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Review article

Variations in multiple sclerosis practice within Europe – Is it time for a new treatment guideline?

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ABSTRACT

In the past 5 years, the combination of developments in diagnostic strategy and approval of new disease-modifying therapies has provided an opportunity to achieve dramatic improvements in patient outcomes in multiple sclerosis (MS). However, across Europe there are several factors that may prevent patients from receiving the best therapy at the appropriate time, and there is variation among countries in terms of which of these factors are most relevant. Here, we review current MS clinical practices in a number of countries in the European Union to identify differences regarding initiation of treatment in patients with clinically isolated syndrome or relapsing–remitting MS, and differences in the timing of treatment switch or escalation. While recognizing that policy is not static in any country, we believe that patients' interests would be better served if a European treatment guideline was developed. Such a guideline could both inform and be informed by national policies, facilitating the dissemination of best clinical practice internationally.

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1. Introduction

In the past 5 years, two developments have had the potential to revolutionize the management of multiple sclerosis (MS). First, the number of approved disease-modifying therapies (DMTs) has increased substantially (Fig. 1), and secondly, early diagnosis of clinically definite MS (CDMS) has been facilitated by the 2010 revisions to the McDonald diagnostic criteria (Polman et al., 2011). To take advantage of these developments and to provide patients with MS the opportunity for the best possible long-term outcomes, neurologists must be able to begin treatment as soon as a proper diagnosis is confirmed. They should also be able to choose a first-line DMT appropriate both to the diagnosis and to the patient's circumstances (e.g. occupation, family-planning considerations).

Variations in MS practice exist across Europe in terms of when treatment is initiated, switched or escalated, and in terms of which treatments can be prescribed. The latter factor goes beyond the constraints of EU label indications, being driven by national or local guidelines, reimbursement policies and cultural influences. Here, we briefly review international guidelines for diagnosis and treatment initiation, then summarize regional variations in practice based on national or local policies. We also consider the various treatment options available to patients with relapsing MS and examine the approaches taken in different countries to determine which DMT to use in which patient.

2. Diagnostic criteria

The McDonald criteria were first published in 2001 (McDonald et al., 2001), revised in 2005 (Polman et al., 2005) and updated most recently in 2010 (the evolution of these criteria is summarized in Table 1) (Polman et al., 2011, 2005; McDonald et al., 2001). The 2001 guidelines were a landmark in MS treatment, both because they integrated magnetic resonance imaging (MRI) and clinical criteria for diagnosis of relapsing disease in patients presenting with a clinically isolated syndrome (CIS), and because they established criteria for the diagnosis of primary progressive disease. Exclusion of other possible causes of symptoms at clinical presentation, such as neuromyelitis optica, and the requirement for evidence that central nervous system (CNS) lesions are disseminated in both time (DIT) and space (DIS), remain central to the diagnosis of relapsing MS. The 2010 revisions acknowledged that the presence of both asymptomatic gadolinium-enhancing (Gd+) and non-enhancing MRI lesions at any time provides evidence of DIT, obviating the need for confirmation with another MRI scan (Polman et al., 2011; Montalban et al., 2010). The 2010 revisions also adopted simpler criteria for DIS (Swanton et al., 2006, 2007) than were used previously (McDonald et al., 2001; Polman et al., 2005; Barkhof et al., 1997; Tintore et al., 2000), requiring the presence of at least one T2 CNS lesion in at least two of the following four regions: periventricular; juxtacortical; infratentorial; and spinal. In view of this simplification, the 2010 guidelines also proposed that findings from analysis of cerebrospinal fluid (CSF), such as increased immunoglobulin G index or oligoclonal bands on isoelectric focusing analysis, should no longer be needed as an adjunct to MRI evidence of DIS (Polman et al., 2011). This proposal has caused some controversy, because the absence of oligoclonal bands in CSF should call a diagnosis of MS into question, and ignoring such evidence contradicts the diagnostic recommendation to exclude other causes of disease (Sandberg-Wollheim and Olsson, 2013; Tur and Montalban, 2013; Hutchinson, 2013).

Stated aspirations of the 2010 revisions to the McDonald criteria were to increase diagnostic sensitivity without compromising specificity, while simultaneously simplifying the requirements for demonstration of DIS and DIT with fewer MRI scans than were previously necessary (Polman et al., 2011). These goals seem to have been realized; analyses of sample populations that compare the effectiveness of the 2005 and 2010 criteria have indicated that more patients receive diagnoses of CDMS earlier in the disease course when using the most recent revisions than when using the older versions (Fig. 2), and earlier diagnosis affords the possibility of earlier counselling and treatment (Kang et al., 2014; Runia et al., 2013; Brownlee et al., 2014). One of these studies, however, did note that up to one-third of patients with retrospective diagnoses of CDMS made using the 2010 criteria had experienced no further clinical events after 6 years of follow up (Brownlee et al., 2014). It is possible that this proportion of individuals would have been smaller if CSF analysis remained a requirement for differential diagnosis.

3. Treatment initiation in CIS

Definitions vary, but one relatively recent definition proposed that CIS can be considered "to be a single episode with neurological symptoms suggestive of a demyelinating disease, in a patient having lesions of a shape and location typical for MS, and for whom a thorough differential diagnosis has been completed"

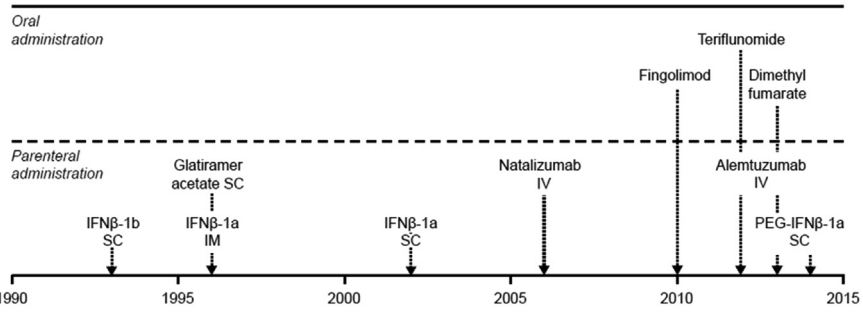

Fig. 1. Timeline of approvals of disease-modifying therapies for RRMS by the European Medicines Agency. IFN, interferon; IM, intramuscular; IV, intravenous; PEG, polyethylene glycol; RRMS, relapsing–remitting multiple sclerosis; SC, subcutaneous.

Table 1
Evolution of the McDonald criteria for diagnosis of relapsing MS.

Clinical presentation	Additional data needed for diagnosis		
	2001 guideline (McDonald et al., 2001)	**2005 revision** (Polman et al., 2005)	**2010 revision** (Polman et al., 2011)
≥2 Attacks:[a] objective clinical evidence of ≥2 lesions	None[b]	None[b]	None[b]
≥2 Attacks:[a] objective clinical evidence of 1 lesion with reasonable historical evidence of a previous attack[c]	NA	NA	None[b,d]
≥2 Attacks:[a] objective clinical evidence of 1 lesion	DIS: Barkhof et al. (1997) and Tintore et al. (2000) MRI criteria met, or ≥2 MRI lesions and +ve CSF,[e] or a further attack implicating a different CNS site	DIS: Barkhof et al. (1997) and Tintore et al. (2000) MRI criteria met, or ≥2 MRI lesions and +ve CSF,[e] or a further attack implicating a different CNS site	DIS: ≥1 T2 lesion in ≥2 of 4 MS-typical regions of the CNS;[g] or a further attack implicating a different CNS site
1 Attack:[a] objective clinical evidence of ≥2 lesions	DIT: specific MRI criteria met,[f] or a second attack	DIT: specific MRI criteria met,[f] or a second attack	DIT: simultaneous asymptomatic Gd+ and non-enhancing lesions at any time; or a new T2 and/or Gd+ lesion on follow-up MRI, irrespective of timing relative to the baseline scan; or a second attack
1 Attack:[a] objective clinical evidence of 1 lesion (CIS)	DIS and DIT as defined above	DIS and DIT as defined above	DIS and DIT as defined above

CIS, clinically isolated syndrome; CNS, central nervous system; CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; NA, not applicable.

[a] The supporting definition of an 'attack' (exacerbation, relapse) has evolved since the guidelines were originally published. The elements that are unchanged are that the episode of neurological disturbance should be typical of MS, of ≥24 h' duration in the absence of fever or infection, and related to an acute inflammatory demyelinating event. The 2010 revision takes greater account of historical patient-reported attacks than earlier versions of the guideline: the episode *"should be documented by contemporaneous neurological examination but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event."* This is further qualified: *"Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms."*

[b] The original 2001 guideline stated: *"No additional tests are required; however, if tests [magnetic resonance imaging (MRI), cerebral spinal fluid (CSF)] are undertaken and are negative, extreme caution should be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture." The 2005 revision added that "… some objective evidence to support a diagnosis of MS"* was needed. In 2010, the guidance was further qualified: *"… it is desirable that any diagnosis of MS be made with access to imaging …"*.

[c] *"Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings"* (Polman et al., 2011).

[d] Diagnostic criteria introduced in 2010: *"Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings."*

[e] *"Positive CSF determined by oligoclonal bands detected by established methods (preferably isoelectric focusing) different from any such bands in serum or by a raised IgG index"* (McDonald et al., 2001; Polman et al., 2005).

[f] A Gd+ lesion on a scan ≥3 months after the attack demonstrates DIT if not located at the site implicated in the attack. If there is no Gd+ lesion at this time, a follow-up scan is required (ideally 3 months later); a new T2 or Gd+ lesion at follow-up fulfils DIT. If the initial scan is <3 months after the attack, another scan must be obtained ≥3 months after the attack. A new Gd+ lesion at this time demonstrates DIT, but if no Gd+ lesion is seen, a further scan ≥3 months after the first scan that shows a new T2 or Gd+ lesion will suffice.

[g] Periventricular, juxtacortical, infratentorial or spinal cord.

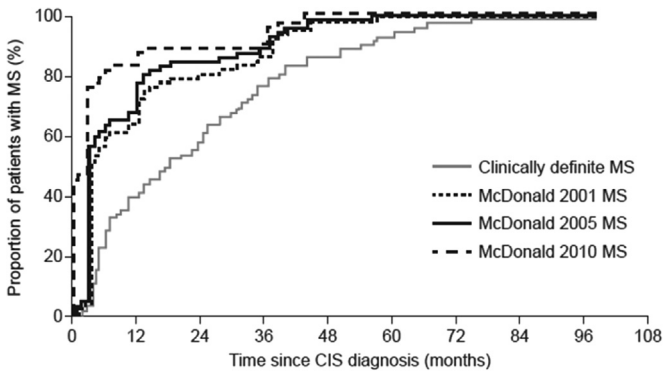

Fig. 2. Kaplan–Meier curve showing time to diagnosis of clinically definite MS using the Poser criteria (Poser et al., 1983) and time to diagnosis using the McDonald criteria applied retrospectively, in patients with CIS (reproduced from Brownlee et al. (2014) with permission from BMJ Publishing Group Ltd.). CIS, clinically isolated syndrome; MS, multiple sclerosis.

(Hartung et al., 2011). Among the countries considered here, DMT would be initiated in Denmark, Germany and Portugal based on these criteria, but further evidence might be needed before MS treatment would be initiated in England, France, Italy and Poland. Among those countries that do advocate DMT initiation in patients with CIS, there is variation in both the diagnostic guidelines and the choice of first-line treatment.

In all countries, treatment is initiated when clinical and MRI evidence, and very often findings from lumbar puncture, have been assessed (Table 2). In Portugal, unambiguous evidence of a relapse (including optic neuritis) accompanied by spinal or brainstem lesions would be sufficient to begin therapy; however, in France, and in many centres in England, Italy and Poland, evidence of a second relapse is usually required before treatment can begin. Exceptions to this are made when the first relapse is severe, although the definition of what constitutes a severe relapse varies considerably. Relapses that affect motor function are sometimes regarded as more serious than those affecting sensory function. In

Table 2
Diagnostic criteria for treatment initiation in CIS based on guidelines or the neurologist's opinion.

Country	Clinical evidence	MRI evidence	CSF evidence	Comments
Denmark	Severity of relapse interferes with daily living	DIS meets the McDonald 2010 criteria. One large T2 or Gd+ lesion could justify treatment; size, location and activity of lesions are most important	Evidence of oligoclonal bands	Other diagnoses must be excluded; one large T2 or Gd+ lesion could justify treatment; size, location and activity of lesions are most important
France	Evidence of a second relapse unless the first relapse is very severe[a]	T2 and Gd+ MRI lesions	Evidence of oligoclonal bands	Lesion activity is key; treatment initiation is important when Gd+ lesions are observed
Germany	Evidence of a demyelinating event	One large T2 or Gd+ lesion could justify treatment; size, location and activity of lesions are most important	CSF evidence is also a requirement for differential diagnosis under German guidelines	The emphasis placed on treatment increases with MRI lesion count
Italy	Evidence of a second relapse unless the first relapse is very severe[a]	Size, location and activity of lesions are most important	CSF examination is not mandatory but is recommended for differential diagnosis	Some centres treat if lesions are seen in the brainstem or spinal cord
Poland	Evidence of a second relapse unless the first relapse is very severe[a]	One large T2 and a Gd+ lesion or two small T2 lesions could justify treatment	Evidence of oligoclonal bands	A minimum of two MRI lesions or intrathecal oligoclonal antibody bands in the CSF
Portugal	A typical relapse, affecting motor or sensory function	Typical lesions providing evidence of DIS	Evidence of oligoclonal IgG bands in CSF but no corresponding IgG in serum	A minimum of three MRI lesions or lesions in the brainstem or spinal cord in a typical patient with CIS
UK[b]	Evidence of a second relapse unless the first relapse is very severe[a]	DIS meets the McDonald 2010 criteria. One large T2 or Gd+ lesion could justify treatment; size, location and activity of lesions are most important	CSF examination is not mandatory but is usually performed for differential diagnosis	Other diagnoses must be excluded; one large T2 or Gd+ lesion could justify treatment; size, location and activity of lesions are most important

CIS, clinically isolated syndrome; CSF, cerebral spinal fluid; DIS, dissemination in space; Gd+, gadolinium-enhancing; Ig, immunoglobulin; MRI, magnetic resonance imaging.

[a] The definition of what constitutes a severe relapse varies across countries.
[b] Guidance pertains to England and Wales but not Scotland or Northern Ireland.

Italy, less importance is placed on clinical symptoms of relapse and more on the evidence of MRI disease activity. In France, the level of disability following a relapse is what informs treatment decisions, and the situation is similar in England except that it is the impact of the relapse on the individual that guides the decision to treat, rather than the overall level of disability accrued.

Radiologically, the size, activity or location (e.g. brainstem or spinal cord) of MRI lesions are generally more important considerations than their number, although the number can also influence the decision to treat. Some countries set a threshold lesion count below which treatment is likely to be postponed pending follow-up. For example, neurologists in Poland and Portugal tend not to start treatment unless at least three lesions are seen, but this guiding principle does not ignore lesion location: lesions in the brainstem are of greater concern than ones found in the periventricular region. No threshold lesion count is set in Denmark, England, France, Germany or Italy, but in practice, a patient with a very low lesion burden will generally be counselled and offered the options of treatment initiation or review at follow-up, according to their preference. The association between high lesion burden and poor long-term prognosis among patients presenting with CIS (O'Riordan et al., 1998) is also recognized and practice in some European countries is guided accordingly.

The presence of oligoclonal bands in CSF continues to be an important diagnostic marker in many countries. In Denmark, France, Germany and Poland, lumbar puncture is highly recommended both for securing a diagnosis and for treatment initiation, with DMT being started most likely if a patient presenting with CIS has oligoclonal bands on analysis of their CSF. Without the latter evidence, treatment initiation in these countries would probably be postponed pending follow-up. One reason why lumbar puncture may not be used routinely for diagnosis in some countries is the associated hospitalization cost; another reason may be the reduction in reliance on corroborative CSF evidence in the revised 2010 McDonald criteria (Polman et al., 2011).

Regarding choice of DMT at treatment initiation, all of the injectable MS DMTs, except PEGylated IFN beta-1a, are indicated in CIS, having been shown to reduce the rate of conversion to CDMS relative to placebo in phase 3 trials (intramuscular [IM] interferon [IFN] beta-1a in the 'Controlled High-risk subjects Avonex Multiple sclerosis Prevention Study' [CHAMPS] (Jacobs et al., 2000), subcutaneous [SC] IFN beta-1a in the 'Early Treatment Of Multiple Sclerosis' [ETOMS] trial (Filippi et al., 2004), IFN beta-1b SC in the 'BEtaferon in Newly Emerging multiple sclerosis For Initial Treatment' [BENEFIT] trial (Kappos et al., 2006), and glatiramer acetate [GA] SC in the 'Early glatiramer acetate treatment in delaying conversion to clinically definite multiple sclerosis in subjects Presenting with a Clinically Isolated Syndrome' [PreCISe] trial (Comi et al., 2009)). More recently, the oral DMT teriflunomide was also shown to delay conversion to CDMS in the 'Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis' [TOPIC] trial (Miller et al., 2014); at the time of writing, PEGylated IFN beta-1a was not under evaluation in patients with CIS. As well as delaying conversion, early treatment can also improve long-term outcomes; for example among patients randomized to IFN beta-1b in BENEFIT, the risk of conversion to CDMS was lower and cognitive function was better at 8 years than among those randomized to placebo (Edan et al., 2014).

Generally, the injectable therapies are the ones offered first line to patients in countries where the policy is to treat individuals with CIS and, subject to availability and reimbursement considerations, the choice of DMT is normally at the discretion of the neurologist; however, there are exceptions. For example, current guidelines in Denmark prioritize teriflunomide for first-line treatment of CIS, with IFN beta-1a (IM or SC) as next-line options if teriflunomide is unsuitable. In Poland, IFN beta-1b is the most widely used first-line option and its use is also common in Portugal, although the majority of Portuguese clinics favour IFN beta-1a IM. As noted above, treatment is initiated in France if the first relapse is very severe, in which case any of the first-line options can be used.

4. Diagnosis and treatment of MS

The challenge of making a definitive diagnosis, and the inherent variability in the MS disease course that can confound accurate prognosis (Alkhawajah and Oger, 2011), are both reasons to act conservatively when initiating treatment; however, the pathophysiological processes that cause focal inflammatory CNS damage, diffuse neurodegenerative damage and brain atrophy are evident at the earliest stages of MS (Bermel and Bakshi, 2006) and these processes are associated with the long-term accumulation of physical and cognitive deficits. While acknowledging that a proportion of patients with a diagnosis of MS will experience a relatively benign disease course, it seems prudent to initiate DMT as soon as a diagnosis of MS is confirmed. In most of the countries considered here, the 2010 revised McDonald criteria have been adopted for diagnosis, except Portugal, which supports the use of the 2005 revisions.

As noted above, the 2010 revisions to the McDonald criteria have enabled more rapid diagnosis of MS than was possible previously. Removal of such a heavy reliance on the timing and availability of follow-up MRI should be a great advantage in countries where routine access to MRI remains limited. Furthermore, patients should learn quickly whether there is evidence of DIT rather than living with a diagnosis of CIS for an extended period. No evidence of DIT would suggest that their disease is at an early stage and should be monitored, and evidence of DIT should accelerate the diagnosis of MS, theoretically affording patients access to treatment options other than IFN beta or GA. Although IFN beta and GA are prescribed in England, the National Institute for Health and Care Excellence (NICE) does not recommend using these agents to treat patients with MS, on the basis of their clinical and cost-effectiveness (National Institute for Health and Care Excellence (NICE), 2014). Recent Association of British Neurologists (ABN) guidelines (2015) note that dimethyl fumarate and fingolimod (if patients are eligible to receive it) are likely to be more effective than either teriflunomide or the first-line injectable DMTs (Scolding et al., 2015).

First-line oral agents are the preferred choice of treatment for patients with relapsing MS in Denmark, followed by PEGylated IFN beta-1a, with IFN-beta and GA continuing to be options; the use of PEGylated IFN beta-1a is currently under review in England. In the absence of tolerability issues, it seems likely that patients will find oral treatments more convenient than parenteral ones, which may impact on adherence, but it will be some time before the ramifications of the decision to deprioritize the long-established injectable DMTs become clear in routine clinical practice. Potentially running counter to this apparent shift from injectable to oral DMTs, PEGylated IFN beta-1a has been developed for first-line treatment and is administered subcutaneously every 2 weeks, which some patients may find more convenient than taking a daily pill. Anecdotally, there is also evidence that patients in Poland trust the efficacy of parenteral treatments more than that of medicines taken orally. Despite their approval status, teriflunomide and dimethyl fumarate are not currently reimbursable in Poland, and thus are not prescribed; patients in Poland with relapsing MS generally receive IFN beta-1b SC first line.

Neurologists in Germany may prescribe any of the approved MS DMTs, including PEGylated IFN beta-1a, oral azathioprine and intravenous immunoglobulin although the last two options are

rarely used, and reimbursement for immunoglobulin treatment can be problematic and must be cleared with health insurance organizations before being prescribed.

5. Treatment switch

Regardless of which MS DMT a patient receives, it must be effective for that individual, and the patient must persist with treatment to benefit from it. Disease breakthrough (relapse and/or MRI activity) because of an inadequate therapeutic effect is justification for switching agents, but disease breakthrough is almost inevitable if adherence is poor. The inability to persist with a DMT usually reflects poor tolerability, but given the number of DMTs now available, this problem should in theory be solved by switching to a different option. Unfortunately, in several countries, health policy dictates that treatment switch is not possible for reasons of poor tolerability alone. The practice is therefore to wait for disease breakthrough before switching therapy, which means that the patient's condition must deteriorate before he or she can receive a different DMT.

First-line injectable therapies have well-established safety profiles, and are well tolerated in real-world settings (Hupperts et al., 2014). Despite this, continuation of therapy and adherence to the prescribed regimen remain suboptimal for injectable treatments, and this is largely attributable to issues such as injection-site reactions and flu-like symptoms (Giovannoni et al., 2012). Real-world evidence for the tolerability of teriflunomide and dimethyl fumarate is limited, but there appears to be a proportion of individuals who experience intolerable gastrointestinal or dermatological side effects when taking dimethyl fumarate (Cohn et al., 2014).

Intolerable side effects are sufficient grounds to switch treatment in Germany and Denmark, and also in France and Italy, providing therapy is switched to a same-line alternative. Guidelines for treatment switch in England are under review, but currently, in common with several countries in Europe, treatment may not be switched for tolerability reasons alone.

The need to switch treatment is of course not related only to tolerability and adherence. In Denmark and Italy, patients receiving IFN beta can switch treatments if they register a persistently high titre of neutralizing antibodies over a period of 3–6 months; similarly, the ongoing presence of antibodies to natalizumab can justify treatment switch. Finally, elevated levels of hepatic enzymes during IFN beta therapy can justify a change of treatment. Switching among any of the approved DMTs is clearly complicated by the fact that not all treatment options are offered or reimbursed in all countries.

6. Monitoring treatment response

Routine monitoring of treatment response is not widely practised; indeed, in some countries, review of treatment tends to be prompted by patient-reported disease breakthrough. This disease breakthrough may be a result of poor treatment adherence rather than lack of efficacy, but without routine follow-up both gradual disease worsening and ongoing subclinical disease progression can easily be overlooked. The practice of waiting for the clinical manifestation of disease progression before reviewing treatment inevitably means waiting for CNS damage to accumulate, and once lost, brain tissue is generally not regained.

When follow-up occurs, there are substantial inadequacies in existing clinical measures of disease progression (Uitdehaag, 2014). The Expanded Disability Status Scale (EDSS) is widely used but has limited sensitivity in detecting changes in response to

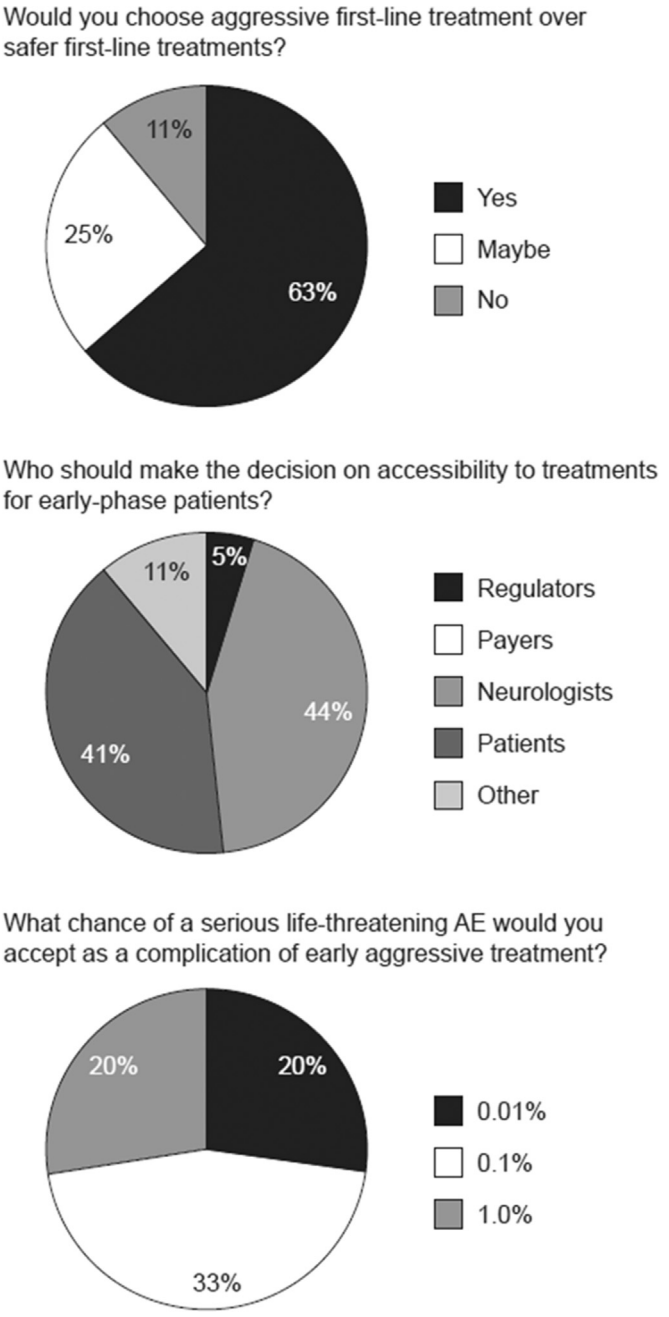

Fig. 3. Informal patient survey data – patients with MS were asked a series of questions at St Bartholomew's Hospital, London, UK, to assess their attitudes to treatment. Data from http://www.touchneurology.com/system/files/private/articles/10817/pdf/bruck.pdf (Sorensen et al., 2013). AE, adverse event; MS, multiple sclerosis.

treatment (Rabadi and Vincent, 2013). Responding to this unmet need, the MS Outcomes Assessment Consortium (MSOAC) aims to validate a new multidimensional measure of disability that will be reliable and practical to use, be sensitive to treatment effects, yield measurements that are meaningful to the patient, and be cost-effective for the assessment of endpoints in future trials of MS therapies (Multiple Sclerosis Outcome Assessment Consortium, 2015). To meet this objective, data have been collected relating to the use of the MS Functional Composite (MSFC) assessment instrument, of other disability measures such as 'low-contrast visual acuity' measurements, and of cognitive assessments such as the symbol digit modalities test.

Monitoring subclinical disease progression, and adapting

treatment to mitigate or pre-empt it, is one of the great challenges in MS management. Assessment of MRI lesion activity is common, but the use of MRI methods to monitor changes in brain volume (Smith et al., 2002), which may provide a more complete picture of accumulating CNS damage than lesion activity alone, is unavailable to many neurologists. Progress is being made in identifying drug-response biomarkers to aid treatment decisions, and biomarkers for risk stratification (Comabella and Vandenbroeck, 2011; Pravica et al., 2013). Increasingly, clinical trials address this challenge of monitoring disease progression by including composite measures of disease activity among their pre-specified endpoints. Such measures typically examine whether patients are free from evidence of clinical disease (relapses, disability progression) and evidence of disease on MRI scans (Gd+ and T2 lesions) (Bevan and Cree, 2014; Havrdova et al., 2009, 2014; Giovannoni et al., 2011), the treatment goal being no evidence of disease activity (NEDA) (Banwell et al., 2013). The component measures included in the NEDA assessment will probably change over time, but adoption of NEDA as a measure of treatment success in wider clinical practice, rather than solely in clinical trials, could have a major impact on patient outcomes.

7. Treatment escalation

Pragmatically, it could be argued that DMTs, which have been shown to slow disability progression and reduce rates of brain atrophy in patients with relapsing MS, should be used as early as possible in the disease course, provided that they are well tolerated and have an acceptable safety profile. Although this approach may lead to over-treatment in some patients, it may confer enormous long-term benefits in others. While at odds with current national guidelines, support is growing for the adoption of a more aggressive approach to treatment early in the MS disease course, and an informal survey has suggested that patients would be less hesitant about initiating relatively aggressive treatment than might be expected (Fig. 3) (Sorensen et al., 2013).

At present, treatment escalation from first-line options is typically to fingolimod or natalizumab. There are factors to consider before switching to either of these drugs (first-dose cardiac monitoring for fingolimod (Singer, 2013) and John Cunningham virus profiling for natalizumab (Hunt and Giovannoni, 2012)), and based on their current indication in most countries in Europe, neither could be used at an early stage of the disease course (except in rapidly evolving severe RRMS). However, evidence of a shift towards earlier and more aggressive treatment strategies than ones traditionally adopted was provided by the indication assigned to alemtuzumab in 2013 (adult patients with RRMS with active disease defined by clinical or imaging features). The use of alemtuzumab remains at the discretion of the treating neurologist. It is unusual for it to be used as a first-line agent, although its first-line use in England and Germany is increasing, and the frequency of its use varies considerably both across countries and among different clinics within countries. However, the low disease threshold for its use that has been agreed by the European Medicines Agency sets a precedent for all DMTs in MS.

Current practice across Europe is to consider changing treatment in response to clinical disease activity (a relapse and/or deterioration in EDSS score) although in several countries evidence of subclinical MRI disease activity is an increasingly important part of the decision-making process. In Denmark, MRI has generally been used only following a clinically significant event, relapse being the trigger for treatment review. A similar situation applies in England, with treatment escalation being contingent on a relapse and evidence of MRI lesion activity. Recently, however, routine 6- or 12-monthly MRI follow-ups have become more common in Denmark and treatment can be escalated on the basis of MRI evidence alone. In France, the threshold for treatment escalation is two clinically significant relapses in 1 year and evidence of Gd+ lesions on MRI. In Italy and Portugal, clinical disease activity is the primary reason to escalate treatment, but relevant MRI activity (e.g. spinal cord or large T2 or Gd+ lesions) can also be a sufficient reason. For example, treatment may not be changed if a patient has a low number of small new T2 lesions (diameter 1–2 mm), because this probably indicates that the patient has good CNS-repair mechanisms; however, evidence of a Gd+ lesion or one large T2 lesion may prompt treatment review because these signs suggest that either the repair mechanisms or the treatment are not working effectively. The criteria for treatment escalation in Poland are slightly different: the patient must have had at least two moderate relapses within the preceding year, or one serious relapse within the previous 6 months, and have at least two Gd+ or T2 lesions. In Germany, official guidelines demand clinical activity plus MRI signs of ongoing disease; however, in many cases one relapse per year of any severity and accompanying MRI activity, or even MRI activity alone can be sufficient grounds for escalation.

8. National guidelines in Europe

No overarching guidelines are available for the management of MS across Europe. In Denmark, guidelines are generated by the Council for the Use of Expensive Hospital Medicines (Rådet for Anvendelse af Dyr Sygehusmedicin [RADS], 2015), with the most recent revision published in 2015. Specific recommendations are made for treatment initiation criteria and for the follow-up regimen, as well as clear directives for choice of DMT at initiation (based on disease activity), switching due to intolerance (based on the treatment being discontinued) and treatment escalation. In France, guidelines are produced by the French National Authority for Health (Haute Autorité de Santé [HAS], 2006). The main guidelines are being revised because of the recent dramatic increase in the number of available drugs (Maurice, 2014), so current specific guidance on pharmacological therapy dates from 2006. Therefore, the document does not include the McDonald 2010 revisions, nor any of the DMTs approved more recently than natalizumab.

In Germany, the Competence Network on Multiple Sclerosis has been authorized by the German Society of Neurology (Deutsche Gesellschaft für Neurologie, DGN) to revise and to develop further the German MS guidelines (Competence Network on Multiple Sclerosis, 2015). Importantly, patients in Germany have access to all drugs approved by German or European regulatory authorities, regardless of whether the drugs are recommended by a clinical guideline (Maurice, 2014). Publications from DGN are very forward-looking; for example, they include a discussion of individualized risk–benefit assessment of DMTs (including those still in development) for patients with MS and examine the potential impact of biomarkers (Salmen et al., 2014).

There is no national guideline for MS treatment in Italy, although the Italian Neurological Society (Società Italiana di Neurologia (SIN)) publishes recommendations regarding the facilities that should be offered and the expected expertise of medical teams in each of the country's accredited MS health centres. There are also several initiatives being undertaken regionally to produce treatment guidelines. In Poland, the Ministry of Health publishes guidelines regarding the use of DMTs in patients with MS, including which drugs should be used for first- and second-line treatment (currently fingolimod and natalizumab). This guidance also stipulates that patients should be assessed once a year. In Portugal, guidelines for the use of MS-modifying therapy were last

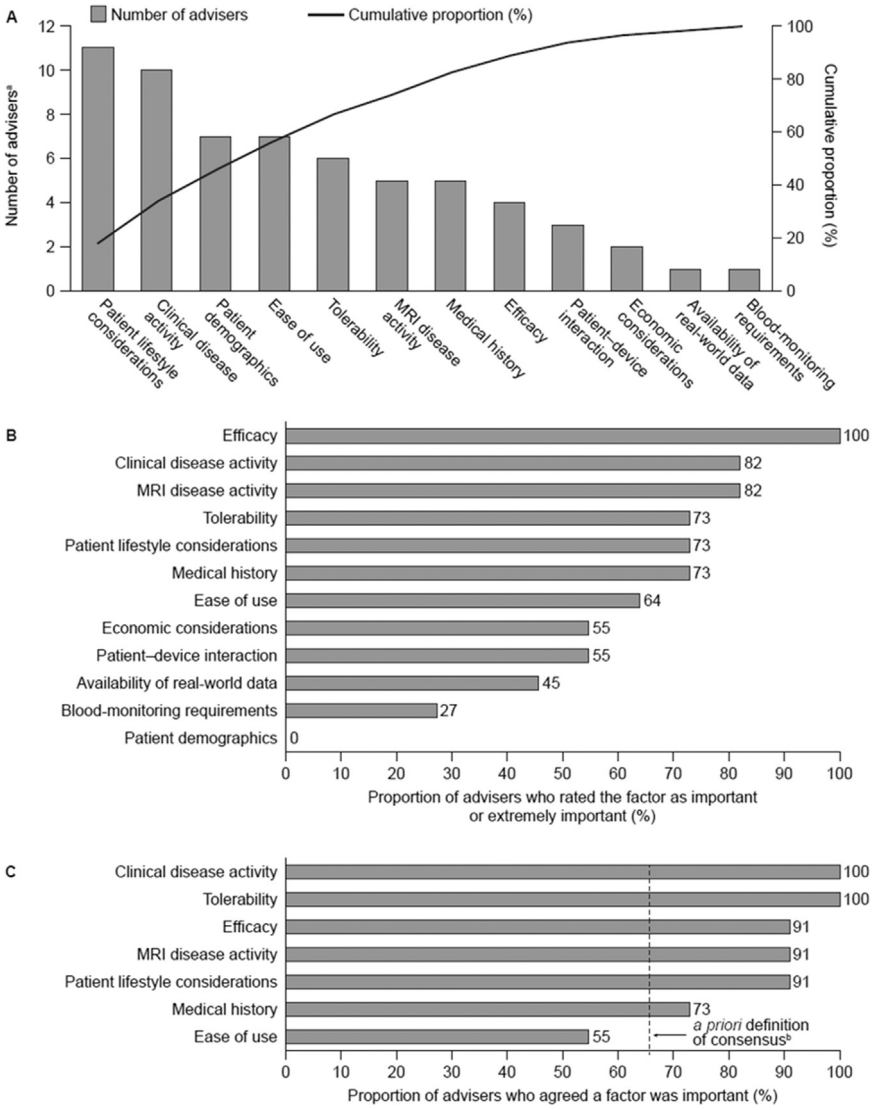

Fig. 4. Results from a modified Delphi consensus to determine which factors are important when selecting first-line therapy in patients with CIS. (A) Open-text responses, (B) responses rated by importance, (C) responses versus a threshold for consensus, defined *a priori*. [a]The frequency with which each response was given did not influence the subsequent round of consensus. [b]66% agreement; defined *a priori* as the point at which consensus was reached on the most important attributes of a disease-modifying therapy. CIS, clinically isolated syndrome; MRI, magnetic resonance imaging.

released by the Department of Quality in Health, from the Directorate-General of Health in 2012 (Direção-Geral da Saúde (DGS), 2012), although a new revision is in preparation. The guidance identifies first- and second-line treatment options, and aligns their use with a verified clinical algorithm designed to facilitate the evaluation of treatment after 1 year.

Treatment guidance in the UK is prepared and published regionally: NHS England commissioning policy, which takes account of recommendations from NICE, dictates which MS DMTs are available in England; recommendations made by the Scottish Medicines Consortium underpin the guidance used by NHS Scotland. The Department of Health, Social Services and Public Safety in Northern Ireland reviews guidance issued by NICE to assess its relevance in that region, and there is a similar relationship in Wales between NICE and the All Wales Medicines Strategy Group. NICE released new guidelines in 2014 (National Institute for Health and Care Excellence (NICE), 2014) which focused on general approaches to disease management, such as the need to provide proactive multidisciplinary care. No treatment algorithm was proposed, although evidence summaries and recommendations for the use of different DMTs are reported in NICE's various technology appraisals (IFN beta and GA, 2002; natalizumab, 2007; fingolimod, 2012; teriflunomide, 2014; alemtuzumab, 2014; and dimethyl fumarate, 2014) (NICE, 2015).

9. Development of a European treatment guideline in MS

Any group tasked with developing new guidelines for the management of MS faces the challenge of achieving clinically appropriate guidance that is evidence-based and offers consistency of approach, and yet incorporates sufficient flexibility to enable individualized treatment. In the case of guidelines to be applied across Europe, this challenge is further complicated by the need to accommodate regional variation in the availability of treatments and services, as well as variation in costing models and public opinion. The need for European guidelines to allow for differences in treatment availability fits well with the trend for promoting individualized management in MS: guidance should offer neurologists the freedom to choose a treatment appropriate to the patient's circumstances. Current national guidelines in countries such as England and France emphasize the value of care from

multidisciplinary teams, and new recommendations could support this endeavour to work with the patient to tailor treatment strategy on an individual basis. While not all DMTs may be available in all countries, it is nonetheless valuable for neurologists across Europe to benefit from shared experiences of all therapies.

An example of how current clinical opinion might be used to inform the development of European guidelines was gained during discussions that formed part of an advisory meeting attended by the authors that was held in June 2014 (sponsored by Novartis Pharma AG, Basel, Switzerland). A modified Delphi consensus exercise (Bousquet et al., 2012) was performed, with the aim of establishing which considerations are most important to neurologists when choosing an initial treatment in patients with CIS. Participants were asked to volunteer the considerations they regarded as most important; their responses were grouped and the groupings checked independently. Participants were asked individually to rank the grouped responses and then to confirm whether they agreed with the overall ranking. Key factors identified in this process included disease activity (clinical and MRI), treatment efficacy and tolerability, patients' lifestyle considerations and medical history (Fig. 4).

When participants were subsequently asked to rate their experience of different first-line therapies in terms of these consensus factors, their perceptions were not entirely consistent with head-to-head trial data. This suggests that clinical opinion based on real-world experience should be considered alongside findings from randomized trials. This type of consensus-building approach could be adopted to identify criteria that aid diagnosis or signpost the need for treatment switch or escalation, or that compare the merits of different DMTs at each stage of the disease course. The process might also be used to consolidate expert clinical opinion on research priorities, such as identification and verification of biomarkers that identify patients likely to be unresponsive to a particular treatment. It is worth noting that a modified Delphi consensus process is being considered by the MSOAC Task Force to assist in the development of the new disability assessment.

10. Conclusions

While variations in clinical practice are not intrinsically problematic, guidance based on a broad consensus of opinion should steer neurologists towards the best treatment selection and avert any shortcomings in treatment as rapidly as possible. These issues underline the need for a European treatment guideline, particularly if such a guideline could bring clarity to the process of therapy initiation and escalation, and whether MRI evidence alone can justify changing treatment. Engaging in the process of developing a consensus guideline may also focus attention on factors such as whether current label restrictions always serve the best interests of patients in the long term. Even if observance of an international guideline was entirely discretionary, its existence would provide a useful point of reference for best practice and may circumvent some duplication of effort expended in developing guidelines at national level.

Ethical standards

This review does not disclose new clinical trial or patient data.

Conflict of interest

Martin Marziniak has received lecture fees, travel grants and fees for consulting from: Bayer, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Teva. **Karima Ghorab** has received travel grants and fees for consulting from Teva, Biogen and Novartis. **Wojciech Kozubski** has received honoraria for lecturing and has received financial research support from Bayer, Teva, Biogen Idec, Sanofi-Aventis and Novartis. **Claudia Pfleger** has received travel grants and fees for consulting from Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Teva. **Lívia Sousa** has received fees from Novartis, Biogen Idec, Merck Serono, Sanofi-Aventis (Genzyme), Allergan, Bayer Schering, and Teva for participating in advisory boards or as lecturer. **Karen Vernon** has received lecture fees, travel grants and fees for consulting from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis and Teva. **Mauro Zaffaroni** has received honoraria for consulting or lecturing and travel grants for attending meetings from Almirall, Biogen Idec, Genzyme, Novartis and Teva. **Sven G. Meuth** has received honoraria for lecturing and travel expenses for attending meetings and has received financial research support from Bayer, Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi-Aventis and Teva.

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