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Review Article

NEDA treatment target? No evident disease activity as an actionable outcome in practice

Natalie E. Parks[a,b,*], Eoin P. Flanagan[a], Claudia F. Lucchinetti[a], Dean M. Wingerchuk[c]

[a] Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA
[b] Division of Neurology, Dalhousie University, 1341 Summer Street, Halifax, NS B3H4K4, Canada
[c] Department of Neurology, Mayo Clinic, 13400 E Shea Boulevard, Scottsdale, AZ 85259, USA

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ABSTRACT

"No evident disease activity" (NEDA) is a proposed measure of disease activity-free status in multiple sclerosis (MS) that is typically defined as absence of relapses, disability progression, and MRI activity over a defined time period. NEDA is increasingly reported in randomized controlled trials of MS disease modifying therapies where it has some perceived advantages over outcomes such as annualized relapse rate. NEDA has also been proposed as a treatment goal in clinical care. At this point, the long-term implications of early NEDA remain largely unknown. We review current NEDA definitions, use in clinical trials, and its prospects for routine use as an actionable treatment target in clinical practice.

1. Introduction

Multiple sclerosis (MS) is a disabling disease with a 3-fold increase in unemployment and average loss of 10 quality-adjusted life years compared with the general population [1]. At onset, 80–85% of patients have relapsing remitting MS (RRMS) heralded by a clinical attack whereas the remaining 15–20% have primary progressive MS and experience gradually progressive neurologic deficits from onset [2,3]. Although the pathogenesis of MS remains uncertain, inflammatory demyelination results in clinical relapses and focal magnetic resonance imaging (MRI) lesions, whereas neurodegeneration contributes to disease progression and brain atrophy; inflammation and neurodegenerative mechanisms likely coexist [4].

Currently approved disease modifying therapies (DMTs) largely target the inflammatory phase of MS. First-line DMTs include self-injectable medications (interferon-β, glatiramer acetate) or newer oral immunomodulatory medications (fingolimod, dimethyl fumarate, teriflunomide), while other highly active therapies or those with special risk profiles (e.g., natalizumab, alemtuzumab, daclizumab) are usually used as later-line therapies. Available DMTs reduce relapse rate and slow the accrual of MRI lesion number or volume. Some DMTs also reduce the proportion of patients who experience disease progression during the course of a randomized controlled trial (RCT) and possibly much longer [5].

In clinical practice, DMTs are offered to patients with RRMS given proven ability to reduce relapses although DMT may also delay disability progression and reduce the rate of conversion to secondary progressive MS (SPMS) [5,6]. The recent approval of the anti-CD20 monoclonal antibody ocrelizumab is a milestone because of its efficacy for both relapsing and primary progressive forms of MS [7,8].

At present, we lack validated clinical or laboratory biomarkers to guide initial or subsequent DMT selection. Various methods to adjudicate treatment failure for the purpose of switching DMTs have been proposed and typically included thresholds for relapse number or frequency, accumulation of new MRI lesions, or disability progression. Recently, a composite measure of disease status termed "no evident disease activity" (NEDA) has been reported as a tertiary or exploratory outcome in DMT RCTs and observational studies. NEDA definitions aim to capture multidimensional aspects of MS disease activity and progression, which are the clinical outcomes related to inflammatory and degenerative pathology. NEDA has been proposed as a surrogate for disease activity-free status [9,10]. Given the availability of DMTs that suppress inflammatory disease activity and may affect neurodegenerative disease mechanisms, there is increasing interest in treating to a target of NEDA [11,12]. In this review, we examine the role of NEDA definitions as actionable treatment targets in routine clinical practice.

2. Definitions of NEDA

The most common NEDA definition, often referred to as NEDA-3, requires that a patient experience no relapses, progression, or MRI activity during a specified time period [11–13]. Relapses are defined as

* Corresponding author at: Dalhousie Multiple Sclerosis Research Unit, 1341 Summer Street, Room 623, Halifax, NS B3H4K4, Canada.
E-mail addresses: nparks@dal.ca (N.E. Parks), flanagan.eoin@mayo.edu (E.P. Flanagan), clucchinetti@mayo.edu (C.F. Lucchinetti), wingerchuk.dean@mayo.edu (D.M. Wingerchuk).

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Table 1
Post-hoc analysis of NEDA-3 in clinical trials.

Study	Duration (years)	% NEDA	
ADVANCE [31]	1	34% peginterferon-β***	15% placebo
AFFIRM [32]	1	47% natalizumab***	15% placebo
SELECT [33]	1	39% daclizumab***	11% placebo
FREEDOMS/FREEDOMSII [13]	2	31% fingolimod***	10% placebo
AFFIRM [32]	2	37% natalizumab***	7% placebo
DEFINE/CONFIRM [34]	2	23% dimethyl fumarate***	11% placebo
TEMSO [34]	2	23% teriflunomide 14 mg*** 18% teriflunomide 7 mg*	14% placebo
CARE-MSI[a][20]	2	39% alemtuzumab**	27% interferon-β
CARE-MSII[a][21]	2	32% alemtuzumab***	14% interferon-β
OPERA I[a][7]	2	48% ocrelizumab***	29% interferon-β
OPERA II[a][7]	2	48% ocrelizumab***	25% interferon-β

P-value for study DMT vs comparator * < 0.05; ** < 0.01; ****P*-value < 0.001.
[a] Pre-specified endpoint.

new or worsening neurological symptoms persisting ≥ 24 h in the absence of fever/infection [3]. Progression may be defined as an increase in the Expanded Disability Status Scale (EDSS) score by ≥ 1 point (or by ≥ 1.5 point if EDSS 0; ≥ 0.5 points if EDSS ≥ 5.5) that is sustained on re-examination for ≥ 3–6 months [13] although there is variation in the definition of progression between studies [12]. MRI activity refers to any new or enlarging T2 lesions or gadolinium-enhancing lesions [11,13].

Although NEDA-3 accounts for many aspects of disease activity, it may not adequately capture the neurodegenerative processes of MS, especially in early disease stages. Brain atrophy is correlated with and predictive of longer-term disability progression and cognitive decline [14–18]. In addition, treatment with several DMTs including fingolimod and alemtuzumab is associated with reduced brain atrophy rates [19–21]. As a result, an expanded NEDA definition that includes a measure of brain volume loss, NEDA-4, was recently proposed [13]. Brain volume loss per year is typically 0.1–0.3% in healthy controls compared with 0.5–1.35% in MS patients [13,14]. As a result, NEDA-4 uses a brain volume loss threshold of 0.4%/year which has 80% specificity in discriminating MS from healthy controls [13,22]. NEDA-4 is a more stringent measure given the added dimension that must also be satisfied to achieve disease activity free status.

Although inflammatory MRI activity is incorporated into the definition of NEDA-3, this typically refers only to activity on MRI brain [6,7,20,21]. Clearly, spinal cord pathology is important in MS as outlined by studies showing cervical lesion load is associated with disability independent of atrophy and the potential for a solitary demyelinating spinal cord lesion to cause progressive disease in progressive solitary sclerosis [23,24]. Inflammatory disease activity in the spinal cord undoubtedly has clinical implications and should be incorporated into the definition of NEDA.

Although EDSS is the most widely accepted clinical disability measure, there are a number of alternative measures of disability including the multiple sclerosis functional composite (MSFC) [25]. The MSFC combines 25-foot walk, 9-hole peg test, and paced auditory serial addition test (PASAT) to determine a numerical score evaluating three neurologic domains including cognition. Similar to brain atrophy providing a radiologic correlate for neurodegeneration, optical coherence tomography (OCT) demonstrates that reduced peripapillary retinal nerve fiber layer thickness correlates with EDSS disability progression [26]. Serum or cerebrospinal fluid neurofilament light chain level is a candidate for a biochemical marker of neuronal damage with higher neurofilament light chain level correlating with greater risk of relapses and EDSS progression [12,27]. These additional measures may provide further dimensions to assess in an expanded definition of NEDA.

At present, there are no standardized recommendations for the frequency of clinical or radiographic examination in NEDA assessments, although 1 year has been recommended to assess for disease activity [28,29].

3. NEDA as a randomized controlled trial outcome measure

NEDA has been examined as a potential composite endpoint for RCTs because individual key outcomes such as relapses and disability progression occur infrequently during typical 1–3 year trials [9,30]. The most commonly used primary outcome in MS RCTs, annualized relapse rate, has been declining over time in both placebo and treatment arms, thus requiring increasingly greater power to establish efficacy [9]. The dichotomous outcome of proportion of subjects with 3-month (or 6-month) confirmed EDSS progression also occurs in only a small minority of subjects, especially among those with shorter disease duration. Although MRI is a potential surrogate marker for long-term functional outcome, no conventional MRI measure is yet sufficiently validated to substitute for clinical outcomes [6,25].

NEDA-3 has primarily been evaluated in DMT clinical trials by post-hoc analysis although RCTs of alemtuzumab and ocrelizumab included NEDA-3 as a pre-specified endpoint (Table 1). Active treatment has consistently achieved significantly higher levels of NEDA-3 at 1–2 years compared to placebo [13,31–34]. In addition, alemtuzumab and ocrelizumab achieved a higher proportion of NEDA-3 at 2 years compared to interferon-β [7,20,21]. Interestingly, NEDA-3 status at 2 years among patients treated with DMT in many clinical trials is similar to the 27.5% NEDA-3 seen in a longitudinal cohort study at 2 years where the average patient was on DMT (primarily first-line injectable therapy) for approximately 75% the study duration [35]. In trials of ocrelizumab compared to interferon-β the proportion with NEDA-3 following interferon-β treatment for 2 years was 25–29%, similar to the proportion in the longitudinal cohort study, while there were a significantly higher proportion with NEDA-3 following ocrelizumab treatment at 48% [7]. This observation does not account for more highly active RRMS patients likely being recruited to clinical trials or that cohort studies may include a small proportion of patients on second-line DMT.

NEDA-4 has been used to examine clinical trial data for fingolimod. This confirms that NEDA-4 is more difficult to achieve at 2 years compared to NEDA-3 [13]. NEDA-3 occurred in 31.0% taking fingolimod and 9.9% taking placebo, compared to NEDA-4 being achieved in 19.7% taking fingolimod and 5.3% taking placebo. Using both measures, the group receiving DMT had significantly higher proportion of NEDA compared to placebo.

4. NEDA in observational studies

In a cohort of 72 recently diagnosed RRMS patients, 54% fulfilled NEDA-3 criteria after 1 year [36]. Among those with disease activity, there were more patients on first-line therapy compared to no DMT or second-line therapy. NEDA-3 at 1 year was achieved by 71% not using