and in a long-term observational study. On the contrary, when alemtuzumab was first studied later in the disease course, results were disappointing. However, the risk of developing manageable but potentially severe systemic autoimmune diseases within the years following the last course of alemtuzumab make it, like mitoxantrone, more suitable for patients with early aggressive MS. More recently, cladribine an oral immunosuppressant, showed interesting results in a phase III study extension suggesting its potential induction effect, since after two cycles of treatment (5 days repeated 1 month later) at one year of interval, the remained low up to 4 years of follow-up, in the absence of any new treatment. However, today other immunosuppressive drugs have proved to be strongly and rapidly efficacious in treating highly active MS patients but through a mechanism of continuous immunosuppression (i.e., natalizumab and ocrelizumab). Indeed, disease activity can reappear rapidly after stopping these drugs, sometimes associated with a rebound of the

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inflammatory process, which is the contrary of a mechanism of induction that is associated with a remnant effect. Taking into account advantages and disadvantages of the different DMDs, which enriched the today therapeutic arsenal for MS, we propose in this paper some algorithms summarizing our reflexion about using an escalation strategy or an induction strategy according to disease course and activity.

1. Definitions of escalation and induction

The concept of induction treatment followed by a long-term maintenance treatment combining different drugs was first demonstrated in oncology. For example, in acute lymphoblastic leukaemia, the use of induction regimens associating bone marrow transplantation and combinations of cytotoxic drugs has raised event-free survival rates over 80% after five years in young patients, while this condition was previously rapidly fatal [1]. In MS, in theory two opposite schemes of therapeutic strategies using the different disease-modifying drugs (DMD) available can be discussed [2–4]: the escalating approach and the induction therapy. An induction therapy is associated with a more aggressive effect on the immune system that seems to have more relevant short- and long-lasting beneficial effects. This old concept is probably close to the emerging concept of ''Pulsed immune reconstitution therapy'' (PIRT) for the treatment of MS [5].

1.1. *Escalating treatment*

Escalating treatment means to start with the safest DMDs. If they failed, the escalation to more aggressive second-line and then third-line DMDs is warranted. The escalating approach sees as first-line treatment glatiramer acetate and beta-interferons, teriflunomid, dimethylfumarate, and eventually fingolimod. Second-line DMDs, i.e. natalizumab and ocrelizumab are responsible for a selective continuous immunosuppression. Third-line DMDs i.e. mitoxantrone and alemtuzumab are respectively non-selective and selective PIRT. Finally, more intensive immunosuppression with autologous bone marrow transplantation and high dose cyclophosphamide can be considered as last line of rescue therapy. Recently approved, daclizumab and cladribine may complete this therapeutic panel, probably as second-line treatments. The advantage of escalation scheme is to allow many patients to have a satisfying control of the disease while receiving relatively safe drugs and never escalating to more aggressive therapy. But the disadvantage is to expose 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. Then the key to the success of the escalation strategy is to define upfront with the patient the exact suboptimal response threshold at which the next-level therapeutic option should be introduced, without crossing the line of irreversible further sequelae.

1.2. *Induction treatment*

Induction treatment means to start with a strong immune-intervention. The advantage is to facilitate an earlier achievement of ''no evidence of disease activity'', which is the gold standard for MS treatment in some schools of thoughts. But the disadvantage is the risk to expose some patients needlessly to serious side effects that are well known with the strongest immunosuppressive agents for MS. Then the key to the success of induction strategy is to use immunosuppressants for the minimum amount of time needed to gain adequate control over disease activity, i.e., to start with a strong immunossuppression followed by a maintenance therapy with safer drugs for a de-escalation. Considering the potential serious side effects of the immunosuppressive therapeutic candidates for an induction, this strategy has generally been reserved for patients with very active or aggressive disease at onset. In these patients, it is recognised that the risk of early disability is high and that once neurological function is lost it cannot be restored. In such patients, this disease-inherent risk can be considered to outweigh the risk of potential serious side effects of powerful immunosuppressant drugs. The aim of this strategy is to prevent early structural damage related to inflammatory-mediated demyelination and axonal loss. This induction treatment strategy may be a useful and conservative way to use these highly effective therapies while minimising exposure and the subsequent safety risks.

2. Patients candidates for an induction strategy

Over the past two decades, important epidemiological, radiological and therapeutic studies provided evidence for the concept of early treatment in patients with a diagnosis of MS, which is shared by Consensus Groups. The goal of DMDs is to prevent accumulation of sustained neurological disability and in particular to prevent from the risk of transition to a secondary progressive (SP) MS. Today, the prognostic factors associated with a high risk of long-term disability are well established and there is strong evidence that it is mostly defined in the early phase of the disease. It now seems clear that patients who experience frequent relapses in the earliest stages of disease and those who accumulate a large number of T2 focal lesions visible on MRI, with particular concern for spinal cord lesions, become disabled more quickly than those

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