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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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who do not [6–8]. This is well illustrated by the concept of MS as a two stage disease with a first phase depending of focal CNS inflammatory lesions and a second phase independent from focal CNS inflammatory lesions but driven by a neurodegenerative process [6]. Because the target of all approved DMDs is the focal inflammation, which predominates at the beginning of the disease course, it is logical to concentrate all the therapeutic efforts in the early (first) phase of the disease. Indeed, if some positive effect was recently described in progressive forms of MS with ocrelizumab and siponimod [9,10], results should be interpreted cautiously because when considering patients without any clinical or radiological sign of inflammation, current DMDs might not be expected to be as effective while the focal inflammatory process is less relevant and their action on the neurodegenerative process uncertain. This is probably because the immune derangement characterising MS increases over time and probably also shift from a peripheral immune-pathological profile to a central nervous system compartmentalised profile in late MS [11]. Having said that, should we consider that the initial treatment of early active RR MS should be with a potent induction therapy rather than standard immunomodulation then escalation for most patients with early RRMS, moving from the concept of ''earlier treatment better for RRMS'' to the concept of ''earlier maximally efficacious treatment better for RR MS''? No, this approach should be considered for a selected group of RR MS patients having negative prognostic factors [4]: pure relapsing MS, young, highly active with ≥ 2 relapses within the previous 12 months, severe relapse resulting in EDSS score ≥ 4, worsening EDSS score due to relapses (increase of ≥ 2 points within the previous 12 months, ≥ 2 additional gadolinium-enhancing lesions) (réf article drugs). Furthermore, an interesting algorithm proposed by the MAGNIMS group can be used to identify patients at risk of disability worsening according to clinical and radiological markers of MS activity recorded during the first year of treatment with a first-line DMD [12]. This algorithm was determined on the basis of 1280 naïve patients, treated for at least one year with an interferon-beta and followed for two additional years. The percentage of patients with increased EDSS score during the two following years were of 22% for patients having one relapse or ≥ 3 new T2 lesions (score 1) during the first year and 29% for patients having one relapse and ≥ 3 new T2 lesions (score 2) during the first year. These results provide a useful daily life tool for monitoring the response to a first-line treatment and the potential need to switch to another DMD. Taking into account these considerations, some strategic propositions are summarized for using DMDs in Figs. 1 and 2: how to start according to clinical and radiological activity during the 12 previous months and how to switch using the score of Sormani [12] during a first year of exposure to a first-line therapy: in typical RR MS patients, start with a first-line therapy; in highly active MS patients, start with a second-line therapy preferring natalizumab and ocrelizumab in JC virus negative patients for a continuous immunosuppression, or with mitoxantrone and alemtuzumab in JC virus positive patients for a pulsed immune reconstitution with a remnant effect eventually followed by a maintenance therapy. A switch to another first-line therapy might be considered for patients having a score 1 of Sormani and a switch to a second- or third-line therapy might be considered for patients having a score 2 of Sormani during the first year of a first-line DMD therapy.

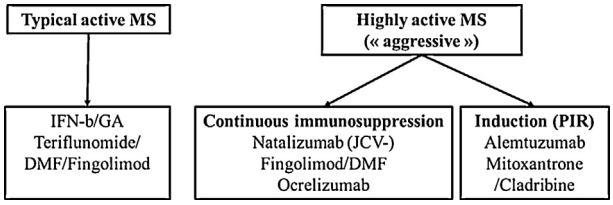


Fig. 1 – Starting a disease-modifying drug (DMD) in RRMS according to clinical and MRI activity during the previous 12 months. GA: glatiramer acetate; IFN-b: interferon-beta; DMF: dimethylfumarate; JC−: seronegative for JC virus; PIRT: pulsed immune reconstitution therapy.

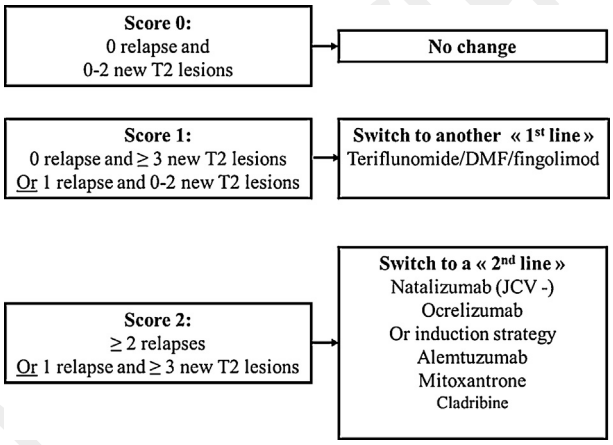


Fig. 2 – When and how to switch? GA: glatiramer acetate; IFN-b: interferon-beta; DMF: dimethylfumarate; JC−: seronegative for JC virus; PIRT: pulsed immune reconstitution therapy.

3. Three drugs can be considered to have an induction effect

Mitoxantrone was the first drug studied in an induction protocol scheme in relapsing MS and was for almost 10 years the only immunosuppressant to be approved in this indication in most countries. Indeed, mitoxantrone was licensed in October 2000 by the Food and Drug Administration (FDA) in worsening RR, SP and relapsing progressive MS patients and in several European countries in 2002, to be administered every three months (12 mg/m^2; maximum cumulative dose 140 mg/m^2). Then, in October 2003 the Agence française de sécurité sanitaire pour les produits de santé (AFSSAPS) approved mitoxantrone for treatment of aggressive relapsing MS given monthly for 6 months (12 mg/m^2; maximum cumulative dose 72 mg/m^2). In consequence, there is long-term data to support its strong rapid and sustained efficacy in the indication of relapsing aggressive MS taking into account its safety profile that is well documented [13–17]. In the 2000s, phases II and III studies [18–21] were designed to compare

alemtuzumab with interferon-beta 3 times a week in active MS patients, showing a rapid strong and sustained action on the inflammatory process and decreased risk of sustained disability worsening more specifically in patients who were non responders to a first-line DMD. Alemtuzumab was approved by the FDA in November 2011 and in Europe in September 2013 in relapsing MS, given at the dose of 12 mg per day for 5 days repeated during three days 1 year later. But if long-term follow-up of patients confirmed the remnant effect of the drug with sustained efficacy, severe autoimmune adverse effects were well documented. Alemtuzumab might then be like mitoxantrone a good candidate for induction therapy in young early highly active relapsing MS patients. More recently cladribine, an oral immunosuppressant, was approved in august 2017 by the European Medicines Agency (EMA) in patients with very active relapsing MS, on the basis of two phase III studies versus placebo and their extensions [22,23]. The drug might also be a good candidate for an induction therapeutic scheme because it is given at the dose of 3.5 mg/kg as following: 5 days of oral treatment the first month and the second month, followed by the same scheme the second year, with a remnant effect the third and fourth years.

These three drugs showed a very rapid significant control of the inflammatory process, more specifically in highly active MS patients for mitoxantrone and alemtuzumab, sustained for several years after a short administration of the treatment, with maintenance therapy with a safer drug in the case of mitoxantrone, there are indeed few studies on the long-term efficacy of induction strategies followed by a maintenance therapy [15–17]. These observations support the hypothesis that these three drugs can be classified as PIRT.

On the contrary, natalizumab a highly selective strong approved immunosuppressive drug in MS [24], cannot be recommended for induction use because its withdrawal was commonly followed within few months by the reoccurrence of disease activity [25,26]. The anti-CD20 ocrelizumab is not either a good candidate for an induction strategy since the treatment has to be administered every 6 months [27] to avoid the reoccurrence of disease activity.

3.1. *Mitoxantrone: the first treatment to demonstrate an induction action*

Mitoxantrone, an anthracenedione, is a synthetic antineoplastic agent first discovered in1978. It has proven therapeutic efficacy in advanced breast cancer, non-Hodgkin's lymphoma, acute lymphoblastic leukemia, chronic myeloid leukemia and liver and ovarian carcinomas [28–32]. Soon after its introduction as a cytotoxic agent in cancer chemotherapy, it was found to be immunosuppressive. Wang et al. showed that in vitro alloreactivity was almost completely abrogated by mitoxantrone. The drug interfered only with lymphocytes capable of proliferating in response to newly presented antigens without affecting precursor populations. The effects were remarkably long-lasting [33,34]. Then the drug was studied in MS for its immunosuppressive properties.

3.1.1. *The pivotal trial [13]*

The French and British randomised controlled trial [9], evaluated the short-term benefits of mitoxantrone treatment for six months in 42 patients with very active RR or SP MS, defined as the occurrence of two or more relapses without recovery or disability progression by more than two points in the previous twelve months, together with MRI evidence of active disease. Patients were randomised to receive either mitoxantrone (20 mg) and methylprednisolone (1 g) intravenously every month or methylprednisolone alone over six months. The primary outcome was the proportion of patients developing new gadolinium-enhancing T1 lesions on monthly MRI scans. In the mitoxantrone group, the proportion of patients without new enhancing lesions (90%) was significantly higher than in the control group (31%). Sixty-six percent of patients in the mitoxantrone group remained relapse-free during the six-month treatment period, compared to 33% in the control group. Indeed, a total of 31 relapses were recorded in the control group, corresponding to an annualised relapse rate of 3.0, similar to that observed before treatment, whereas in the mitoxantrone group, only seven relapses were recorded (annualised relapse rate of 0.7). Similarly, with respect to disability progression, twelve out of 21 patients in the mitoxantrone group improved by at least one point on the EDSS and only one deteriorated. In contrast, in the control group, six deteriorated and only three improved.

3.1.2. *Long-term efficacy of mitoxantrone*

An observational 5-year follow-up study [14]. Following the successful completion of the pivotal trial described above, an observational study was performed in Rennes's MS centre, evaluating prospectively for 5 years one hundred consecutive highly active RR MS patients, using the French regimen [9]. The majority of patients (73%) were assigned to a maintenance treatment following induction with mitoxantrone. In 21 patients, this consisted of quarterly boosters with mitoxantrone. The majority of the remainder received an immunomodulatory treatment, principally an interferon-β preparation, since glatiramer acetate was not available in France for most of the recruitment period. In the year preceding treatment, the annualised relapse rate in the patient group was 3.29, and the EDSS score had increased by a mean of 2.2 points. In addition, gadolinium-enhancing lesions were visible on MRI for 84% of the sample. These patients thus presented very active disease. In the first year following the first administration of mitoxantrone, the annualised relapse rate declined to 0.29 and was reduced by 91%. This reduction was maintained over the five-year observation period, the annual relapse rate oscillating between 0.3 and 0.4. Around one-third of patients remained free of relapses for the five-year period, with a median time to first relapse of 2.72 year. Likewise, the proportion of patients whose disability deteriorated by at least one point on the EDSS, confirmed at three months, decreased from 88% in the year preceding treatment to 5% over the first year. Overall, disability improved or stabilised in 59% of patients throughout the five-year observation period. Potential determinants of a good treatment response were evaluated: the proportion of patients whose disability worsened at one and two years was significantly lower ($P < 0.007$) in patients whose EDSS score was ≤ 4 when treatment was started. Moreover, the five patients who worsened during the first year of treatment were significantly older ($P < 0.02$) when

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treatment was started (41 years) than those whose disability stabilised or improved (32 years). The twenty patients who converted to a secondary progressive course during the follow-up period were significantly ($P < 0.02$) more disabled (mean EDSS score: 4.8) at the start of treatment than those who did not (mean EDSS score: 3.9). All these observations indicate that mitoxantrone is more effective in the long-term when started early in the disease.

3.1.3. *Scheme of induction therapy with mitoxantrone, followed by a maintenance treatment with interferon-β [15]*

A French-Italian randomised controlled trial comparing induction with mitoxantrone followed by maintenance therapy with interferon-β 1b to monotherapy with interferon-β 1b included patients with RR MS who had experienced at least two relapses with incomplete recovery in the previous year and who displayed gadolinium-enhancing lesions on MRI. Fifty-five patients were randomised to the mitoxantrone induction regimen used in the previous studies for six months, followed by a thee-month wash-out period and then interferon-β 1b. The other study arm (54 patients) received interferon-β 1b for three years combined with methylprednisolone 1 g for the first six months. The clinical and demographic features of the patients at inclusion were comparable in the two groups. Patients underwent a complete neurological examination every three months and spin-echo MRI at inclusion and months 9, 24 and 36. A rater blinded to treatment assignment evaluated the MRI scans. Compared with the interferon-beta group, in the mitoxantrone group the time to sustained 1 EDSS point worsening was delayed by 18 months ($P < 0.012$). The 3-year risk of sustained disability was reduced by 65% (12% vs. 34%). The number of patients needed to be treated with mitoxantrone before interferon-beta to avoid one sustained disability event during the 36 months was six. The mean EDSS was improved by 0.45 point at the last observation in the mitoxantrone group (from 4.16 to 3.66; $P < 0.007$), and remained unchanged in the interferon-beta group (from 3.86 to 3.76 $P = 0.771$). When considering the level of disability at screening (EDSS ≤ 4 vs. EDSS > 4), the 3-year risks of sustained worsening were respectively 3.9%, 30.8%, 22.3% and 40.3% in patients with baseline EDSS ≤ 4 in the mitoxantrone and interferon-beta groups, and in patients with EDSS > 4 in the mitoxantrone and interferon-beta groups. The study suggested that this induction strategy with mitoxantrone may be more effective in patients with a lower disability. The proportion of patients who remained relapse-free was increased in the mitoxantrone group ($P < 0.008$). From baseline to the last observation in the mitoxantrone group, the annualised relapse rate was lower (0.4 vs. 1.1 $P < 0.03$) and the time to first relapse after treatment institution was delayed by 21 months compared with the interferon-beta group ($P < 0.001$). The proportion of patients who remained free of relapses throughout the follow-up period was 53% in the induction group and 26% in the interferon-beta group ($P < 0.01$). On MRI, the mean number of new T2 lesions was significantly lower in the mitoxantrone group at each of the time points, as well as the mean number of Gd-enhancing lesions at month 9 ($P < 0.012$), and the percentage of patients without any Gd-enhancing lesion was higher in the mitoxantrone group ($P < 0.010$).

3.1.4. *Scheme of induction therapy with mitoxantrone, followed by a maintenance treatment with glatiramer acetate [17]*

In this small controlled study forty RR MS patients with 1–15 gadolinium-enhancing lesions on screening brain MRI and EDSS scores 0–6.5, were randomized to receive short-term induction therapy with mitoxantrone (three monthly 12 mg/m^2 infusions) followed by 12 months of daily glatiramer acetate (GA) therapy 20 mg/day subcutaneously (M-GA, $n = 21$) or daily GA 20 mg/day for 15 months (GA, $n = 19$). MRI scans were performed at months 6, 9, 12 and 15. The primary measure of outcome was the incidence of adverse events; secondary measures included number of Gd-enhanced lesions, confirmed relapses and EDSS changes. Except age, baseline demographic characteristics were well matched in both treatment arms. Both treatments were safe and well-tolerated. M-GA induction produced an 89% greater reduction [relative risk (RR) = 0.11, $P = 0.0001$] in the number of Gd-enhancing lesions at months 6 and 9 and a 70% reduction (RR = 0.30, $P = 0.0147$) at months 12 and 15 versus GA alone. Mean relapse rates were 0.16 and 0.32 in the M-GA and GA groups, respectively.

3.1.5. *Mitoxantrone safety profile [16]*

From 2001, a French multicentre study was conducted prospectively in a large cohort of MS patients and annually updated up to at least 5 years after initiation of mitoxantrone therapy in order to determine its long-term safety profile in MS. Eight hundred and two patients from 12 MS centres (308 RR, 352 SP and 142 PP) received mitoxantrone monthly for 6 months (87%) or every 3 months (13%). Patients underwent clinical and hematologic evaluations before every mitoxantrone infusion and every 6–12 months up to 5 years after mitoxantrone start. Echocardiograms were performed at the start and end of mitoxantrone and up to 5 years after. The cohort was followed for 5354 patient-years (mean). One out of 802 patients (0.1%) presented with acute congestive heart failure and 39 out of 794 patients (4.9%) presented with asymptomatic left ventricular ejection fraction reduction under 50% [persistent in 11 patients (28%), transient in 27 patients (69%), on the last scan at year 5 in 1 patient]. Two cases of therapy-related leukaemia (0.25%) were detected 20 months after MITOX start (one death and one with more than 10 years confirmed remission). Of the 317 women treated before the age of 45, 17.3% developed a persistent age-dependant amenorrhea (5.4% before 35-year-old, 30.7% after 35-year-old). This is the only one prospective published study of a large cohort with at least 5 years of follow-up. It provided good insights into the long-term safety profile of the use of mitoxantrone according to the French induction treatment protocol in MS patients.

These studies using a mitoxantrone induction regimen in patients with very aggressive RR MS suggest that this can be beneficial for reducing strongly disease activity, particularly when followed by a maintenance therapy with a safer disease-modifying immunomodulatory treatment. With the treatment protocol recommended for use in France (six-monthly administrations of mitoxantrone iv at a cumulative dose of 72 mg/m^2), mitoxantrone is generally well-tolerated but the risk of leukaemia and of decrease of the left ventricular

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ejection fraction justify to monitor white blood cells count every three months and the cardiac function by echocardiogram every year for 5 years after the last course of mitoxantrone.

3.2. *Alemtuzumab as an induction treatment in multiple sclerosis*

First licensed for treatment of patients with chronic lymphocytic leukaemia, alemtuzumab (initially called Campath-1H) was assessed in MS from 1991. This humanized anti-CD52 monoclonal antibody induces an immune-mediated rapid and profound depletion of lymphocytes, followed by differential recovery of lymphocyte subsets characterized by a rapid recovery of a normal B-cells number within 3 months, but prolonged and sustained suppression of CD4 T cells [35]. First studied in progressive active forms of MS, the drug showed a rapid and sustained control of the focal inflammatory markers of MS activity but failed to stop the progressive accumulation of disability [36,37]. For this reason, the idea of moving to an earlier use of the treatment conducted to design phases II and III studies [18–20] in the 2000s to focus on early highly active RR MS patients who were naïve or suboptimal responders to a first-line of DMD. The three studies were controlled compared to reference DMD available at that time, i.e. interferon-beta. These three large and well-designed controlled trials support its use as an induction treatment in early highly active RR MS and more particularly in patients who failed to respond to a first-line of DMD.

3.2.1. *The phase II randomised trial CAMMS223 [18]*

Three hundred and thirty-four previously untreated early RR MS patients with EDSS scores ≤ 3.0 and a disease duration ≤ 3 years were randomized to receive either subcutaneous interferon-beta-1a (at a dose of 44 μg) three times per week or annual intravenous 5 day cycles of alemtuzumab (at a dose of either 12 mg or 24 mg per day) for 36 months. In September 2005, alemtuzumab therapy was suspended after immune thrombocytopenic purpura developed in three patients, one of whom died. Alemtuzumab significantly reduced the rate of sustained accumulation of disability by 71%, as compared with interferon-beta-1a (9.0% vs. 26.2%; $P < 0.001$) and the annualized rate of relapse by 74% (0.10 vs. 0.36; $P < 0.001$). The mean EDSS score improved by 0.39 point in the alemtuzumab group and worsened by 0.38 point in the interferon-beta-1a group ($P < 0.001$). In the alemtuzumab group, the T2 lesion burden was reduced, as compared with that in the interferon-beta-1a group ($P = 0.005$). From month 12 to month 36, brain volume increased in the alemtuzumab group but decreased in the interferon-beta-1a group ($P < 0.02$).

3.2.2. *The CARE-MS 1 phase III trial [19]*

In this 2 year randomised trial, 581 MS patients aged 18–50 years with previously untreated RR MS were randomly allocated to receive intravenous alemtuzumab 12 mg per day given for 5 days at baseline and for 3 days at 12 months, or subcutaneous interferon-beta-1a 44 μg three times per week. Coprimary endpoints were relapse rate and time to 6 month sustained accumulation of disability in all patients who received at least one dose of study drug. Seventy-five out of 187 (40%) patients in the interferon-beta-1a group relapsed (122 events) compared with 82 out of 376 (22%) patients in the alemtuzumab group (119 events; rate ratio 0·45; $P < 0.0001$), corresponding to a 54·9% improvement with alemtuzumab. Fifty-nine percent of patients in the interferon-beta-1a group were relapse-free at 2 years compared with 78% of patients in the alemtuzumab group ($P < 0.0001$). However, benefit in terms of disability endpoints noted in CAMMS223 was not observed here: 20 (11%) of patients in the interferon-beta-1a group had sustained accumulation of disability compared with 30 (8%) in the alemtuzumab group (hazard ratio: 0.70; $P < 0.22$).

3.2.3. *The CARE-MS 2 phase III trial [20]*

In this 2 year randomised trial, 638 patients with RR MS and at least one relapse on interferon-beta or glatiramer acetate were selected. Eligible participants were randomly stratified to receive either subcutaneous interferon-beta-1a 44 μg three times per week, or intravenous alemtuzumab 12 mg or 24 mg per day for 5 days at baseline and for 3 days at 12 months. Coprimary endpoints were relapse rate and time to 6 month sustained accumulation of disability, comparing alemtuzumab 12 mg and interferon-beta-1a in all patients who received at least one dose of study drug. One hundred and four out of 202 (51%) patients in the interferon-beta-1a group relapsed (201 events) compared with 147 out of 426 (35%) patients in the alemtuzumab group (236 events; $P < 0.0001$), corresponding to a 49.4% improvement with alemtuzumab. Ninety-four (47%) patients in the interferon-beta-1a group were relapse-free at 2 years compared with 278 (65%) patients in the alemtuzumab group ($P < 0.0001$). Forty (20%) patients in the interferon-beta-1a group had sustained accumulation of disability compared with 54 (13%) in the alemtuzumab group (hazard ratio: 0.58; $P = 0.008$), corresponding to a 42% improvement in the alemtuzumab group.

3.2.4. *Alemtuzumab long-term efficacy and safety in phases II and III trials extensions [38,39]*

Patients who completed the core phases II and III studies were eligible to enroll in a long-term extension study in which they could receive retreatment with alemtuzumab, if they met specific disease activity criteria: ≥ 1 protocol-defined relapse, or ≥ 2 new/enlarging T2 hyperintense or new gadolinium (Gd)-enhancing T1 brain or spinal cord lesions on MRI. Other DMTs could be administered at the investigator's discretion. For the CARE-MS studies, data are available for 6 years of treatment (2 years of the core study plus 4 years of the extension). For the CAMMS223 study, patients completing the 3-year core study could enter an extended follow-up period (minimum additional 2 years), and then in 2010, they could enroll in the same extension study as patients from the CARE-MS studies, for a total available follow-up of 10 years. If we focus on long-term results in patients who received alemtuzumab while they were suboptimal responders to a DMD (CARE-MS 2 patients), 393 out of 435 entered the extension, and 344 remained on study through Year 6. Fifty-five percent of patients required only the initial two courses of alemtuzumab with 30%, 12%, 2%, and 1% receiving a third, fourth, fifth, or sixth course, respectively. Investigators cited relapse as the most common

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reason for retreatment. Relapse reduction with alemtuzumab was durable over the long-term with an annual relapse rate of 0.28 for Years 0–2 and 0.20 for Years 3–6, 89% of patients free from sustained disability worsening from baseline for Years 0–2 and 72% for Years 3–6. The proportion of patients with confirmed disability improvement increased from Year 2 to Year 6, indicating that patients continued to experience improvement during the extension study. The proportion of patients who converted from RRMS to SP MS following alemtuzumab treatment was estimated to 1.1% over 6 years in CARE-MS 1 and 3.7% in CARE-MS 2, using a definition of SPMS recently developed by Lorscheider et al. based on data from the MSBase registry (réf [20,21]). While SPMS conversion among the MSBase cohort was calculated at 18% over 5.8 years' follow-up [39]. MRI results confirmed the sustained long-term control of disease activity with 76% of patients free of MRI activity at Year 2 and 69% at Year 6, and 91% of patients free of Gd-enhancing lesions at Year 2 and Years 3 – 6. Interestingly, the median yearly brain volume loss decreased progressively over 2 years in alemtuzumab-treated patients and remained low in Years 3–6 (median yearly brain volume loss from −0.07 to −0.19%; in Years 3–6) (réf [32]). The most frequent adverse event associated with alemtuzumab is the injection associated reaction (mostly mild to moderate and manageable using pretreatment with methylprednisolone). Infections were more frequent with alemtuzumab than interferon-beta, but the incidence declined from 63.2% in Year 1 and to 43.4% in Year 6 in CARE-MS 2. Rates of serious infections were low in each year (< 3%). The most frequent were herpetic infections justifying the now recommended prevention with acyclovir during the month following the last cycle and the more frequent opportunistic infections were listeria monocytogenes (estimated frequency: 0.26%), followed by cytomegalovirus (estimated frequency: 0.13%). There have been no medically confirmed cases of progressive multifocal leukoencephalopathy (PML) in MS without relevant pretreatments (natalizumab-associated PML). For the autoimmune side effects, the pooled CARE-MS patients who received alemtuzumab 12 mg ($n = 811$) presented a cumulative incidence of thyroid events of 42% over 6 years with a peak of incidence within 2 years of the last alemtuzumab treatment course, a spontaneous resolution for 20.7% of cases, conventional oral medications for 79.0%, iodine ablation for 9.0% and thyroidectomy for 8.5%. Serious thyroid AEs peaked at Year 3 (3.1%) and subsequently declined. Data on idiopathic thrombopenic purpura (ITP) showed a cumulative incidence of 2.0% in patients treated with alemtuzumab 12-mg dose successfully treated with first-line therapy in most of the cases (corticosteroids with or without intravenous immunoglobulin) and sometimes requiring second-line therapy with rituximab or plenectomy with durable remission. Four cases of autoimmune nephropathy were reported [two cases of membranous glomerulonephritis, one case was glomerulonephritis with anti-glomerular basement membrane (GBM) antibodies, and one was anti-GBM disease], treated with plasmapheresis, cyclophosphamide, and steroids or angiotensin-converting enzyme inhibitors and diuretics. These safety profile considerations justify a monitoring of platelets counts, renal function monthly and thyroid function every three months for 4 years after the last course of alemtuzumab.

3.3. *Cladribine as an induction treatment in multiple sclerosis?*

Intracellular accumulation of the active metabolite of cladribine, 2-chlorodeoxyadenosine triphosphate, results in the disruption of cellular metabolism, the inhibition of DNA synthesis and repair, and subsequent apoptosis. The accumulation of the cladribine nucleotide produces rapid and sustained reductions in CD4+ and CD8+ cells and rapid, though more transient, effects on CD19+ B cells, with relative sparing of other immune cells. A short period of administration of cladribine was associated with rapid and sustained effect on clinical and MRI markers of MS activity [22,23].

3.3.1. *The CLARITY phase III trial [22]*

In this 2-Year placebo controlled phase III trial, 1326 RR MS patients were randomized to receive cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year). The primary end point was the rate of relapse at 96 weeks. Results with the licensed dose of 3.5 mg/kg showed a significantly lower annualized rate of relapse than in the placebo group (0.14 vs. 0.33; $P < 0.001$), a higher relapse-free rate (79.7% vs. 60.9%; $P < 0.001$), a lower risk of 3-month sustained progression of disability (hazard ratio: 0.67; 95% confidence interval [CI], 0.48 to 0.93; $P = 0.02$), and significant reductions in the brain lesion count on MRI ($P < 0.001$ for all comparisons). The most frequent adverse events were lymphocytopenia (21.6% vs. 1.8%) and herpes zoster (8 patients vs. no patients).

3.3.2. *CLARITY 2-year Extension study [23]*

A total of 806 patients were assigned to treatment: patients from placebo recipients from CLARITY received cladribine 3.5 mg/kg; cladribine recipients were re-randomized 2:1 to cladribine 3.5 mg/kg or placebo, with blind maintained. Results of the 2-year extension study were crucial for the development of cladribine, first because they were reassuring in term of safety profile and second because efficacy data were of particular interest in the group of patients who received cladribine 3.5 mg/kg during the two first years and then a placebo during the third and fourth year, in favor of an induction action. Indeed, if lymphopenia was the most frequent adverse effects, the frequency of lymphopenia grade 3 or 4 was of 11.4% during the two first years and 5% during the extension, with recovery to grade 0–1 by study end. The occurrence of opportunistic infections was reassuring (no case of progressive multifocal leukoencephalopathy) and the frequency of herpes zoster infections in the 3.5 mg/kg was of 2%. The frequency of malignancies was of 1.4% (similar to the general population). Moreover, the potential induction action of the drug was demonstrated in the group receiving Cladribine 3.5 mg/kg in CLARITY core study and then placebo during the third and fourth year: efficacy improvements were maintained in these patients with approximately 75% relapse-free and 72.4% free of 3-month sustained progression of disability. In fact, cladribine tablets treatment for 2 years followed by 2 years' placebo treatment produced durable clinical benefits similar to 4 years of cladribine treatment with

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a low risk of severe lymphopenia. No clinical improvement in efficacy was apparent following further treatment with cladribine tablets after the initial 2-year treatment period.

4. Conclusion

The current challenge in therapeutic strategy is to identify the most effective drug and strategy during a specific phase of the disease of each single patient. Both escalating and induction strategies can be successfully applied on the basis of clinical and radiological tools. Induction therapy means performing a strong immunossuppression followed by a maintenance therapy with a safe drug. Among FDA and EMA approved immunossuppressants, mitoxantrone, alemtuzumab and cladribine are 3 candidates that deserves consideration for an induction strategy. However, natalizumab in JC negative patients is a better candidate for an escalating strategy, like probably ocrelizumab but longer term data are needed. Induction therapy is beneficial for a selected group of early aggressive RRMS, having negative predictive factors. Monitoring over the first few years significantly refines prediction and facilitates selection of those requiring aggressive treatment. MRI is a key prognostic marker. The goal of minimal MRI activity over the first few years after clinical onset is important for defining the therapeutic strategy. New MRI techniques (brain and spinal cord imaging) should help us to identify those RR 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...

Disclosure of interest

The authors declare that they have no competing interest.

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