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REVIEW

Is it time to target no evident disease activity (NEDA) in multiple sclerosis?

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Abstract
The management of multiple sclerosis is becoming increasingly complex with the emergence of new and more effective disease-modifying therapies (DMT). We propose a new treatment paradigm that individualises treatment based on a choice between two interchangeable therapeutic strategies of maintenance-escalation or induction therapy. We propose treating-to-target of no evident disease activity (NEDA) as defined using clinical and MRI criteria. This algorithm requires active monitoring with a rebaselining MRI, at a point in time after the specific DMT concerned has had sufficient time to work, and at least annual MRI studies to monitor for subclinical relapses. Disease activity on the maintenance-escalation therapy arm of the algorithm indicates a sub-optimal treatment response and should trigger a discussion about switching, or escalating, therapy or the consideration of switching to the induction therapy arm of the algorithm. In comparison, disease activity on an induction therapy arm would be an indication for retreatment or a switch to the maintenance-escalation therapy arm. We envisage the definition of NEDA evolving with time as new technological innovations are adopted into clinical practice, for example the normalisation of whole, or regional, brain atrophy rates and cerebrospinal fluid neurofilament levels

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Contents

The availability of new and more effective disease modifying therapies (DMTs) for treating relapsing forms of multiple sclerosis (MS) is challenging the old paradigm of simply reducing relapse rates and the consequences of relapses. Data has emerged which shows that both relapses and ongoing focal inflammatory activity on MRI (new or enlarging T2-lesions and gadolinium (Gd)-enhancing lesions) are associated with a worse short to intermediate-term prognosis, contradicting oft-quoted natural history studies (Dobson et al., 2014; Bermel et al., 2010). Moreover, why the prognosis of relapses and subclinical MRI activity on DMTs differs from that seen on placebo-treatment, or in natural history studies of MS, fundamentally questions the role of focal inflammatory lesions in the pathogenesis of relapsing MS (Bermel et al., 2010). As a result of these observations MSologists are redefining their primary aim of treatment as now being **"no evident disease activity"** (NEDA) (Banwell et al., 2013). At present, NEDA is a composite of three related measures of disease activity: (i) no relapses; (ii) no disability progression and (iii) no MRI activity (new or enlarging T2 lesions or Gd-enhancing lesions, which in our view represent "subclinical relapses") (Giovannoni et al., 2011; Havrdova et al., 2009) and is derived from the post-hoc analyses of contemporary phase 3 clinical trials, for example natalizumab and cladribine (Giovannoni et al., 2011; Havrdova et al., 2009).

NEDA is an important goal for treating individual patients with relapsing disease, and potentially as an outcome in future clinical trials (Hartung and Aktas, 2011). The problem with the latter is that until MRI activity is accepted as a surrogate marker of CNS inflammatory activity by regulators, NEDA is unlikely to be used as a primary outcome in clinical trials. However, what about using NEDA as a treatment goal in clinical practice? Before you can adopt NEDA in day-to-day clinical practice you need to decide when to "rebaseline" treated patients and how frequently MRI studies need to be performed as most DMTs take several weeks or months to have an appreciable effect. We therefore suggest that patients starting on DMT have a new baseline MRI after the onset of action of the DMT. The timing of the baseline MRI should be based on the pharmacodynamics of the DMT concerned; it simply needs to occur after a period of time when we are confident that the drug has had a sufficient period of time to start working. Therefore any disease activity destined to happen in the weeks or months after starting a therapy, before the DMT is effective, should not counted as disease activity that is unresponsive to treatment. For example, with natalizumab therapy the proportion of patients with NEDA increases from 51% in year one to 70% in year two when the trial participants were rebaselined at 12 months (Havrdova et al., 2009). For interferon-beta, teriflunomide, dimethyl fumarate and natalizumab we would recommend rebaselining at 3–6 months, for glatiramer acetate 9–12 months, and for alemtuzumab approximately 12 months after the last course of infusions, or 24 months after the initial start of treatment. Please note the disparity in time for glatiramer acetate and alemtuzumab. Serial MRI studies have indicated that glatiramer acetate reaches its peak level of activity on MRI after 7 months hence the recommendation to rebaseline beyond this time point (Comi et al., 2001). The rules for induction therapy are different to that of escalation. In the case of an induction agent such as alemtuzumab, which is given as a course of five consecutive days infusions in year 1 and three consecutive days infusions in year 2, breakthrough disease activity is used as an indicator to retreat rather than to switch therapy; therefore there is little point in doing a rebaselining MRI until after the second course of therapy has had a chance to work and is close enough to the time when a third, or subsequent course, can be given if deemed necessary (Coles et al., 2012b). The question of how many annual cycles need to be given before considering that a person has failed alemtuzumab, or another induction, therapy is open to argument. In the 7-year follow-up study of 87 subjects treated as part of the open-label alemtuzumab cohort in Cambridge, 45 (52%) received just the two planned cycles of alemtuzumab 12 months apart (Tuohy et al., 2014). Further cycles were only offered if a relapse occurred: 31 patients (36%) received three cycles; seven patients (8%) four cycles; and only one patient five cycles (Tuohy et al., 2014). Based on these data it seems as if the majority of patients respond, at least clinically, in the intermediate term to alemtuzumab therapy. We would therefore consider breakthrough activity beyond five cycles of alemtuzumab therapy a treatment failure and patients should then be considered for alternative therapies.

We recommend doing both a FLAIR, T2 and Gd-enhanced T1 MRI; if there are Gd-enhancing lesions on the rebaselining MRI, indicative of a subclinical relapse, this would indicate that there is breakthrough disease and a need to switch treatment, or in the case of alemtuzumab, and other induction agents, to have a repeat course of therapy. Please note that the timing of the rebaselining MRI is not set in stone and will be influenced by pragmatic local considerations, such as the availability of MRI. It is important that if you do implement a local strategy of treating to the target of NEDA that you involve your neuroradiology colleagues. Looking for new, or enlarging, T2-lesions requires neuroradiologists to be diligent in how they compare and report MRI studies, which is different to diagnostic studies (Erbayat Altay et al., 2013).

NEDA raises another issue in relation to whether or not the underlying treatment strategy is an induction or maintenance therapy. Disease activity on a maintenance therapy, provided the patient has been adherent to treatment, can be interpreted as a sub-optimal or non-response (Dobson et al., 2014). In contrast, disease activity on an induction therapy, for example alemtuzumab, is generally considered as being an indication to retreat the patient (Coles et al., 2012a, 2012b; Cohen et al., 2012).

A potential criticism of NEDA is the inclusion of disease progression, separate to that of incomplete recovery from relapses, as a component of the composite. Progressive disability in the absence of relapses may have little to do with ongoing focal inflammatory activity and may simply represent a dying back central axonopathy as a result of preceding focal inflammatory lesions (Banwell et al., 2013). This process is often referred to as post-inflammatory neurodegeneration, or non-relapsing progressive MS, and underpins the so-called two-stage disease hypothesis (Confavreux et al., 2000; Leray et al., 2010). As age is one of the most powerful predictors of the onset of this phase of the disease, it is reasonable to hypothesise that ageing may be contributing to disability accrual during the non-relapsing deteriorating phase of MS (Scalfari et al., 2010). It remains uncertain whether or not this stage of the disease can be modified with current immunomodulatory therapies, and some colleagues will no doubt feel uncomfortable switching, or stopping a DMT, based on non-relapse associated increase in disability alone. There is a strong argument for not including non-relapsing disability progression as part of the definition of NEDA. We anticipate data from ongoing extension and registry studies will clarify this point.

We predict that the definition of NEDA will evolve with technological innovations and clinical practice. A future definition of NEDA will likely need to include patient-related outcome measures (PROs or PROMS), focal grey matter disease activity, a whole and/or a regional brain atrophy metric and possibly fluid biomarkers, for example cerebrospinal fluid neurofilament levels (Giovannoni and Nath, 2011; Giovannoni, 2010). Importantly, a recent meta-analysis by Sormani et al. (2014) demonstrates that both focal inflammatory lesions, as measured by increased T2-lesion load over 2-years, and neurodegeneration, measured using whole brain volume loss in year two, explained 75% of the variance of disability progression over 2 years on DMT, which was better than either metric alone. Therefore, it would seem appropriate to include some metric to indicate the slowing or normalisation of brain atrophy rates in future definitions of NEDA. This is particularly pertinent now that we have therapies that have been shown reduce the rate of brain atrophy in treated patients (Cohen et al., 2012, 2010; Coles et al., 2012a; Kappos et al., 2010; Miller et al., 2007). Of note, Sormani et al. (2014) deliberately removed brain volume changes during year one from their meta-analysis to exclude the so-called "pseudoatrophy" effect, resulting from the reduced inflammatory activity and associated oedema when anti-inflammatory agents are initiated in people with active MS (Zivadinov et al., 2008).

Some commentators are very critical of NEDA as a treatment target and feel we need to be more pragmatic; they claim that a zero tolerance target would mean the majority of patients would end up being on "more risky" high efficacy therapies. Hence they are promoting a strategy that allows some disease activity using for example the Rio (Rio et al., 2009), or modified Rio (Sormani et al., 2013), scores as a treatment target. Our argument is that if you accept the science supporting the concept that "focal inflammation is bad" for MS and that inflammation is associated with poor short, intermediate and long-term outcomes, then if the majority of patients end up on the so-called "risky high-efficacy" therapies because of breakthrough activity, then this is what they require to treat their MS. Induction of long-term remission or, NEDA, is the treatment target in rheumatoid arthritis (Solomon et al., 2014), inflammatory bowel disease (Levesque et al., 2014) and other organ-specific autoimmune diseases; why would we want to treat MS differently compared to these other inflammatory diseases?

Recent evidence indicates that patients with MS treated-to-target of NEDA do better than those with breakthrough disease (at a clinical or subclinical level). We therefore encourage MSologists to implement NEDA as a principal aim in the management of relapsing MS. Figure 1 is a flowchart of how we have implemented treat-2-target of NEDA at our

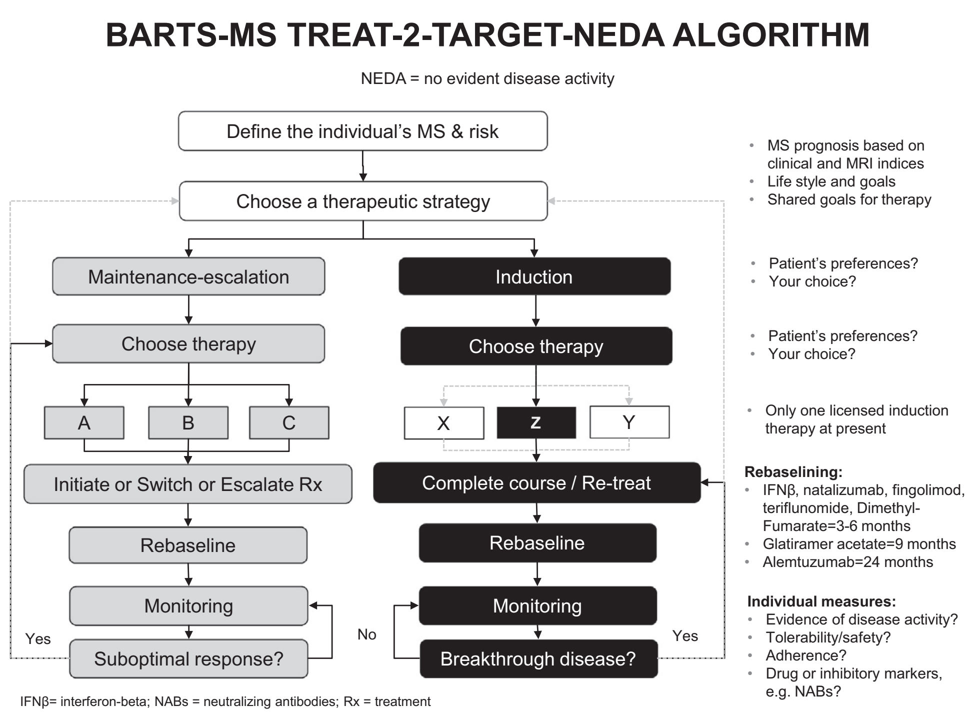

Figure 1 Treatment algorithm for implementing a treat-2-target strategy for the management of disease-modifying therapies in patients with active multiple sclerosis.

institution. The important take-home message is that the treatment goals in MS have moved and now require the setting of targets and active monitoring of outcomes. Finally, there is an evident need to regularly update the definition of NEDA as new technologies become available and are validated as predictors of a treatment response; we envisage this definition changing in the near future to include a brain volume metric.

Conflicts of interest

GG has received compensation for participating on Advisory Boards in relation to clinical trial design, trial steering committees and data and safety monitoring committees from Abbvie, Bayer-Schering Healthcare, Biogen-Idec, Eisai, Elan, Fiveprime, Genzyme, Genentech, GSK, GW Pharma, Ironwood, Merck, Merck-Serono, Novartis, Pfizer, Roche, Sanofi-Aventis, Synthon BV, Teva, UCB Pharma and Vertex Pharmaceuticals.

SG has received travel grants from Teva and Novartis, and has received compensation for consultancy or lecture fees from Novartis.

BT has received travel grants and consultant fees for attending advisory boards from Biogen-Idec, TEVA, Merk-Serono, Novartis and Genzyme.

CO has no conflicts of interest.

KS has received speaking honoraria from, and/or served on advisory boards for Novartis, Biogen, Teva, Merck-Serono and Merck Inc, and has received travel support from Genzyme.

MM received unrestricted funding from Merck-Serono and travelling support from Bioge-Idec and AbbVie.

References

Banwell B, Giovannoni G, Hawkes C, Lublin FD. Editors' welcome and a working definition for a multiple sclerosis cure. Mult Scler Relat Disord 2013;2:65–7.

Bermel RA, Weinstock-Guttman B, Bourdette D, Foulds P, You X, Rudick RA. Intramuscular interferon beta-1a therapy in patients with relapsing-remitting multiple sclerosis: a 15-year follow-up study. Mult Scler 2010;16(5):588–96. [PubMed PMID: 20167591; Epub 2010/02/20.eng].

Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362(5):402–15. [PubMed PMID: 20089954; Epub 2010/01/22.eng].

Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, 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 (9856):1819–28. [PubMed PMID: 23122652; Epub 2012/11/06. eng].

Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012a;380(9856):1829–39. [PubMed PMID: 23122650; Epub 2012/11/06.eng].

Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, et al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 clinical trial. Neurology 2012b;78(14):1069–78. [PubMed PMID: 22442431. Epub 2012/03/24.eng].

Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging - measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol 2001;49(3):290–7. [PubMed PMID: 11261502. Epub 2001/03/23.eng].

Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. N Engl J Med 2000;343(20):1430–8. [PubMed PMID: 11078767. Epub 2000/11/ 18.eng].

Dobson R, Rudick RA, Turner B, Schmierer K, Giovannoni G. Assessing treatment response to interferon-beta: is there a role for MRI? Neurology 2014;82(3):248–54. [PubMed PMID: 24336144; Pubmed Central PMCID: 3902760; Epub 2013/12/18. eng].

Erbayat Altay E, Fisher E, Jones SE, Hara-Cleaver C, Lee JC, Rudick RA. Reliability of classifying multiple sclerosis disease activity using magnetic resonance imaging in a multiple sclerosis clinic. JAMA Neurol 2013;70(3):338–44. [PubMed PMID: 23599930; PubMed Central PMCID: 3792494; Epub 2013/04/20.eng].

Giovannoni G. Cerebrospinal fluid neurofilament: the biomarker that will resuscitate the 'Spinal Tap'. Mult Scler 2010;16(3):285–6. [PubMed PMID: 20203146; Epub 2010/03/06.eng].

Giovannoni G, Nath A. After the storm: neurofilament levels as a surrogate endpoint for neuroaxonal damage. Neurology 2011;76(14):1200–1. [PubMed PMID: 21346219; Epub 2011/02/25.eng].

Giovannoni G, Cook S, Rammohan K, Rieckmann P, Sorensen PS, Vermersch P, 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(4):329–37. [PubMed PMID: 21397565].

Hartung HP, Aktas O. Evolution of multiple sclerosis treatment: next generation therapies meet next generation efficacy criteria. Lancet Neurol 2011;10(4):293–5. [PubMed PMID: 21397566. Epub 2011/03/15.eng].

Havrdova E, Galetta S, Hutchinson M, Stefoski D, Bates D, Polman CH, 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-Remitting Multiple Sclerosis (AFFIRM) study. Lancet Neurol 2009;8(3):254–60. [PubMed PMID: 19201654. Epub 2009/02/10.eng].

Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362(5):387–401. [PubMed PMID: 20089952; Epub 2010/01/22.eng].

Leray E, Yaouanq J, Le Page E, Coustans M, Laplaud D, Oger J, et al. Evidence for a two-stage disability progression in multiple sclerosis. Brain 2010;133(Pt 7):1900–13. [PubMed PMID: 20423930; PubMed Central PMCID: 2892936; Epub 2010/04/29. eng].

Levesque BG, Sandborn WJ, Ruel J, Feagan BG, Sands BE, Colombel JF. Converging goals of treatment for inflammatory Bowel disease, from clinical trials and practice. Gastroenterology 2014. [PubMed PMID: 25127678].

Miller DH, Soon D, Fernando KT, MacManus DG, Barker GJ, Yousry TA, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. Neurology 2007;68(17):1390–401. [PubMed PMID: 17452584; Epub 2007/04/25.eng].

Rio J, Castillo J, Rovira A, Tintore M, Sastre-Garriga J, Horga A, et al. Measures in the first year of therapy predict the response to interferon beta in MS. Mult Scler 2009;15(7):848–53. [PubMed PMID: 19542263].

Scalfari A, Neuhaus A, Degenhardt A, Rice GP, Muraro PA, Daumer M, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain 2010;133 (Pt 7):1914–29. [PubMed PMID: 20534650; PubMed Central PMCID: 2892939; Epub 2010/06/11.eng].

Solomon DH, Bitton A, Katz JN, Radner H, Brown EM, Fraenkel L. Review: treat to target in rheumatoid arthritis: fact, fiction, or hypothesis? Arthritis Rheumatol 2014;66(4):775–82. [PubMed PMID: 24757129; PubMed Central PMCID: 4012860].

Sormani MP, Rio J, Tintore M, Signori A, Li D, Cornelisse P, et al. Scoring treatment response in patients with relapsing multiple sclerosis. Mult Scler 2013;19(5):605–12. [PubMed PMID: 23012253].

Sormani MP, Arnold DL, De Stefano N. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Ann Neurol 2014;75(1):43–9. [PubMed PMID: 24006277; Epub 2013/09/06.eng].

Tuohy O, Costelloe L, Hill-Cawthorne G, Bjornson I, Harding K, Robertson N, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. J Neurol Neurosurg Psychiatry 2014. [PubMed PMID: 24849515].

Zivadinov R, Reder AT, Filippi M, Minagar A, Stuve O, Lassmann H, et al. Mechanisms of action of disease-modifying agents and brain volume changes in multiple sclerosis. Neurology 2008;71(2):136–44. [PubMed PMID: 18606968; Epub 2008/07/09.eng].