

Commentary on theECTRIMS–EAN guideline for pharmacological treatment of multiple sclerosis

Alan J. Thompson

Over the past 35 years, multiple sclerosis (MS) has moved from an untreatable neurological condition to one with a rich and complex armamentarium, at least for the relapsing–remitting form of the condition. This transformational change is unlike anything seen in other neurological conditions.¹ The available treatments address a range of mechanisms (though some remain non-specific), and vary in efficacy, route of administration and side-effect profile. The approach and access to treatment also vary considerably though there is a growing consensus in support of early intervention,² which is facilitated by increasingly accessible and accurate diagnostic criteria.³ Terms such as first-line and second-line treatments, escalation protocols and ‘induction and maintenance’ therapy are frequently used with the ultimate goal of treatment being ‘no evidence of disease activity’ (NEDA).⁴ While the current range of treatments has allowed the concept of personalized medicine to be entertained,⁵ it can result in major challenges for decision-making for clinician and patient alike. A common understanding of what the evidence from clinical trials is telling us is a critical basis for supporting this decision-making.

The recent guidance produced by the European Committee for Treatment and Research in MS (ECTRIMS) and the European Academy of Neurology (EAN) is the first attempt to provide a resource which can support decision-making around the use of so-called disease-modifying treatments (DMTs) in MS.^{6,7} This European guideline is based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group.⁸ The guideline, which aims to be a useful adjunct to clinical practice, addresses 10 specific clinical questions, three regarding treatment interventions and the remainder addressing issues relating to clinical

management. It encompasses treatment efficacy, response criteria, strategies to address suboptimal response, as well as escalation, safety concerns and treatment strategies in pregnancy. The 27 authors hail from 12 European countries which espouse a variety of approaches to licensing and prescribing of agents.

It is clear from the outset that this is a pragmatic effort to support the MS clinician and the patient in their decision-making but does not and cannot replace clinical judgement. It is also evident that the patient is placed at the very heart of any decision-making and this is emphasized throughout the guideline. Altogether, the guideline makes 23 recommendations of varying strength. It is perhaps surprising that only 3 of the recommendations are regarded as strong, while, of the remainder, 9 are weak and a further 9 are based on consensus statements. This gives some indication of the level of evidence available, rarely as robust as would be hoped for.

One of the strengths of the 10 questions posed is that they are directly related situations faced by the clinician in clinical practice rather than an academic exercise unrelated to the real world. A good example is the question concerning clinically isolated syndrome (CIS): ‘*In patients with CIS what is the benefit for starting treatment with a disease-modifying drug compared with no treatment?*’. In this particular instance the single recommendation supporting treatment was based on strong evidence and that is when the guideline is at its best. Regrettably, this is only possible in a minority of recommendations. When discussing progressive MS, the situation is more challenging, all four recommendations to consider a particular agent are based on weak evidence and even within those four some are weaker than others,

Ther Adv Neurol Disord

2018, Vol. 11: 1–2

DOI: 10.1177/
1756286418770378

© The Author(s), 2018.

Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

for example the suggestion that cladribine may be considered in secondary progressive MS has very little evidence to support it.

For the more complex question ‘*In patients with relapsing MS treated with interferon or glatiramer acetate and evidence of disease activity, what is the benefit of switching between interferons and glatiramer acetate versus moving to more efficacious drugs?*’ there is a strong recommendation to do the latter, associated with a consensus statement describing the factors that need to be considered when escalating treatment. This raises another issue which is not discussed in the paper, the use of the term efficacious and how the different levels of efficacy should be defined. This approach also presupposes an escalation philosophy rather than the ‘induction and maintenance’ approach favoured by many clinicians.

As the evidence base reduces, only weak recommendations are possible and there is a greater reliance on consensus statements. This is very much the case in relation to MS treatments during pregnancy where the complexity of protecting the foetus while managing the mother’s condition can result in difficult decision-making, not least given the paucity of rigorous data available.⁹

Overall, this guideline will hopefully be seen as a good start but, as is so often the case, it serves to emphasize the paucity of robust evidence available to us to support our decision-making. There will be other guidelines and a practice guideline from the American Academy of Neurology on the efficacy and safety of DMTs in MS will be published shortly. Inevitably there will be some differences, but hopefully the basic tenets will be the same. Finally, we should remember that neither will even begin to approach the global issue of limited and poor access both across the globe and within individual countries.¹⁰

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

In the past year, Alan Thompson has received honoraria/support for travel for consultancy from Eisai, Biogen (Optum Insight), Hoffman La Roche, and

Excemed. He received support for travel from the International Progressive MS Alliance, as Chair of their Scientific Steering Committee and the National MS Society (USA) as member of their Research Programs Advisory Committee. He receives an honorarium from SAGE Publishers as Editor-in-Chief of *Multiple Sclerosis Journal*, and a free subscription from Elsevier as a board member for the *Lancet Neurology*.

References

1. Thompson AJ, Baranzini SE, Geurts J, *et al.* Multiple sclerosis. *Lancet* 2018. In press.
2. Giovannoni G, Butzkueven H, Dhib-Jalbut S, *et al.* Brain health: time matters in multiple sclerosis. *Mult Scler Relat Disord* 2016; 9(Suppl. 1): S5–S48.
3. Thompson AJ, Banwell BL, Barkhof F, *et al.* Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162–173.
4. Miller AE. Multiple sclerosis should be treated using a step-down strategy rather than a step-up strategy-commentary. *Mult Scl* 2016; 22: 1402–1404.
5. Gafson A, Craner MJ and Matthews PM. Personalised medicine for multiple sclerosis care. *Mult Scler* 2017; 23: 362–369.
6. Montalban X, Gold R, Thompson AJ, *et al.*ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler* 2018; 24: 96–120.
7. Montalban X, Gold R, Thompson AJ, *et al.*ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis *Eur J Neurol* 2018; 25: 215–237.
8. Guyatt GH, Oxman AD, Vist G, *et al.* GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* 2011; 64: 407–415.
9. Marrie RA. Maternal and fetal risks of natalizumab exposure in utero: a fine balance. *Neurology* 2018; 90: 443–444.
10. Browne P, Chandraratna D, Angood C, *et al.* Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. *Neurology* 2014; 83: 1022–1024.