

Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis



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Treatment decisions in multiple sclerosis are complex given the large number of disease-modifying therapies with diverse safety and efficacy profiles. The importance of early treatment has been recognised but how intensively to treat at onset is not known. Substantial variability exists in treatment selection with weak clinical trial evidence to guide initial treatment choices. Decision-making is made more complicated by variable tolerance for risk of side-effects and inability to accurately predict treatment response. Whether to use moderately effective and safe medications with escalation as needed, or to use higher efficacy medications from the outset, is a key question in clinical practice. Clinical trials in patients with relapsing multiple sclerosis have focused on pairwise comparisons but the effectiveness of different treatment approaches has not been tested. Future pragmatic randomised clinical trials and observational studies will help to inform more rational selection of initial therapies and improve the quality of life of patients with relapsing multiple sclerosis.

Introduction

Multiple sclerosis affects nearly 1 million individuals in the USA¹ and over 2 million worldwide.² Advances have been made in the treatment of relapsing forms through the introduction of anti-inflammatory disease-modifying therapies (DMTs), which decrease the development of new lesions shown by MRI, reduce relapses, and prevent the accumulation of disability. Currently, there are nine DMT classes (glatiramer acetate, β interferons, dimethyl fumarate, sphingosine 1-phosphate receptor modulators [fingolimod and siponimod], teriflunomide, cladribine, natalizumab, anti-B cell monoclonal antibodies [ocrelizumab and rituximab], and alemtuzumab) approved by the US Food and Drug Administration and European Medicines Agency for use in relapsing forms of multiple sclerosis, and these DMTs vary in their mechanism of action, efficacy, ease of use, and overall safety. Treatment decisions in multiple sclerosis have become increasingly complex, and weighing the benefits versus the risks of several different therapies has become a challenge for patients with multiple sclerosis and their clinicians. Patient involvement plays an important part in treatment selection, and DMT decisions are most commonly made jointly by patients and providers.³ Patients and providers have differences in perceptions, goals, and expectations of treatment,⁴ but patient choice and health insurance allowances are often deciding factors.

Use of increasingly effective medications has to be balanced against the risk of serious, life-changing, and occasionally fatal adverse events. Additionally, clinicians must consider convenience, including the route and frequency of administration, and the frequency of safety monitoring, which affect quality of life and co-determine the cost of treatment. Although clinical trials have established the safety and efficacy of individual therapies, the evidence to guide initial treatment selection, inform sequencing of medications, and compare effectiveness of different DMTs is emerging mainly from observational datasets. In this Personal View, we summarise available data and guidelines for initial DMT selection, present

the two treatment approaches, and discuss how future research will inform decision-making.

Initial treatment selection and treatment guidelines

The selection of the first DMT might be important given the benefits of early treatment in patients with multiple sclerosis.⁵ The 2017 revisions of the McDonald diagnostic criteria for multiple sclerosis⁶ enable earlier diagnosis in individuals with perhaps less inflammatory activity than for the clinical trial populations who were diagnosed with the 2010 McDonald criteria.⁷ Five studies (n=1845) have shown that commencing DMTs after a first clinical attack (ie, clinically isolated syndrome) with lesions shown by MRI suggestive of multiple sclerosis, even with modestly effective DMT, improves long-term clinical outcomes.⁸ Starting DMT even before a clinical attack in asymptomatic individuals with MRI studies suggestive of multiple sclerosis (ie, radiologically isolated syndrome) might seem beneficial but is an area of controversy.⁹ Taking into consideration the importance of early therapy, two philosophically different treatment approaches have emerged. One common approach advocates first-line use of moderate-efficacy DMTs, which have generally good safety profiles, with escalation to high-efficacy DMT only in the presence of breakthrough disease activity (ie, relapses or new lesions shown by MRI). The alternative approach involves use of high-efficacy therapies from the outset, with potential exposure to greater risks.

The European Committee for Treatment and Rehabilitation in multiple sclerosis together with the European Academy of Neurology¹⁰ and the American Academy of Neurology¹¹ have created task forces to develop clinical practice guidelines for the use of DMTs in patients with multiple sclerosis. The purpose of these guidelines was to provide clinicians across all practice types with recommendations regarding best management practices for treating patients with multiple sclerosis. These recommendations addressed the management of individuals who are initiating DMTs, switching DMTs, and

Lancet Neurol 2019; 18: 973–80

Published Online
July 30, 2019
[http://dx.doi.org/10.1016/S1474-4422\(19\)30151-6](http://dx.doi.org/10.1016/S1474-4422(19)30151-6)

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	Route	Reduction in annualised relapse rate vs placebo	Rates of NEDA 3	Brain atrophy, % brain volume loss per year (technique and time between measurements)	Major risks and side-effects
Interferon β -1a	Intramuscular	32% ¹²	14.2% at 96 weeks in DECIDE study ¹³	-0.53 from BRAVO study ¹⁴ (JI, year 1–2)	Flu-like symptoms, injection-site reactions, leukopenia, elevated liver enzymes, and depression
Interferon β -1b	Subcutaneous	34% ¹⁵	..	..	Flu-like symptoms, injection-site reactions, leukopenia, elevated liver enzymes, and depression
Interferon β -1a	Subcutaneous	32% ¹⁶	27.1% at 96 weeks in pooled data from OPERA I and OPERA II studies ¹⁷	-0.51 from PRISMS study ¹⁶ (BFV, years 1–2); -0.50 from CARE-MS I study ¹⁸ (BPF, years 1–2); -0.55 in CARE-MS II study ¹⁹ (BPF, years 1–2); and -0.45 in OPERA I and -0.46 in OPERA II (SIENA, weeks 48–96) ¹⁷	Flu-like symptoms, injection-site reactions, leukopenia, elevated liver enzymes, and depression
Pegylated interferon β -1a	Subcutaneous	28% ²⁰	37% at 2 years ²¹ in ADVANCE study	..	Flu-like symptoms, injection-site reactions, leukopenia, elevated liver enzymes, and depression
Glatiramer acetate	Subcutaneous	29% ²²	..	-0.44 in CONFIRM study (SIENA, weeks 48–96) ²³	Injection-site reactions and immediate systemic reactions after injection
Fingolimod	Oral	54% ²⁴	31% at 2 years from pooled FREEDOMS and FREEDOMS II studies ²⁵	-0.37 in FREEDOMS study ²⁴ (SIENA, years 1–2); and -0.48 in FREEDOMS II study ²⁶ (SIENA, years 1–2)	Cardiac events (bradycardia, atrioventricular block, cardiac arrest, and arrhythmias), herpes infection, macular oedema, elevated liver enzymes, lymphopenia, and rare cases of progressive multifocal leukoencephalopathy
Teriflunomide	Oral	31% ²⁷	23% from TEMSO study ²⁸ post-hoc analysis	-0.51 in TEMSO (SIENA, 48–96 weeks) ²⁷	Teratogenesis, liver dysfunction, reactivation of latent tuberculosis, and hair loss
Dimethyl fumarate	Oral	53% in DEFINE study ²⁹ and 44% in CONFIRM study ³⁰	26% at 2 years from pooled CONFIRM study and DEFINE study data ³¹	-0.60 in DEFINE study ²⁹ (SIENA, month 6–24); -0.39 in CONFIRM study ³⁰ (SIENA, week 48–96)	Gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhoea), flushing, lymphopenia, and rare cases of progressive multifocal leukoencephalopathy
Cladribine	Oral	58% ³²	46% at 2 years in CLARITY study ³³	..	Lymphopenia, herpes zoster, and teratogenesis
Natalizumab	Intravenous	68% ³⁴	37% at 2 years in AFFIRM study ³⁵	-0.24 in AFFIRM study ³⁶ (BPF, years 1–2)	Infusion reactions, progressive multifocal leukoencephalopathy, lymphopenia, and elevated liver enzymes
Alemtuzumab	Intravenous	55% (compared with interferon beta-1a) ¹⁸	39% at 2 years in CARE-MS I study ¹⁸	-0.25 in CARE-MS I study ¹⁸ (BPF, years 1–2); and -0.22 in CARE-MS II study ¹⁹ (BPF, years 1–2)	Infusion reactions, infections, autoimmune thrombocytopenia, autoimmune thyroid disease, and autoimmune kidney disease
Ocrelizumab	Intravenous	47% (compared with interferon beta-1a) ¹⁷	47.7% at 96 weeks ³⁷	-0.34 in OPERA I study ¹⁷ and -0.36 in OPERA II study ¹⁷ (SIENA, weeks 48–96)	Infusion reactions and herpes infections

Efficacy is measured by reduction in annualised relapse rate, whereas effectiveness is shown by rates of NEDA 3 and brain atrophy. NEDA 3=no evidence of disease activity 3. BPF=brain parenchymal fraction. BPV=brain parenchymal volume. JI=jacobian integration. SIENA=structural image evaluation of normalised atrophy. ..=not available.

Table: Efficacy, effectiveness, and safety outcomes from phase 3 trials of approved disease-modifying therapies for relapsing remitting multiple sclerosis

See Online for appendix

considering stopping DMT use. The recommendations related to initial DMT selection from both task forces are detailed in the appendix pp 2–3. The expert guidelines were created following a strict methodology for inclusion of evidence and development of recommendations mainly on the basis of clinical trial data, and thus only partially and imperfectly guide clinical decision-making. Future research will better inform clinical guidelines.

Efficacy and safety of DMTs

All the approved DMTs have been evaluated in phase 3 studies for their efficacy on reduction of the annualised relapse rate (table). Efficacy is here defined as quantification of the effect of a therapy on disease outcomes under ideal circumstances, with investigator defined outcomes—ie, will a treatment work? Effectiveness is here defined as quantification of the effect of therapy on disease outcomes under usual circumstances, with holistic outcomes—ie, when does a treatment work? The DMTs with highest efficacy are the monoclonal antibody therapies: alemtuzumab

(target anti-CD52),^{18,19} natalizumab (target anti- α 4-integrin),³⁶ and ocrelizumab (target humanised anti-CD20).¹⁷ Despite the absence of phase 3 trial data, rituximab (target chimeric anti-CD20) is also widely used as a DMT on the basis of favourable efficacy data observed in a phase 2 study,³⁸ open label observational cohorts,³⁹ and the similarity in mechanism of action of rituximab to ocrelizumab for which there are phase 3 data.¹⁷

The common treatment-related adverse events of multiple sclerosis DMTs are shown in the table. In phase 3 trials of the injectable and oral DMTs, adverse events tended to be mild to moderate, with a few notable exceptions: bradycardia and atrioventricular block with fingolimod,⁴⁰ gastroenteritis with dimethyl fumarate,²⁹ and lymphopenia with cladribine.⁴¹ Infusion reactions are common to all the monoclonal antibodies, occurring with the highest frequency during early infusions but rarely resulting in treatment discontinuation. Autoimmunity is reported to be a delayed adverse event in almost half of those who receive alemtuzumab for multiple sclerosis.⁴²

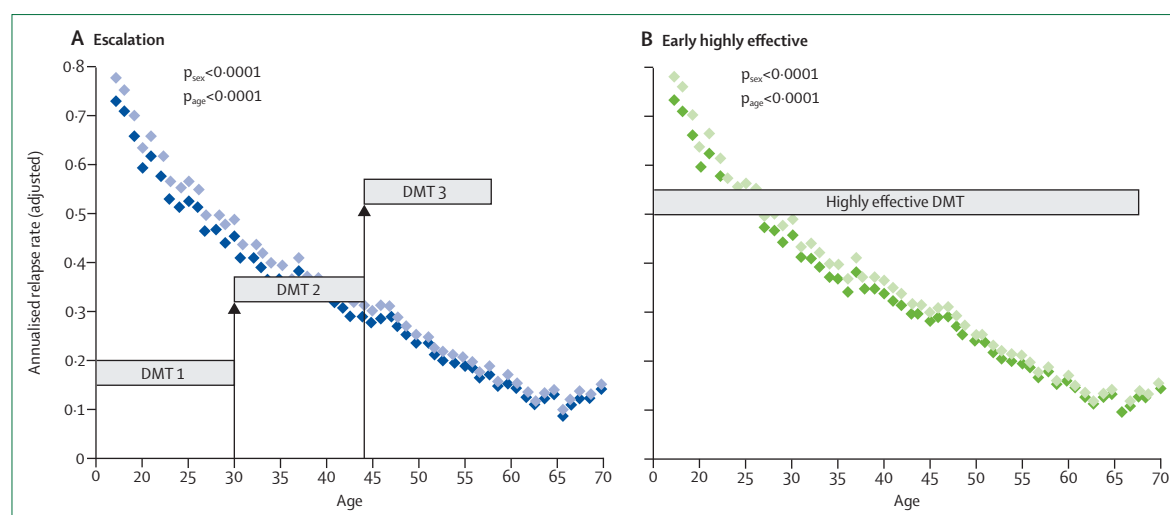


Figure: Relapse incidence and escalation versus early highly effective treatment approaches in patients with relapsing multiple sclerosis
 Incidence of relapses in male and female patients with relapse onset disease course adjusted for chronological age and disease duration based on MSBase registry data (adapted with permission from Kalincik and colleagues)⁴⁷. Superimposed on the incidence of relapses are schematics of escalation approach (multiple bars) and early highly effective approach (single bar). (A) Female incidence is represented as light blue diamonds and male incidence is represented as blue diamonds. (B) Female incidence is represented as light green diamonds and male incidence is represented as green diamonds. DMT=disease-modifying therapy.

Opportunistic and often life-threatening infections, such as herpetic infections, listeria meningitis, and tuberculosis, were reported during trials of several of the DMTs with lymphocyte-depleting effects, often coinciding with higher grades of lymphopenia. Progressive multifocal leukoencephalopathy was identified as a potentially fatal treatment-related adverse event during postmarketing surveillance of natalizumab,⁴³ and has been reported with a much lower incidence in other DMTs.⁴⁴ Blood monitoring programmes are now recommended, including by clinical guidelines^{10,11} for the safe prescription of almost all DMTs, and a risk-stratification programme has been introduced to reduce the incidence of progressive multifocal leukoencephalopathy associated with natalizumab. The long-term risk of newer cell depleting agents is unknown, by contrast with the known favourable safety profile of injectable agents available for over 20 years.^{45,46} Due to the risk of adverse events reported for some of the high-efficacy DMTs (eg, occurrence of progressive multifocal leukoencephalopathy and novel autoimmunity), they are reserved for patients with the most active forms of multiple sclerosis, or in cases of DMT failure. However, some high-efficacy therapies might prove to have relatively benign safety profiles to be confirmed with long term follow up.

Escalation approach

The first-line use of a moderate-efficacy, relatively safe DMT, followed by a period of surveillance, is probably the most common therapeutic approach (figure).⁴⁸ In many patients starting a DMT, the disease will respond to the first medication prescribed, and certain prognostic indicators including sex might help with selection of patients for a given therapy (panel). However, if the

first-line DMT inadequately suppresses disease activity, the most reasonable response would seem to be an escalation in treatment.⁵⁰ Treatment escalation is the provision of an alternative, more effective medication that offers better disease control than the patient's present therapy. Given the known pathological heterogeneity with variable amounts of inflammation associated with multiple sclerosis, escalation is a logical choice to match disease activity and treatment effects.⁵¹ The concept of treating to target implies treatment changes when individuals are not meeting certain measures, predicting poor outcome. Common target measures include relapses, and new brain or spinal cord lesions, but are evolving to include brain atrophy, cognition, and biomarkers such as neurofilament levels (panel).^{52,53} No universal accepted method for application of these outcome measures exists, but evidence shows that with presence of breakthrough disease (ie, new lesions or relapses) a switch in DMT reduces disease activity.⁵⁴ Data also show that even switches between injectable therapies might result in improved disease control and stability as measured with the Expanded Disability Status Scale.⁵⁵ Clinicians, however, are typically motivated to switch to a more effective therapy rather than just a therapy with a different mechanism of action on the basis of data showing better outcomes when switching to more potent therapies.^{56,57}

An important controversy in treatment of multiple sclerosis is focused on how strictly to target disease control.⁵⁸ In the past 5–10 years, with the availability of newer and more effective agents, the definition of treatment failure, and hence the threshold for escalation, has been lowered. The decision regarding how to escalate might be influenced by multiple factors including access to specialists with expertise in new multiple sclerosis medications,

Panel: Prognostic markers and treatment outcome measures

Prognostic markers before treatment initiation⁴⁹

Clinical measures

- Male sex
- Older age (symptom onset after age 50 years)
- Severity and frequency of relapse
- Rapid accrual of disability
- Relapse type (motor or brainstem vs sensory)

MRI measures

- T2 lesion burden
- Gadolinium enhancing lesion
- Visible brain atrophy (subjective)
- Presence of persistent T1 hypointense lesions
- Spinal cord or infratentorial lesions

Proposed treatment outcome measures

Clinical

- Relapses
- Disability accrual
- Cognitive screening

MRI

- New T2 lesions in the brain or spinal cord
- New gadolinium enhancing lesions in the brain or spinal cord
- Brain volume loss

Biomarker

- Neurofilament levels in CSF
- Neurofilament levels in blood

attitudes of patients and doctors to risk, availability of therapies and disease monitoring, and local regulatory requirements and guidelines.

Most neurologists consider relapses as a clear indication of treatment failure, and frequently the occurrence of a relapse on moderate-efficacy DMT would lead to an escalation in treatment.⁴⁸ However, a study⁵⁹ suggests that relapses are frequently unreported, or prove challenging to diagnose. MRI of the brain looking for subclinical disease activity, as assessed by new T2 or contrast enhancing lesions, is commonly used to monitor effectiveness. Monitoring for new asymptomatic spinal cord lesions, cortical lesions, and brain atrophy have been proposed⁵² but are not validated. The Rio score (original and modified) is one method to assess DMT response.^{60,61} The score was developed on the basis of the observation that development of new lesions while on β -interferon treatment predicts a high risk of future relapse and disability progression. Brain atrophy, although useful in clinical trials, has not been validated as an individualised prognostic indicator in clinical practice.⁶² Other clinical–radiological composite scores include a strict target of no evidence of disease activity (ie, absence of new lesions, relapses, and disability progression).⁶³ Adding other

components such as patient-reported outcomes or cognitive scores to complement the relapses and MRI indices during monitoring of DMT success has been also suggested, but are not completely validated.⁵² A key feature of monitoring instruments is their responsiveness to minor or subclinical activity that heralds imminent preventable reactivation of the disease, to enable escalation to occur before the accrual of further disability. Risks are also associated with potential undertreatment of multiple sclerosis with low-efficacy therapies, including risk of accumulated disability and future progression.⁵ Most patients who escalate their DMT have already experienced a sustained accumulation of disability while receiving moderate-efficacy therapy.⁶⁴ This finding might provide an argument for placing heightened emphasis on subclinical markers of disease activity in escalation algorithms.

Early, highly effective treatment

The term early, highly effective therapy is subject to interpretation, and can be intuitively understood as commencement of high-efficacy therapy shortly after fulfilling diagnostic criteria of multiple sclerosis (figure).^{65–67} From the treatment sequencing perspective, the use of high-efficacy therapies in patients who are treatment naïve can be considered to represent an intensive treatment strategy, especially in countries in which an escalation approach to therapy is mandated. Alternatively, a biologically driven definition of early treatment can be based on patient age or low level of neurological disability. From a pathological perspective, treating early and effectively might prevent epitope spreading and intervening during a crucial early treatment window which might be at least partly related to younger age (<40 years).⁶⁸

Even though no randomised controlled trials have directly compared the effects of early and delayed high-efficacy therapies, subgroup analyses of the pivotal trials (12 studies, $n=12\,317$) have partly clarified the question of treatment timing.⁶⁹ The effect of fingolimod, cladribine, alemtuzumab, and natalizumab on relapse frequency or disability outcomes, or both, was relatively more pronounced in younger patients (with the cutoff of 31 or 40 years) than in older patients.^{33,65,70,71} Furthermore, patients treated earlier after disease onset had a greater benefit from fingolimod, cladribine, and alemtuzumab with regards to relapse or disability outcomes, or both, than did those treated later.^{65,71} A greater reduction in relapse rate by natalizumab⁷¹ and of disability worsening by alemtuzumab⁶⁵ was reported among patients with lower Expanded Disability Status Scale scores (<2 for natalizumab and ≤ 3.5 for alemtuzumab). A relatively greater relapse rate effect was reported with fingolimod when patients had no previous exposure to DMTs than in those who switched to fingolimod from other therapies.⁷³ However, subgroup and post-hoc analysis should be interpreted with caution given multiplicity problems and small sample sizes.⁷⁴

Observational data not only complement the results of clinical trials, but also enable direct comparisons of treatment effectiveness in different clinical scenarios, conditional on sufficient control of confounding, in particular of indication bias.⁷⁵ In the natalizumab observational programme, patients with lower disability or those who were treatment-naïve when starting natalizumab had the lowest rates of on-treatment relapses.⁷⁶ Those who started natalizumab earlier after disease onset had less on-treatment relapses than did those patients starting later.^{66,67} An international observational study⁷⁷ from MSBase (a comprehensive international registry of multiple sclerosis patients) showed a significantly greater effect of high-efficacy DMTs (n=430 patients) on relapses when commenced earlier after diagnosis (≤ 1 year vs > 4 years) and at younger age (< 38 years) than with low-efficacy DMT (n=1295 patients). A higher probability of disability improvement was also reported in patients with lower disability (Expanded Disability Status Scale ≤ 3.5) than in those with higher disability (> 3.5).⁷⁷ The potential of high-efficacy therapies to delay secondary progression of disability was greater when these were commenced within 5 years from first multiple sclerosis presentation.⁷⁸

Although the evidence supporting early introduction of high-efficacy DMTs is still scarce, the results of subgroup analyses from trials and observational studies converge. Early introduction of potent DMTs seems to improve the control of relapse activity and delay accumulation of disability more efficiently. However, high-efficacy therapies are also associated with higher risks. Therefore, in a variable disease with variable individual treatment response,⁷⁹ learning to identify patients in whom the benefit from aggressive therapeutic approaches outweighs the associated risks is imperative.⁸⁰

Designing trials to compare escalation and early highly effective approaches

A substantial unmet need exists for evidence that informs selection in initial DMT in patients with relapsing-remitting multiple sclerosis. Treatment decisions should be informed by robust, preferably randomised clinical trial data. Whether the short-term effects of individual DMTs reported during phase 3 studies correlate with clinically meaningful and long-term outcomes is unclear. Long-term observational studies are useful, but are often limited by factors including attrition bias, ascertainment bias due to less stringent methods of measuring outcomes than clinical trials, and the heterogeneity in DMT schedules that emerge over time obscuring the relationship between any single DMT and clinical outcome.⁸¹ Comparison of individual DMTs in clinical trials would be inherently difficult because of several factors. The randomisation of patients to receive a low-efficacy or high-efficacy therapy for several years will become increasingly ethically challenging, and even subclinical disease activity might become a reason to seek consent for continued participation and therefore potentially study withdrawal. Pairwise

comparisons are also expensive given the large sample sizes required, and results would apply only to specific medications, informing practice in a narrow fashion with knowledge that is not applicable to new therapies entering the market. An alternative is to design clinical trials that compare the overall treatment approach rather than specific medications. In this type of design, patients could be randomised either to escalation or an early high-efficacy treatment approach. Individual selection of medication can then be decided clinically within each randomised group by the patient and their clinical care team. The advantage of this design includes the ability to compare the treatment approach while still allowing selection of specific medications based on individual patient characteristics. Treatment can still be tailored in relation to safety and efficacy considerations. The opportunity to freely switch therapy during the study might favour recruitment and retention of participants, in turn producing results that are applicable to a wider population. This pragmatic design, which focuses on the comparison of treatment approaches rather than individual medications, could yield results that guide the overall treatment philosophy, making results applicable not only to currently available therapies but also to new therapies.

Two large randomised clinical trials, funded by the Patient Centered Outcomes Research Institute in 2017, examine early, highly effective and escalation approaches in patients with multiple sclerosis (appendix p 3). Determining the Effectiveness of early Intensive Versus Escalation approaches for the Treatment of Relapsing-remitting Multiple Sclerosis (DELIVER-MS, NCT03535298) is an international, pragmatic randomised clinical trial with an additional observational cohort, which will recruit 800 patients with early relapsing-remitting multiple sclerosis from 24 sites in the USA and the UK (DO and NE are co-principal investigators and ET and SMP are co-investigators). The study will follow up patients for 36 months with an intermediate primary outcome of brain volume loss from baseline to 36 months. Brain volume loss was selected as the primary outcome as the best available short-term measure to predict long-term disability.⁸² A proportion of individuals will likely not opt for randomisation, which represents a threat to generalisability. Rather than losing the information on these patients, they will be followed up in an observational study that parallels the randomised controlled study in all aspects. Traditional Versus Early Aggressive Therapy for Multiple Sclerosis Trial (TREAT-MS, NCT03500328) is a randomised controlled trial jointly and independently evaluating among patients with higher and lower risk of disability accumulation whether a traditional (ie, escalation approach) or early aggressive (ie, high-efficacy) therapy approach influences intermediate-term risk of disability. The study will recruit 900 patients with relapsing-remitting multiple sclerosis across over 40 centres in the USA, and will also compare disability risk between individuals who switch from a first-line medication to a high-efficacy medication

Search strategy and selection criteria

This Personal View is based on the cumulative literature archives of the authors. Additionally, we searched PubMed for human studies published in English from Jan 1, 2006, until Feb 18, 2018, with the search terms “multiple sclerosis”, “treatment approach”, “relapsing-remitting”, “guidelines”, “early treatment”, “highly effective”, “escalation”, “induction”, “observational”, “clinical trial”, and “design”. Papers were reviewed and selected by authors on the basis of effect and overall scientific quality.

versus those who switch to another first-line therapy. The short-term nature of these studies is a clear limitation, and long-term extension to 5 years and 10 years will be needed. The studies have been harmonised and results will be pooled between both studies. Both studies also have robust engagement plans with involvement of a wide group of stakeholders.

Conclusions and future directions

Treatment of multiple sclerosis has advanced enormously over the past 20 years with a real effect on the lives of patients with multiple sclerosis.⁸³ The field of multiple sclerosis is privileged with many effective therapeutic options that reduce relapses and delay the development of disability related to multiple sclerosis.⁸⁴ However, the optimal treatment strategy for use in patients with early multiple sclerosis is still under debate and current practice varies enormously.⁸⁵ Well powered randomised controlled trials are needed to compare treatment approaches in a pragmatic fashion. Observational data leveraging clinical data registries will be an invaluable adjunct to answer treatment approach questions, especially in groups of patients for whom randomisation is not feasible. Clinicians should be open in discussions with patients on what is known and where gaps exist about multiple sclerosis treatment approaches. Comparative effectiveness studies in relapsing multiple sclerosis are feasible and will help to inform how patients start their treatment journey, and should be a priority. Results of DELIVER-MS and TREAT-MS will help to shape treatment approaches. Future work should be directed at further refining a personalised approach to DMT decision-making.

Contributors

DO, ET, TK, SMP, and NE collected references, reviewed data, and drafted and edited the manuscript. DO finalised the manuscript.

Declaration of interests

DO reports grants from the US National Institute of Health, the National Multiple Sclerosis Society, the Patient-Centered Outcomes Research Institute, and the Race to Erase Foundation, and grants and personal fees from Genzyme, Genentech, Roche, and Novartis, and personal fees from Merck, outside the submitted work. ET reports personal fees, non-financial support, and travel compensation from Merck, grants and non-financial support from Biogen Idec, and non-financial support from Novartis, outside the submitted work. TK reports grants, personal fees, and non-financial support from Biogen, personal fees and non-financial support from Genzyme-Sanofi, Merck, and Novartis; and personal fees

from Roche, WebMD Global, Teva, and BioCSL, outside the submitted work. SMP reports research support from the Guthy Jackson Charitable Foundation. NE reports personal fees and non-financial support from Biogen; and personal fees from Roche, Genzyme-Sanofi, Merck, and Novartis, outside the submitted work. DO and NE are the co-principal investigators of DELIVER-MS and ET and SMP are co-investigators of the DELIVER-MS study.

Acknowledgments

We thank Amanda Mendelsohn and Mary Reagan for assistance with the figure.

References

- Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: a population-based estimate using health claims data. *Neurology* 2019; **92**: e1029–40.
- GBD 2016 Multiple Sclerosis Collaborators. Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; **18**: 269–85.
- Cofield SS, Thomas N, Tyry T, Fox RJ, Salter A. Shared decision making and autonomy among US participants with multiple sclerosis in the NARCOMS registry. *Int J MS Care* 2017; **19**: 303–12.
- Tintoré M, Alexander M, Costello K, et al. The state of multiple sclerosis: current insight into the patient/health care provider relationship, treatment challenges, and satisfaction. *Patient Prefer Adherence* 2017; **11**: 33–45.
- Cerqueira JJ, Compston DAS, Gherdes R, et al. Time matters in multiple sclerosis: can early treatment and long-term follow-up ensure everyone benefits from the latest advances in multiple sclerosis? *J Neurol Neurosurg Psychiatry* 2018; **89**: 844–50.
- Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; **17**: 162–73.
- Zhang Y, Salter A, Cutter G, Stüve O. Clinical trials in multiple sclerosis: milestones. *Ther Adv Neurol Disord* 2018; **11**: 1756286418785499.
- Armoiry X, Kan A, Melendez-Torres GJ, et al. Short- and long-term clinical outcomes of use of beta-interferon or glatiramer acetate for people with clinically isolated syndrome: a systematic review of randomised controlled trials and network meta-analysis. *J Neurol* 2018; **265**: 999–1009.
- Okuda DT. Radiologically isolated syndrome should be treated with disease-modifying therapy—yes. *Mult Scler J* 2017; **23**: 1818–19.
- Montalban X, Gold R, Thompson AJ, et al.ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler J* 2018; **24**: 96–120.
- Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. *Neurology* 2018; **90**: 777–88.
- Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol* 1996; **39**: 285–94.
- Kappos L, Havrdova E, Giovannoni G, et al. No evidence of disease activity in patients receiving daclizumab versus intramuscular interferon beta-1a for relapsing-remitting multiple sclerosis in the DECIDE study. *Mult Scler* 2017; **23**: 1736–47.
- Vollmer TL, Sorensen PS, Selmaj K, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. *J Neurol* 2014; **261**: 773–83.
- Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. *Neurology* 1993; **43**: 655–61.
- Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet* 1998; **352**: 1498–504.
- Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017; **376**: 221–34.
- Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012; **380**: 1819–28.

- 19 Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012; **380**: 1829–39.
- 20 Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *Lancet Neurol* 2014; **13**: 657–65.
- 21 Arnold DL, Calabresi PA, Kieseier BC, et al. 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* 2014; **14**: 240.
- 22 Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. *Neurology* 1995; **45**: 1268–76.
- 23 Miller D, Fox R, Phillips JT, et al. Effects of BG-12 on magnetic resonance imaging (MRI) endpoints in patients with relapsing-remitting multiple sclerosis (RRMS): data from the phase 3 CONFIRM study (S11.001). *Neurology* 2012; **78**: S11.001.
- 24 Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; **362**: 387–401.
- 25 Kappos L, De Stefano N, Freedman MS, et al. Inclusion of brain volume loss in a revised measure of 'no evidence of disease activity' (NEDA-4) in relapsing-remitting multiple sclerosis. *Mult Scler* 2015; published online Nov 19. DOI:10.1352458515616701.
- 26 Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; **13**: 545–56.
- 27 O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011; **365**: 1293–303.
- 28 Freedman M, O'Connor P, Wolinsky J, et al. Teriflunomide Increases the proportion of patients free from disease activity in the TEMSO phase III study (PD5.007). *Neurology* 2012; **78**: PD5.007.
- 29 Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012; **367**: 1098–107.
- 30 Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012; **367**: 1087–97.
- 31 Havrdova E, Giovannoni G, Gold R, et al. Effect of delayed-release dimethyl fumarate on no evidence of disease activity in relapsing-remitting multiple sclerosis: integrated analysis of the phase III DEFINE and CONFIRM studies. *Eur J Neurol* 2017; **24**: 726–33.
- 32 Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010; **362**: 416–26.
- 33 Giovannoni G, Cook S, Rammohan K, et al. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. *Lancet Neurol* 2011; **10**: 329–37.
- 34 Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; **354**: 899–910.
- 35 Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Recurring Multiple Sclerosis (AFFIRM) study. *Lancet Neurol* 2009; **8**: 254–60.
- 36 Miller DH, Soon D, Fernando KT, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. *Neurology* 2007; **68**: 1390–401.
- 37 Havrdová E, Arnold DL, Bar-Or A, et al. No evidence of disease activity (NEDA) analysis by epochs in patients with relapsing multiple sclerosis treated with ocrelizumab vs interferon beta-1a. *Mult Scler J - Exp Transl Clin* 2018; **4**: 2055217318760642.
- 38 Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008; **358**: 676–88.
- 39 Salzer J, Svenningsson R, Alping P, et al. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. *Neurology* 2016; **87**: 2074–81.
- 40 Calabresi PA, Radue E-W, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; **13**: 545–56.
- 41 Leist TP, Comi G, Cree BAC, et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. *Lancet Neurol* 2014; **13**: 257–67.
- 42 Tuohy O, Costelloe L, Hill-Cawthorne G, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. *J Neurol Neurosurg Psychiatry* 2015; **86**: 208–15.
- 43 Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol* 2010; **9**: 438–46.
- 44 Oshima Y, Tanimoto T, Yuji K, Tojo A. Drug-associated progressive multifocal leukoencephalopathy in multiple sclerosis patients. *Mult Scler J* 2018; **25**: 1141–49.
- 45 Ziemssen T, Ashtamker N, Rubinchick S, Knappertz V, Comi G. Long-term safety and tolerability of glatiramer acetate 20 mg in the treatment of relapsing forms of multiple sclerosis. *Expert Opin Drug Saf* 2016; **16**: 247–55.
- 46 de Jong HJ, Kingwell E, Shirani A, et al. Evaluating the safety of β -interferons in MS: a series of nested case-control studies. *Neurology* 2017; **88**: 2310–20.
- 47 Kalincik T, Vivek V, Jokubaitis V, et al. Sex as a determinant of relapse incidence and progressive course of multiple sclerosis. *Brain* 2013; **136**: 3609–17.
- 48 Fernández O, Delvecchio M, Edan G, et al. Survey of diagnostic and treatment practices for multiple sclerosis in Europe. *Eur J Neurol* 2017; **24**: 516–22.
- 49 Rush CA, MacLean HJ, Freedman MS. Aggressive multiple sclerosis: proposed definition and treatment algorithm. *Nat Rev Neurol* 2015; **11**: 379–89.
- 50 Grand'Maison F, Yeung M, Morrow SA, et al. Sequencing of disease-modifying therapies for relapsing-remitting multiple sclerosis: a theoretical approach to optimizing treatment. *Curr Med Res Opin* 2018; **34**: 1419–30.
- 51 Metz I, Weigand SD, Popescu BFG, et al. Pathologic heterogeneity persists in early active multiple sclerosis lesions. *Ann Neurol* 2014; **75**: 728–38.
- 52 Giovannoni G, Turner B, Gnanapavan S, Offiah C, Schmierer K, Marta M. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? *Mult Scler Relat Disord* 2015; **4**: 329–33.
- 53 Barro C, Benkert P, Disanto G, et al. Serum neurofilament as a predictor of disease worsening and brain and spinal cord atrophy in multiple sclerosis. *Brain* 2018; **141**: 2382–91.
- 54 Kalincik T, Horakova D, Spelman T, et al. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. *Ann Neurol* 2015; **77**: 425–35.
- 55 Carrá A, Onaha P, Luetic G, et al. Therapeutic outcome 3 years after switching of immunomodulatory therapies in patients with relapsing-remitting multiple sclerosis in Argentina. *Eur J Neurol* 2008; **15**: 386–93.
- 56 Lorscheider J, Benkert P, Lienert C, et al. Comparative analysis of natalizumab versus fingolimod as second-line treatment in relapsing-remitting multiple sclerosis. *Mult Scler J* 2018; **24**: 777–85.
- 57 Chalmer TA, Kalincik T, Laursen B, Sorensen PS, Magyari M, Members of Danish Multiple Sclerosis Group. Treatment escalation leads to fewer relapses compared with switching to another moderately effective therapy. *J Neurol* 2018; published online Dec 4. DOI:10.1007/s00415-018-9126-y.
- 58 Williams OH, Harding KE, Willis M, Pickersgill T, Wardle M, Robertson NP. Disease modifying treatments in MS: induction or escalation? *J Neurol Neurosurg Psychiatry* 2015; **86**: e4.
- 59 Tallantyre EC, Causon EG, Harding KE, Pickersgill TP, Robertson NP. The aetiology of acute neurological decline in multiple sclerosis: experience from an open-access clinic. *Mult Scler* 2015; **21**: 67–75.
- 60 Rio J, Castillo J, Rovira A, et al. Measures in the first year of therapy predict the response to interferon beta in MS. *Mult Scler* 2009; **15**: 848–53.

- 61 Sormani MP, Rio J, Tintore M, et al. Scoring treatment response in patients with relapsing multiple sclerosis. *Mult Scler* 2013; **19**: 605–12.
- 62 Barkhof F. Brain atrophy measurements should be used to guide therapy monitoring in MS—NO. *Mult Scler J* 2016; **22**: 1524–26.
- 63 Giovannoni G, Bermel R, Phillips T, Rudick R. A brief history of NEDA. *Mult Scler Relat Disord* 2018; **20**: 228–30.
- 64 Harding K, Williams O, Willis M, et al. Clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with multiple sclerosis. *JAMA Neurol* 2019; published online Feb 18. DOI:10.1001/jamaneurol.2018.4905.
- 65 Coles AJ, Fox E, Vladic A, et al. Alemtuzumab versus interferon β -1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. *Lancet Neurol* 2011; **10**: 338–48.
- 66 Putzki N, Yaldizli O, Bühler R, Schwegler G, Curtius D, Tettenborn B. Natalizumab reduces clinical and MRI activity in multiple sclerosis patients with high disease activity: results from a multicenter study in Switzerland. *Eur Neurol* 2010; **63**: 101–06.
- 67 Putzki N, Yaldizli O, Maurer M, et al. Efficacy of natalizumab in second line therapy of relapsing-remitting multiple sclerosis: results from a multi-center study in German speaking countries. *Eur J Neurol* 2010; **17**: 31–37.
- 68 Ruggieri S, Pontecorvo S, Tortorella C, Gasperini C. Induction treatment strategy in multiple sclerosis: a review of past experiences and future perspectives. *Mult Scler Demyelinating Disord* 2018; **3**: 5.
- 69 Merkel B, Butzkueven H, Traboulsee AL, Havrdova E, Kalincik T. Timing of high-efficacy therapy in relapsing-remitting multiple sclerosis: A systematic review. *Autoimmun Rev* 2017; **16**: 658–65.
- 70 Miller DH, Soon D, Fernando KT, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. *Neurology* 2007; **68**: 1390–401.
- 71 Hutchinson M, Kappos L, Calabresi PA, et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *J Neurol* 2009; **256**: 405–15.
- 72 Agius M, Meng X, Chin P, Grinspan A, Hashmonay R. Fingolimod therapy in early multiple sclerosis: an efficacy analysis of the TRANSFORMS and FREEDOMS studies by time since first symptom. *CNS Neurosci Ther* 2014; **20**: 446–51.
- 73 Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; **362**: 402–15.
- 74 Tanniou J, van der Tweel I, Teerenstra S, Roes KCB. Subgroup analyses in confirmatory clinical trials: time to be specific about their purposes. *BMC Med Res Methodol* 2016; **16**: 20.
- 75 Kalincik T, Butzkueven H. Observational data: Understanding the real MS world. *Mult Scler J* 2016; **22**: 1642–48.
- 76 Butzkueven H, Kappos L, Pellegrini F, et al. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results. *J Neurol Neurosurg Psychiatry* 2014; **85**: 1190–97.
- 77 Kalincik T. Timing of high-efficacy disease modifying therapies for relapsing-remitting multiple sclerosis. Oct 27, 2017. <https://onlinelibrary.ectrims-congress.eu/ectrims/2017/ACTRIMS-ECTRIMS2017/202594/tomas.kalincik.timing.of.high-efficacy.disease.modifying.therapies.for.html?f=media=3> (accessed Sept 7, 2018).
- 78 Brown JWL, Coles AJ, Horakova D, et al. Association of initial disease-modifying therapy with conversion to secondary progressive multiple sclerosis among patients with relapsing-remitting multiple sclerosis. *JAMA* 2019; **321**: 175–187.
- 79 Kalincik T, Manouchehrinia A, Sobisek L, et al. Towards personalized therapy for multiple sclerosis: prediction of individual treatment response. *Brain* 2017; **140**: 2426–43.
- 80 Sormani MP, De Stefano N. Defining and scoring response to IFN- β in multiple sclerosis. *Nat Rev Neurol* 2013; **9**: 504–12.
- 81 Freedman MS. Long-term follow-up of clinical trials of multiple sclerosis therapies. *Neurology* 2011; **76**: S26–34.
- 82 Popescu V, Agosta F, Hulst HE, et al. Brain atrophy and lesion load predict long term disability in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2013; **84**: 1082–91.
- 83 University of California, San Francisco MS-EPIC Team: U of, Cree BAC, Gourraud P-A, et al. Long-term evolution of multiple sclerosis disability in the treatment era. *Ann Neurol* 2016; **80**: 499–510.
- 84 Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. *Lancet* 2018; **391**: 1622–36.
- 85 Marziniak M, Ghorab K, Kozubski W, et al. Variations in multiple sclerosis practice within Europe—is it time for a new treatment guideline? *Mult Scler Relat Disord* 2016; **8**: 35–44.

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