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Title: number of characters = 78

Commentary: number of words = 1748

Number of references = 26

Key words = no evident disease activity, NEDA, multiple sclerosis, disease modifying therapy, MRI, monitoring, treating to target, disease activity free

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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 (1, 2). 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 (2). As a result of these observations MSologists are redefining their primary aim of treatment as now being ‘no evident disease activity’ (NEDA) (3). 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”) (4, 5) and is derived from the post-hoc analyses of contemporary phase 3 clinical trials, for example natalizumab and cladribine (4, 5).

NEDA is an important goal for treating individual patients with relapsing disease, and potentially as an outcome in future clinical trials (6). 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, will be 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 (5). For interferon-beta, teriflunomide, dimethyl fumarate and natalizumab we would recommend rebaselining at 3 to 6 months, for glatiramer acetate 9 to 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 (7).
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 (8). 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 (9). 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 (9). 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 (10).

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 (1). In contrast, disease activity on an induction therapy, for example alemtuzumab, is generally considered as being an indication to retreat the patient (8, 11, 12).

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 (3). This process is
often referred to as post-inflammatory neurodegeneration, or non-relapsing progressive MS, and underpins the so-called two-stage disease hypothesis (13, 14). 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 (15). 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 to 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 (16, 17).

Importantly, a recent meta-analysis by Sormani and colleagues (18) 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 (11, 12, 19-21). Of note, Sormani and colleagues (18) 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 (22).

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 (23), or modified Rio (24), 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 (25),
inflammatory bowel disease (26) 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 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.
Legends

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

**BARTS-MS T2T-NEDA ALGORITHM**

T2T = treating-to-target; NEDA = no evident disease activity

- Define the individual’s MS
- Choose a therapeutic strategy

**Maintenance-escalation**

- Choose therapy
  - A
  - B
  - C

- Initiate or Switch or Escalate Rx
- Rebaseline
- Monitoring
- Treatment failure?

**Induction**

- Choose therapy
  - X
  - Z
  - Y

- Complete course / Re-treat
- Rebaseline
- Monitoring
- Breakthrough disease

**Patient’s preferences?**
- Your choice?

- Only one licensed induction therapy at present

**Rebaselining:**
- IFNβ, natalizumab, fingolimod, teriflunomide, Dimethylfumarate=3-6 months
- Gilenya acetate=9 months
- Alemtuzumab=24 months

**Individual measures:**
- Evidence of disease activity?
- Tolerability/safety?
- Adherence?
- Drug or inhibitory markers, e.g. NABs?
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 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 traveling support from Bioge-Idec and AbbVie.
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Multiple Sclerosis
- MS activity
- MS prognosis
- Life style and goals
- Goal of therapy

Treatment strategy
- Individualise risks and benefits
- Patient preferences
- Neurologists preference

Disease-modifying therapies
- Induction vs. maintenance-escalation
- Relative efficacy
- Tolerance and adverse event profile
- Safety in pregnancy
- Monitoring requirements
- Local guidelines and reimbursement issues

Rebaselining MRI:
- Interferon-β, natalizumab, fingolimod, teriflunomide, dimethyl fumarate = 3-6 months
- Glatiramer acetate=9 months
- Alemtuzumab = 24 months or 12 months post last cycle of treatment

Individual measures:
- Evidence of disease activity (clinical and MRI)
- Tolerability/safety
- Adherence
- Drug or inhibitory markers

Threshold for failure:
- NEDA (no evident disease activity)
- Rio Score
- Modified Rio Score
- National or regional guidelines
1. The new treatment target in relapsing MS is NEDA
2. To target NEDA requires a rebaselining MRI
3. Disease activity on a maintenance therapy indicates a sub-optimal response
4. Disease activity on an induction therapy is an indication to retreat
5. The NEDA definition will evolve with technological innovations