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Expert opinion: Criteria for second-line treatment failure in patients with multiple sclerosis

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A B S T R A C T

Objectives: In the management of multiple sclerosis (MS), defining criteria for identification of suboptimal therapy responses and switching treatment is essential to avoid worsening. Despite the lack of a standardised definition, criteria for first-line treatment are well documented in the literature, based on clinical measures or magnetic resonance imaging (MRI) (gadolinium enhancing [Gd^+] lesions or new/enlarging T2 lesions) assessed during the first 6–18 months after treatment initiation. However, it is unknown whether the same criteria can be used for second-line treatment failure.

Methods: Five regional boards involving 36 French MS experts were convened to discuss published literature regarding criteria for first- and second-line treatment failure, and to identify differences in local therapeutic practices. A national board of 11 experts was subsequently conducted to identify convergences and differences between regions, and to propose second-line criteria for the definition of therapeutic failure.

Results: Published information is lacking regarding second-line treatment failure criteria. In light of this, regional differences in current therapeutic practices are justifiable. Due to the risk-benefit ratio of these treatments and limited options for third-line treatments, the authors recommend a different therapeutic approach when assessing second-line treatment failure. The treatment switch for second-line treatment should be informed by confirmed disease progression, after 6 months, or combined clinical and MRI outcomes, but only after at least 1 year of treatment.

Conclusions: Experts compared therapeutic attitudes and practices regarding second-line treatment failure between French regions. They identified convergences that were used to propose a national agreement on second-line treatment failure criteria, which should be evaluated in real-life prospective cohorts.

1. Introduction

Multiple sclerosis (MS) is a complex disease characterised by periods of relapsing–remitting and progressive disease that are unpredictable and vary widely in individual patients (Scolding et al., 2015; Confavreux et al., 2000; Confavreux and Vukusic, 2006; Confavreux and Vukusic, 2014). Current therapies aim to reduce the risk of relapses, and slow disability progression (Brunetti and Hunter, 2014; Montalban et al., 2018) with disease-modifying therapies (DMTs), which remain the mainstay of chronic treatment for patients with MS (Brunetti and Hunter, 2014). Increasing treatment options offers the opportunity to individualise treatment (Montalban et al., 2018; Marrie and Montalban, 2018); however, understanding the complex treatment landscape remains challenging (Marrie and Montalban, 2018). While guidance regarding choice of individual therapies is relatively limited (Marrie and Montalban, 2018), current European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)/European Academy of Neurology (EAN) and American Academy of Neurology (AAN) treatment guidelines recommend early initiation of DMT in patients with active, relapsing–remitting multiple

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sclerosis (RRMS), defined as the presence of relapses and/or activity documented by magnetic resonance imaging (MRI) (Montalban et al., 2018; Marrie and Montalban, 2018; Rae-Grant et al., 2018). Guidelines also recommend ongoing clinical and MRI assessment for monitoring the disease progression and treatment effectiveness.

Since relapses or new MRI-detected lesions may develop before a newly initiated treatment becomes effective, and because DMTs reduce but do not eliminate relapses and MRI activity (Rae-Grant et al., 2018), deciding if treatment is effective and whether a treatment switch is warranted can be challenging. Moreover, guidance regarding switching between therapies is limited (Montalban et al., 2018; Marrie and Montalban, 2018; Rae-Grant et al., 2018). Conversely, criteria for first-line treatment failure are well documented (Bosca et al., 2008; Prosperini et al., 2009; Tremlett, 2009; Bermel et al., 2013; Sormani et al., 2013; Fred et al., 2014; Sormani et al., 2015; Sormani et al., 2016). Several studies corroborated that the combination of MRI for presence of new lesions and clinical assessment allow the evaluation of disease worsening. Indeed, clinical trials have demonstrated significant correlations between MRI activities and the presence of relapses or disabilities progression or both, in RRMS IFN-β treated patients, after a follow-up of 2, 3 (Río et al., 2009) and 15 years (Bermel et al., 2013). These observations have led to the publication of several expert opinions. Indeed, the importance of performing an annual MRI and/or clinical evaluation for a better disease control was recommended by Lublin et al. publications initially (Fred et al., 2014) then reiterated by Montalban et al., (Montalban et al., 2018). Sormani and colleagues redefined the Rio score for greater accommodation of T2 lesion evaluation (Sormani et al., 2013). First-line failure criteria thus rely on either clinical activity or MRI findings. These studies further established that the combination of clinical relapses and MRI activity significantly increases the risk of disease progression and treatment failure (Fred et al., 2014; Sormani et al., 2016). Beside these studies, another criteria endpoint allowing the definition of first-line failure criteria has emerged. “No Evidence of Disease Activity”, also named NEDA, was originally described in a *post-hoc* analysis of the placebo-controlled, two-year Phase III pivotal trial for natalizumab (Havrdova et al., 2009). It is defined by the composite measure of the absence of confirmed disability worsening (as measured by the Expanded Disability Status Scale (EDSS)) and of clinical and MRI measures of disease activity in relapsing multiple sclerosis (RMS). NEDA has since been widely used in analyses of other DMT and adopted as an outcome measure in RMS clinical trials (Cohen et al., 2012; Arnold et al., 2014; Arnold et al., 2017; Havrdova et al., 2017).

Nevertheless, information regarding criteria (Cohen et al., 2012) for failure of second-line therapy is lacking. This work reviews the therapeutic approaches of French MS experts for failure criteria of second-line treatment and highlights the convergences, which are used as the basis to inform therapeutic decisions.

2. Methods

Because heterogeneous MS therapeutic strategies were observed in France, collegiate boards were runned in order to align practices. A 2-phase approach was set up. Five regional boards comprising of a total of 36 French MS experts (Auvergne-Rhône Alpes [$n = 9$], Grand-Est [$n = 4$], Languedoc-Roussillon [$n = 11$], Ile-De France [$n = 8$], Nord Pas de Calais [$n = 4$]) were conducted between November 2016 and February 2018 (Table 1). The participating experts provided a good representation of practices throughout each region, including university hospitals, regional hospitals, general hospitals and private practices. The experts identified and explained therapeutic practices for the management of MS patients in their region.

Subsequently, a national board involving 11 experts was conducted on March 28, 2018. This national board was composed of an expert from each of the regional boards, as well as invited practitioners and professional society representatives from different regions selected for their expertise in the field. The experts examined and discussed available literature on the monitoring of and failure criteria for the first- and second-line treatments for MS patients, with the aim of identifying second-line treatment failure criteria. The literature review was based on a search of Pubmed, congress presentations covering the previous 10 years and included publications relating to first- or second-line treatment failure criteria. Third-line therapies were also discussed. In addition, the experts discussed collated results from the regional boards. The experts worked in two sub-groups (using a majority consensus methodology), assessing study practices in each region, and identifying convergences and differences. Following discussion of the data, expert opinion was provided to define the criteria for second-line treatment failure.

Table 1
Disease-modifying therapies available for the treatment of MS in Europe (Brunetti and Hunter, 2014; M.P. Novartis Europharm Ltd 2018; Gajofatto and Benedetti, 2015; European Medicines Agency 2016; Pardo and Jones, 2017; Bayer, 2018; M.P. Biogen Idec Ltd 2018; Biogen (Denmark) Manufacturing ApS 2018; M.P. Biogen Idec Ltd 2018; Biogen Inc 2018; Boehringer Ingelheim Pharma GmbH, and Co. KG 2018; Genentech Inc 2018; Merck Serono Europe Ltd 2018; M.P. Novartis Europharm Ltd 2018; Sanofi-Aventis group 2018).

Drug name (brand name)	Indication	Route of administration
First-line therapies		
Interferon β−1b (Betaferon®)	RMS	SC injection
Interferon β−1a (Rebif®)	RMS	SC injection
Interferon β−1a (Avonex®)	RRMS	IM injection
Glatiramer acetate (Copaxone®)	RRMS	SC injection
Interferon β−1b (Extavia®)	RMS	SC injection
Pegylated interferon β−1a (Plegridy®)	RRMS	SC injection
Teriflunomide (Aubagio®)	RRMS	Oral
Dimethyl fumarate (Tecfidera®)	RRMS	Oral
Ocrelizumab (Ocrevus®)	PPMS	IV
Second-line therapies		
Natalizumab (Tysabri®)	HA RRMS, RES RRMS	IV
Fingolimod (Gilenya®)	HA RRMS, RES RRMS	Oral
Mitoxantrone (Novantrone®)	HA RRMS, RES RRMS	IV
Others		
Ocrelizumab (Ocrevus®)	RMS	IV
Cladribine (Mavenclad®)	HA RMS	Oral
Alemtuzumab (Lemtrada®)[a]	active RRMS,	IV

Abbreviations: HA, highly active; IM, intramuscular; IV intravenous; PPMS, primary progressive multiple sclerosis; RES, rapidly evolving severe; RMS, relapsing multiple sclerosis; RRMS, relapsing/remitting multiple sclerosis; SC, subcutaneous.

[a] Difficult access in some countries in Europe. Indications restriction.

3. Results

3.1. Literature review analysis

Published data describes the role of clinical and MRI activity as criteria to define non-responders to first-line treatments (Table 2), mainly interferons. But, it is unknown whether these criteria can be directly applied to second-line treatment failure (Bosca et al., 2008; Prosperini et al., 2009; Tremlett, 2009; Bermel et al., 2013; Sormani et al., 2013; Fred et al., 2014; Sormani et al., 2015; Sormani et al., 2016). Data from the literature for first-line treatments (interferons, teriflunomide, glatiramer acetate) converge, with criteria proposed for the prompt identification of a suboptimal response to first-line therapies based on clinical evaluation or MRI assessed during the first 6–18 months after treatment initiation. Detection of disease activity is defined as either a clinical relapse or Gd^+ lesions or new/enlarging T2 lesions on follow-up compared with baseline scans (Bosca et al., 2008; Prosperini et al., 2009; Tremlett, 2009;

Table 2
Summary of outcomes from the individual boards.

Board	Outcomes
Auvergne-Rhône Alpes	• The criteria of Sormani (Sormani et al., 2013) (i.e., modified Rio criteria) are not transferable to second-line therapy. • There is a need for a stratified medicine. • Therapeutic switch from the second- to third-line treatment if progression or relapse with sequelae. • Switch also on the sole basis of MRI, but there was hesitation in the working group about a switch based exclusively on combined clinical and radiological criteria (MRI + relapse).
Grand-Est	• Therapeutic approaches are more permissive with second-line therapy because of a lack of third-line possibilities. • Change of treatment if true relapse (beware of pseudo-flares that can cause exacerbations without lesions). • Change of treatment if radiological evolution alone after one year of second-line treatment.
Languedoc-Roussillon	• A switch from second- to the third-line treatment is systematically discussed in a multidisciplinary meeting. • A treatment change can be made on the basis of combined clinical and radiological criteria at one year of treatment: o Gd^+ lesion and relapse; o Gd^+ lesion and worsening EDSS; o Gd^+ lesion, relapse and worsening EDSS.
Ile-de France	• A switch from second- to third-line treatment is systematically discussed in a multidisciplinary meeting. • Less strict criteria of second-line treatment failure than for first-line treatment because of a lack of third-line possibilities. • Changing the treatment must be discussed after 1 year of treatment. • Criteria are EDSS, relapse and radiological activity, but without cut-off like Rio Score.
Nord Pas de Calais	• Maintenance of second-line treatment if the patient has a single flare or radiological activity alone. • There is lack of clarity regarding third-line treatment options; there is no consensus, only suggestions.

Bermel et al., 2013; Sormani et al., 2013; Fred et al., 2014; Sormani et al., 2015; Sormani et al., 2016).

Noteworthy publications include the work of Sormani and colleagues (Sormani et al., 2013), with simplification of previously reported Rio criteria (Río et al., 2009), validated in patients receiving first-line IFNβ−1a in the extension phase of the PRISMS study. The predictive value of the original Rio score, which is based on a combination of MRI (> 2 active T2 lesions plus Gd^+ lesions), relapse and Expanded Disability Status Scale (EDSS) criteria, was improved by using only MRI (> 5 new T2 lesions) and relapse criteria (Sormani et al., 2013). The modified Rio score, assessed after one year of IFN therapy, defines 3 scores depending on both the number of relapses and new MRI lesions. This score is then correlated to the risk of disability progression in the subsequent 3 years (Sormani et al., 2013; Sormani et al., 2016).

In addition, Sormani and colleagues showed that the modified Rio score can be successfully applied to patients treated in first line with teriflunomide (Sormani et al., 2015). In this analysis, patients with RRMS who received teriflunomide ($n = 552$) in the 108-week randomised, double-blind, placebo-controlled, phase 3 TEMSO study, where categorised as 0, 1, or 2/3 according to the modified Rio score and compared with those who received placebo ($n = 286$). Similarly to patients treated with IFNβ−1a, MRI flares and lesions in the first 12 months of first-line teriflunomide in clinically stable patients predicted progression of disability (Sormani et al., 2015).

A similar study confirmed the importance of MRI monitoring of patients, but concluded that particular attention should be paid to early Gd^+ lesions while receiving first-line IFNβ, as their presence strongly correlates with severe disability 15 years later (Bermel et al., 2013). This observational study examined data in 136 patients with RRMS who received intramuscular IFNβ−1a in the pivotal, 2-year MSCRG study. Relationships between the worst disability at 15 years (i.e., median change in EDSS score from a baseline of 5) and Gd^+lesions, T2 lesions or relapses during the 2-year trial were explored. MRI activity had high specificity for predicting poor long-term outcomes in IFNβ−1a-treated patients (Gd^+ lesions, odds ratio [OR] 8.96; $p < 0.001$; new T2 lesions, OR 2.90; $p = 0.080$). Moreover, several clinical studies showed the number of patients who had reached clinical NEDA was higher in treatment groups, as compared to placebo, during a 5-years long follow-up (Arnold et al., 2014; Arnold et al., 2017; Havrdova et al., 2017).

Recommendations for criteria for failure of second-line treatments are lacking in the literature, with only three studies exploring the subject (Bates and Bartholomé, 2012; Sormani et al., 2015; Signoriello et al., 2018). Bates et al. first suggested that for second-line natalizumab therapy, disease activity reflected by MRI might not be predictive of clinical activity (Bates and Bartholomé, 2012). The study examined data from the pivotal AFFIRM and SENTINEL studies, which examined the use of natalizumab versus placebo and natalizumab ± IFNβ, respectively, in patients with RRMS (Bates and Bartholomé, 2012). Results showed a reduced annualised relapse rate ($p = 0.004$) despite the presence of Gd^+ lesions ($p = 0.008$) or new or enlarging T2 hyperintense lesions (each $p < 0.0001$), leading the authors to conclude that MRI findings alone may not mandate a switch from natalizumab (Bates and Bartholomé, 2012). Also, of note, before observing the full effectiveness of natalizumab treatment, new early T2 lesions could appear, due to MR imaging at the time. Thus, it is recommended to perform a rebaseline MRI at least 12 months after treatment initiation, regardless of treatment line or to adjust the timing of both MRIs according to treatment speed of action or disease activity (Montalban et al., 2018).

Sormani and colleagues (Sormani et al., 2015) examined data from 1370 patients treated with fingolimod in the FREEDOMS and FREEDOMS II studies to assess whether the addition of brain volume loss to modified Rio criteria improved prediction of disability progression. The one-year measurements allowed the estimation of a 4-year risk of confirmed disease progression (4-year roCDP) of patients, stratified according to their modified Rio score. Independent of the inclusion of brain volume loss, this work successfully used the modified Rio score to predict disease progression (progression free survival) of patients treated with fingolimod (Sormani et al., 2015).

Finally, the work of Signoriello and colleagues showed that Gd^+ lesions occurring in patients on second-line fingolimod treatment were significantly more likely to be asymptomatic than those that appeared during first-line IFNβ−1a (88% vs. 30.9%; $p \leq 0.025$) (Signoriello et al., 2018). This retrospective study assessed the annualised relapse rate (ARR), EDSS and the number of new brain and spinal Gd^+ and T2 lesions in 103 patients with RRMS switching from IFNβ−1a to fingolimod (Signoriello et al., 2018). Lesions appearing in patients on fingolimod (especially Gd^+ lesions) did not necessarily result in an increase in disability, and Gd^+ lesions did not have the same impact on clinical expression when they appeared with IFNβ−1a compared with fingolimod (Signoriello et al., 2018). The authors suggested that conventional MRI as a surrogate measure of response provides only part of the information associated with both new and active lesions during treatment with fingolimod (Signoriello et al., 2018).

Thus, given the lack of data, it is not clear whether it is possible to extrapolate a predictive value of an MRI lesion on disability in a patient treated in first line, to a patient receiving second-line therapy.

3.2. Analyses of regional group practices

Discussions conducted during the regional board meetings highlighted the complexity of care of patients treated in second line, as well as a disparity of practices according to each region (Table 2).

3.2.1. Regional differences

Differences between regions in the methods used for evaluating progression were highlighted. In addition to EDSS, treatment failure was assessed using a variety of measures; including the annual Symbol Digit Modalities Test (SDMT), the 9-Hole Peg Test (9-HPT), the Timed 25-Foot Walk (T25-FW); decreased walking distance despite unchanged EDSS and low-contrast visual acuity.

Moreover, the decision-making regarding the next therapeutic strategy may vary between centres, depending on their level of confidence in unique MRI activity results and a unique relapse. Some regions placed the cut-off at 2 or 3 new T2 lesions, and some regions consider that the decision to change second-line treatment or not could generally be influenced by the clinical symptoms of the relapse (i.e. sensitive versus motor) and by the location of the new lesion (spinal cord or posterior fossa versus supratentorial).

3.2.2. Regional similarities

The board identified points of convergence between the regions in the follow-up of patients receiving second-line treatments and failure criteria (Fig. 1), with various parameters to be evaluated. The response evaluation should be based on disease progression, MRI activity and clinical relapses. Disease progression assessment is based on an annual EDSS. The experts also agreed on the need to develop and validate new tools for the evaluation of disease progression. The most useful tools to be considered are those used in many clinical trials, such as the Shared-Decision-Making questionnaire (SDM), the 9-HPT and the SDMT, the latter highlighting the need to incorporate a cognitive screening test. Any confirmed progression at 6 months defines a therapeutic failure. Otherwise, following the benefit-risk ratio, the decision-making regarding a treatment switch could be discussed after one year of treatment with the multidisciplinary meeting, as explained in Fig. 1. Brain and spinal cord MRI are recommended at 6 months, followed by encephalic MRI alone once a year for up to 5 years. Evidence of brain atrophy is not considered to be clinically relevant. A spinal cord MRI as control can be prescribed in case of clinical activity.

In addition, all regions agreed that "failure" does not mean "inefficacy" or “therapeutic discontinuation or switch” and that confounding factors such as non-compliance or the presence of anti-treatment antibodies and poor prognostic factors (e.g. high baseline EDSS, age, immunosenescence, ethnicity and comorbidities) should be considered when the therapeutic decision is made. Failure criteria are not considered to be valid after 3 years of treatment.

3.3. Proposed criteria for second-line treatment failure

The recommendations made here are proposals from a group of experts. While some of the regional boards date back to 2016 and 2017, expert's medical practices are not considered to have changed significantly in that time. All experts considered that treatment failure with second-line treatments are mainly due to disability progression and a significant proportion switching to secondary progressive multiple sclerosis (SPMS). Thus, based on current practices and expert opinion, the following criteria have been proposed for evaluation and for treatment failure in second line. Compared with first-line failure criteria, it is necessary to be less restrictive with the criteria for second-line treatment failure due to the rather limited third-line therapeutic options as well as the lack of experience concerning outcomes after the switch from second-line to third-line treatments or lateral switch. As opposed to first-line treatment failure criteria, it is recommended that second-line therapeutic failure should be based on both clinical relapses and MRI activity. Disability progression is an essential indicator of second-line treatment response, even if clinical relapses and MRI activity are to be considered.

Second-line treatment failure criteria are thus defined by either a confirmed progression at 6 months or a clinical relapse combined with MRI activity after one year of treatment. Mainly due to the high frequency of pseudo relapses and associated- permanent sequela with second-line therapy (Rae-Grant et al., 2018), a relapse only or an MRI activity alone should not lead to a treatment switch. Further investigation and development of new tools are required to better evaluate disease progression. A lateral switch is systematic in the event of tolerance issues. Failure criteria are valid for up to 3 years of treatment.

Evaluation of the current proposals in real-life prospective cohorts would help provide data useful for defining second-line treatment failure criteria in the future.

4. Discussion

In general, ECTRIMS/EAN and AAN guidelines recommend switching to a more effective drug in patients with evidence of disease activity; however, no distinction is made between lines of therapy (Montalban et al., 2018; Rae-Grant et al., 2018). Disease activity is defined as the appearance of new or unequivocally enlarging T2 lesions measured by brain MRI within 6 months of starting treatment (baseline) and repeated 12 months after treatment initiation (Montalban et al., 2018; Rae-Grant et al., 2018). In addition, monitoring of gadolinium-enhancing (Gd^+) lesions is also recommended for assessment of treatment response (Montalban et al., 2018).

While criteria for first-line treatment failure included the appearance of Gd^+ lesions (Bermel et al., 2013; Sormani et al., 2013), results with second-line therapies were not as clear, with two of the three identified studies showing that the appearance of new Gd^+ lesions and/or T2 lesions did not correlate with relapses/disability with fingolimod

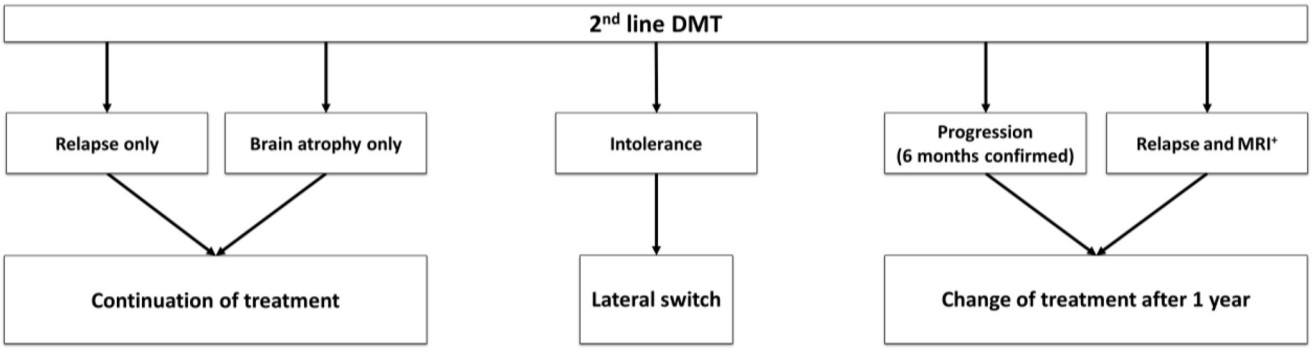

Fig. 1. Expert consensus for failure criteria for second-line treatments.

or natalizumab ± INFβ (Bates and Bartholomé, 2012; Signoriello et al., 2018). The experts believe that there are too few data with second-line treatments and that first-line treatment data are not applicable. Several study have documented a tissue accumulation of gadolinium, thus raising the possibility of toxicity issues as well as the development of neurodegenerative diseases in the long term, particularly with linear agents (Stojanov et al., 2016; Bjørnerud et al., 2017; Rossi Espagnet et al., 2017; Splendiani et al., 2018). The use of gadolinium have been discussed leading to new guidelines for limitation of routine gadolinium injections to specific clinical situations, which will be detailed in next OFSEP's publications.

The counting of T2 lesions is more challenging than Gd^+ lesions. Detection of active T2 lesions in patients with MS can be made more difficult by a high burden of inactive T2 lesions, the presence of small and confluent lesions, inadequate repositioning, and high interobserver variability (Altay et al., 2013; Cabezas et al., 2016). However, measurement of new and/or enlarged T2 lesions should be encouraged. Automatic counting of MRI lesions might help in this respect. Automatic methods appear to be fast and accurate, and avoid the variability introduced by manual analyses (Sweeney et al., 2013; Jain et al., 2015; Dworkin et al., 2018).

Regarding clinical relapses with second-line therapies, progression of disability (as measured by the EDSS) is essential; however, it was agreed that it is necessary to develop and validate tools for evaluating disease progression, in addition to EDSS. An important consideration is that, while the impact of relapses during the first 5 years of the disease is known (Bosca et al., 2008; Prosperini et al., 2009; Tremlett, 2009; Sormani et al., 2013; Sormani et al., 2015; Sormani et al., 2016), data after this period are lacking and it is during this time that second-line treatment is typically initiated.

Paradoxically, it seems that treatment is more permissive in patients receiving second-line therapy than in those receiving first-line, whereas second-line treatment is supposed to be more effective. In our opinion, the concept of first- and second-line MS therapies is artificial, being mainly related to the marketing authorisation process. For example, the SENTINEL (Rudick et al., 2006), TRANSFORMS (Cohen et al., 2010; Cohen et al., 2016) and FREEDOMS trials (Kappos et al., 2010; Kappos et al., 2015) (Kappos et al., 2015)[39][36][35][34]were designed to obtain a first-line marketing authorisation, but natalizumab and fingolimod were instead granted second-line marketing authorisations due to a lack of data regarding their long-term safety (Biogen Idec Ltd 2018; Novartis Europharm Ltd 2018). There was general agreement that long-term monitoring data for second-line treatments are lacking.

It is also important to consider that criteria for second-line failure must take into account the existence of alternatives to treatment: the reduced number of therapeutic alternatives in third line and the accumulation of treatment lines limit a more clear and direct approach. The availability of multiple treatments complicates the treatment choice, and, as mentioned previously, specific guidance is lacking. Guidelines recommend individualised therapy based on factors such as: patient characteristics, disease severity, the presence of comorbidities and likelihood of adherence to treatment, as well as the mechanism of action, efficacy, availability and safety of individual therapies (Montalban et al., 2018; Marrie and Montalban, 2018). In practice, the experts agreed that natalizumab or fingolimod are most commonly used (for approximately 85% of patients in France) after first-line treatments failure. The best treatment options after second-line natalizumab or fingolimod are unknown, but relief of symptoms and improvement in quality of life are important factors to consider when choosing a third-line therapy. Furthermore, the lack of long-term data regarding the efficacy or tolerability of third-line treatments, after a switch from fingolimod or natalizumab, complicates the choice when switching from a second-line to a third-line treatment.

Finally, is it necessary to differentiate between patients with slow-worsening MS, with therapeutic escalation over several years, and those with rapidly worsening MS who are naïve to treatment. Catastrophic MS forms exist either from the outset or occur during evolution and are associated with a rapid increase in EDSS. They require a very fast-acting treatment capable of significantly reducing immune cells. But there is a possibility of a rebound effect with some treatments (Prosperini et al., 2015) and an accumulation of side effects between second- and third-line treatments. It is important to consider efficacy, tolerance, the place in therapeutic succession and patient's profile.

The authors believe that the differences in therapeutic practices between regions highlighted in this report are currently justifiable given the absence of published data.

5. Conclusions

Convergences and differences between regions in France in terms of therapeutic attitudes and practices for second-line treatment failure were identified. These differences were justified in the absence of published recommendations. The authors agreed that criteria for second-line treatment failure must consider either disease progression (according to EDSS) confirmed at 6 months, or clinical relapses and MRI findings (new or increasing T2 and/or Gd^+ lesions) but only after at least 1 year of treatment. The development of new tools is necessary to improve the evaluation of disease progression. These proposals should be evaluated in real-life prospective cohorts.

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CRediT authorship contribution statement

Patrick Vermersch: Conceptualization, Writing - original draft, Writing - review & editing. **Jérôme De Sèze:** Conceptualization, Writing - original draft, Writing - review & editing. **Pierre Clavelou:** Conceptualization. **Françoise Durand-Dubief:** Conceptualization. **Elisabeth Maillart:** Conceptualization. **Claude Mekies:** . **Thibault Moreau:** Conceptualization. **Caroline Papeix:** . **Ayman Tourbah:** Conceptualization. **Pierre Labauge:** Conceptualization, Writing - original draft, Writing - review & editing.

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References

Altay, E.E., Fisher, E., Jones, S.E., Hara-Cleaver, C., Lee, J.C., Rudick, R.A., 2013. Reliability of classifying multiple sclerosis disease activity using magnetic resonance imaging in a multiple sclerosis clinic. JAMA Neurol. 70, 338–344. https://doi.org/10.1001/2013.jamaneurol.211.

Arnold, D.L., Calabresi, P.A., Kieseier, B.C., Liu, S., You, X., Fiore, D., et al., 2017. Peginterferon beta-1a improves MRI measures and increases the proportion of patients with no evidence of disease activity in relapsing-remitting multiple sclerosis: 2-year results from the advance randomized controlled trial. BMC Neurol. 17, 29. https://doi.org/10.1186/s12883-017-0799-0.

Arnold, D.L., Calabresi, P.A., Kieseier, B.C., Sheikh, S.I., Deykin, A., Zhu, Y., et al., 2014. Effect of peginterferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis. BMC Neurol. 14, 240. https://doi.org/10.1186/s12883-014-0240-x.

Bates, D., Bartholomé, E., 2012. Treatment effect of natalizumab on relapse outcomes in multiple sclerosis patients despite ongoing mri activity. J. Neurol. Neurosurg. Psychiatr. 83, 55–60. https://doi.org/10.1136/jnnp-2011-300279.

Bayer A.G. Betaferon 250 microgram/ml, powder and solvent for solution for injection: summary of product characteristics, 2018.

Bermel, R.A., You, X., Foulds, P., Hyde, R., Simon, J.H., Fisher, E., et al., 2013. Predictors of long-term outcome in multiple sclerosis patients treated with interferon beta. Ann. Neurol. 73, 95–103. https://doi.org/10.1002/ana.23758.

Biogen (Denmark) Manufacturing ApS. Tecfidera gastro-resistant hard capsules: summary of product characteristics, 2018.

Biogen Idec Ltd. Avonex 30 micrograms powder and solvent for solution for injection: summary of product characteristics, 2018.

Biogen Idec Ltd. Tysabri 300 mg concentrate for solution for infusion: summary of product characteristics, 2018.

Biogen Inc. Plegridy solution for injection in pre-filled syringe: summary of product characteristics, 2018.

Bjørnerud, A., Vatnehol, S.A.S., Larsson, C., Due-Tønnessen, P., Hol, P.K., Groote, I.R., 2017. Signal enhancement of the dentate nucleus at unenhanced mr imaging after very high cumulative doses of the macrocyclic gadolinium-based contrast agent gadobutrol: an observational study. Radiology 285, 170391. https://doi.org/10.1148/radiol.2017170391.

Boehringer Ingelheim Pharma GmbH & Co. KG. Lemtrada 12 mg concentrate for solution for infusion: summary of product characteristics, 2018.

Bosca, I., Coret, F., Valero, C., Pascual, A.M., Magraner, M.J., Landete, L., et al., 2008. Effect of relapses over early progression of disability in multiple sclerosis patients treated with beta-interferon. Multiple Sclerosis 14, 636–639. https://doi.org/10.1177/1352458507086666.

Brunetti, L., Hunter, S.F., 2014. Implications for multiple sclerosis in the era of the affordable care act: an evolving treatment paradigm. Am. J. Manag. Care 20, S228–S241.

Cabezas, X.M., Corral, J.F., Oliver, X.A., Díez, Y., Tintoré, X.M., Auger, X.C., et al., 2016. Improved automatic detection of new T2 lesions in multiple sclerosis using deformation fields. AJNR Am. J. Neuroradiol. 1–8. https://doi.org/10.3174/ajnr.A4829.

Cohen, J.A., Barkhof, F., Comi, G., Hartung, H.-.P., Khatri, B.O., Montalban, X., et al., 2010. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. New Engl. J. Med. 362, 402–415. https://doi.org/10.1056/NEJMoa0907839.

Cohen, J.A., Coles, A.J., Arnold, D.L., Confavreux, C., Fox, E.J., Hartung, H.-.P., et al., 2012. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 380, 1819–1828. https://doi.org/10.1016/S0140-6736(12)61769-3.

Cohen, J.A., Khatri, B., Barkhof, F., Comi, G., Hartung, H.-.P., Montalban, X., et al., 2016. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised transforms study. journal of neurology. Neurosurg. Psychiatry 87, 468–475. https://doi.org/10.1136/jnnp-2015-310597.

Confavreux, C., Vukusic, S., Moreau, T., Adeleine, P., 2000. Relapses and progression of disability in multiple sclerosis. New Engl. J. Med. 343, 1430–1438. https://doi.org/10.1056/NEJM200011163432001.

Confavreux, C., Vukusic, S., 2006. Natural history of multiple sclerosis: a unifying concept. Brain 129, 606–616. https://doi.org/10.1093/brain/awl007.

Confavreux, C., Vukusic, S., 2014. The clinical course of multiple sclerosis. Handb. Clin. Neurol. 122, 343–369. https://doi.org/10.1016/B978-0-444-52001-2.00014-5.

Dworkin, J.D., Linn, K.A., Shinohara, R.T., Oguz, I., Fleishman, G.M., Bakshi, R., et al., 2018. An automated statistical technique for counting distinct multiple sclerosis lesions. AJNR Am. J. Neuroradiol. 39, 626–633.

European Medicines Agency. Questions and answers on Novantrone and associated names (mitoxantrone 2 mg/ml concentrate for solution for infusion)2016.

Fred, D., Lublin, M., Stephen, C., Reingold, P., Jeffrey, A., Cohen, M., Gary, R., Cutter, P., Sørensen, P.S., et al., 2014. Defining the clinical course of multiple sclerosis the 2013 revisions. Neurology 83, 278–286.

Gajofatto, A., Benedetti, M.D., 2015. Treatment strategies for multiple sclerosis: when to start, when to change, when to stop? WJCC 3, 545. https://doi.org/10.12998/wjcc.v3.i7.545.

Genentech Inc. Ocrevus 300 mg concentrate for solution for infusion: summary of product characteristics, 2018.

Havrdova E., Arnold D.L., Cohen J.A., Hartung H.-.P. Alemtuzumab Care-MS i 5-year follow-up, 2017:10.

Havrdova, E., Galetta, S., Hutchinson, M., Stefoski, D., Bates, D., Polman, C.H., et al., 2009. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the natalizumab safety and efficacy in relapsing-remitting multiple sclerosis (AFFIRM) study. Lancet Neurol. 8, 254–260. https://doi.org/10.1016/S1474-4422(09)70021-3.

Jain, S., Sima, D.M., Ribbens, A., Cambron, M., Maertens, A., Van Hecke, W., et al., 2015. Automatic segmentation and volumetry of multiple sclerosis brain lesions from MR images. NeuroImage 8, 367–375. https://doi.org/10.1016/j.nicl.2015.05.003.

Kappos, L., O'Connor, P., Radue, E.-.W., Polman, C., Hohlfeld, R., Selmaj, K., et al., 2015. Long-term effects of fingolimod in multiple sclerosis: the randomized freedoms extension trial. Neurology 84, 1582–1591. https://doi.org/10.1212/WNL.0000000000001462.

Kappos, L., Radue, E.-.W., O'Connor, P., Polman, C., Hohlfeld, R., Calabresi, P., et al., 2010. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. New Engl. J. Med. 362, 387–401. https://doi.org/10.1056/NEJMoa0909494.

Marrie, R.A., Montalban, X., 2018. Disease-modifying therapy in multiple sclerosis: two guidelines (almost) passing in the night. Multiple Sclerosis J. 24, 558–562. https://doi.org/10.1177/1352458518767323.

Merck Serono Europe Ltd. Rebif 22 micrograms solution for injection: summary of product characteristics, 2018.

Montalban, X., Gold, R., Thompson, A.J., Otero-Romero, S., Amato, M.P., Chandraratna, D., et al., 2018. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Multiple Sclerosis 24, 96–120. https://doi.org/10.1177/1352458517751049.

Novartis Europharm Ltd. Extavia 250 micrograms/ml powder and solvent for solution for injection: summary of product characteristics, 2018.

Novartis Europharm Ltd. Gilenya 0.5 mg hard capsules: summary of product characteristics. 2018.

Pardo, G., Jones, D.E., 2017. The sequence of disease-modifying therapies in relapsing multiple sclerosis: safety and immunologic considerations. J. Neurol. 264, 2351–2374. https://doi.org/10.1007/s00415-017-8594-9.

Prosperini, L., Annovazzi, P., Capobianco, M., Capra, R., Buttari, F., Gasperini, C., et al., 2015. Natalizumab discontinuation in patients with multiple sclerosis: profiling risk and benefits at therapeutic crossroads. Multiple Sclerosis J. 21, 1713–1722. https://doi.org/10.1177/1352458515570768.

Prosperini, L., Gallo, V., Petsas, N., Borriello, G., Pozzilli, C., 2009. One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis. Eur. J. Neurol. 16, 1202–1209. https://doi.org/10.1111/j.1468-1331.2009.02708.x.

Rae-Grant, A., Day, G.S., Marrie, R.A., Rabinstein, A., Cree, B.A.C., Gronseth, G.S., et al., 2018. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Neurology 90, 777–788. https://doi.org/10.1212/WNL.0000000000005347.

Río, J., Castilló, J., Rovira, A., Tintoré, M., Sastre-Garriga, J., Horga, A., et al., 2009. Measures in the first year of therapy predict the response to interferon β in ms. Multiple Sclerosis 15, 848–853. https://doi.org/10.1177/1352458509104591.

Rossi Espagnet, M.C., Bernardi, B., Pasquini, L., Figà-Talamanca, L., Tomà, P., Napolitano, A., 2017. Signal intensity at unenhanced T1-weighted magnetic resonance in the globus pallidus and dentate nucleus after serial administrations of a macrocyclic

gadolinium-based contrast agent in children. Pediatr. Radiol. 47, 1–8. https://doi.org/10.1007/s00247-017-3874-1.

Rudick, R.A., Stuart, W.H., Calabresi, P.A., Confavreux, C., Galetta, S.L., Radue, E.-.W., et al., 2006. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. New Engl. J. Med. 354, 911–923. https://doi.org/10.1056/NEJMoa044396.

Sanofi-Aventis group. Aubagio 14mg film-coated tablets: summary of product characteristics2018.

Scolding, N., Barnes, D., Cader, S., Chataway, J., Chaudhuri, A., Coles, A., et al., 2015. Association of british neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Pract. Neurol. 15, 273–279. https://doi.org/10.1136/practneurol-2015-001139.

Signoriello, E., Doriana, L., Fabrizia, M., Francesco, S., Gabri, N.C., Fabio, B., et al., 2018. Fingolimod reduces the clinical expression of active demyelinating lesions in ms. Mult. Scler. Relat. Disord. 20, 215–219. https://doi.org/10.1016/j.msard.2018.02.002.

Sormani, M.P., Gasperini, C., Romeo, M., Rio, J., Calabrese, M., Cocco, E., et al., 2016. Assessing response to interferon-β in a multicenter dataset of patients with ms. Neurology 87, 134–140. https://doi.org/10.1212/WNL.0000000000002830.

Sormani, M.P., Kappos, L., Sprenger, T., Meier, D.P., Häring, D., Tomic, D., et al., 2015a. Adding brain volume loss to the modified rio scoring system improves prediction of future disability progression : analyses from two fingolimod phase 3 trials. P5.202, 67th American Academy of Neurology annual meeting (AAN) 1.

Sormani, M.P., Rio, J., Tintorè, M., Signori, A., Li, D., Cornelisse, P., et al., 2013. Scoring treatment response in patients with relapsing multiple sclerosis. Multiple Sclerosis J. 19, 605–612. https://doi.org/10.1177/1352458512460605.

Sormani, M.P., Rufi, P., DeStefano, N.T.K., 2015b. Predicting treatment response to teriflunomide in the temso study using the modified rio score. Mult. Scler. 23, 587.

Splendiani, A., Perri, M., Marsecano, C., Vellucci, V., Michelini, G., Barile, A., et al., 2018. Effects of serial macrocyclic-based contrast materials gadoterate meglumine and gadobutrol administrations on gadolinium-related dentate nuclei signal increases in unenhanced T1-weighted brain: a retrospective study in 158 multiple sclerosis (MS) patients. Radiologia Medica 123, 125–134. https://doi.org/10.1007/s11547-017-0816-9.

Stojanov, D.A., Aracki-Trenkic, A., Vojinovic, S., Benedeto-Stojanov, D., Ljubisavljevic, S., 2016. Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple sclerosis: correlation with cumulative dose of a macrocyclic gadolinium-based contrast age. Eur. Radiol. 26, 807–815. https://doi.org/10.1007/s00330-015-3879-9.

Sweeney, E.M., Shinohara, R.T., Shea, C.D., Reich, D.S., Crainiceanu, C.M., 2013. Automatic lesion incidence estimation and detection in multiple sclerosis using multisequence longitudinal mri. Am. J. Neuroradiol. 34, 68–73. https://doi.org/10.3174/ajnr.A3172.

Tremlett, H., Yousefi, M., Devonshire, V., Rieckmann, P., Zhao, Y., 2009. Impact of multiple sclerosis relapses on progression diminishes with time. Neurology 73, 1616–1623. https://doi.org/10.1212/WNL.0b013e3181c1e44f.