View Point

No Evidence of Disease Activity (NEDA) in Multiple Sclerosis - Shifting the Goal Posts

Lekha Pandit

Professor of Neurology, Director of Center for Advanced Neurological Research, KS Hegde Medical Academy, Nitte (Deemed to be University), Mangalore, Karnataka, India

Abstract

A combined endpoint measure to define no evidence of disease activity (NEDA) is becoming increasingly appealing in the treatment of multiple sclerosis (MS). Initial efforts using a 3 parameter NEDA monitored disease activity using clinical and MRI lesion data. Later refinements, introduced more recently, include brain atrophy measurement and cognitive function analysis in defining NEDA-4. Using these stringent criteria clearly differentiated the usefulness of different disease modifying agents (DMDs) in achieving and sustaining NEDA over time. This in turn has changed attitudes and strategies in management of MS.

Keywords: Multiple sclerosis, NEDA-3, NEDA-4

Introduction

With the advent of newer and more aggressive disease modifying therapies (DMTs), there is a real need to define end points that accurately determine efficacy of therapy in multiple sclerosis (MS). There are several factors which influence treatment outcomes in MS, including the heterogeneous nature of the disease, prognostic factors operant at disease onset and the differential response to therapies among patients. Effort has been made to identify parameters which define end point of efficacious therapy and took origin initially in clinical trials for DMT. In relapsing remitting disease the concept of no evidence of disease activity (NEDA) was proposed.[1-3] It referred broadly to stabilization of disease as evidenced by lack of clinical relapses, lack of disease progression measured by expanded disability status scale (EDSS) and absence of new disease activity (new T2 lesions/enhancing lesion) on magnetic resonance imaging (MRI) over a period of observation. Over time, this 3 parameter end point (NEDA-3) has been challenged. The need to include cognitive impairment and quality of life measures was noted. Measures of axonal damage including the use of sensitive biomarkers such as neurofilament light chain levels[4] and volumetry of the brain[5] have been recently included for the purpose of defining NEDA. This article will high light some of these changing perspectives.

The Three Parameter NEDA (NEDA-3)

Treatment of multiple sclerosis (MS) has evolved over time. With the advent of newer and more effective drugs, the definition for efficacy of therapy have become more stringent and ambitious. It is only natural that "no evidence of disease activity" parameters were initially applied in clinical drug trials.[6] There has been no common definitions for the three components that represent NEDA-3. Relapse has been defined in various studies as new or recurrent symptom lasting >24 hours and not preceded by fever (14) and after a 30-day period of clinical stability/improvement.[7,8] Relaspe may also be defined by change in EDSS - Increase in 2 points in ≥1 Kurtzke functional score or 1 point each in ≥2 Kurtzke functional scores (except bowel bladder or cognitive dysfunction), which was not preceded by fever and had a prior disease stability/improvement of 30 days.[7] In the MRI criteria, the appearance of new/enlargement of T2W lesions and gadolinium enhancment have both been considered in different stuides as indicative of new activity.[5] In establishing worsening of disability, persistance of EDSS changes have varied from 3-6 months. A 6-month period of confirmed disability worsening is likely to be more reliable and appears to, in addition, predict long-term disability.[9]

The ability to achieve NEDA-3 and its sustainability over time has been demonstrated in clinical trials to be different among various DMT's. In the OPERA trial that compared Ocrelizumab with Interferon beta-1a (Rebif) in RRMS, NEDA-3 parameters were satisfied in 25-29% of patients receiving Rebif while 48% in the ocelizumab group achieved the same in a 2-year period.[10] The poor sustainability of NEDA-3 with first line injectables was amply demonstrated in the Avonex-Steroids-Azathioprine (ASA) trial.[11] In the

Address for correspondence: Dr. Lekha Pandit, Department of Neurology, KS Hegde Medical Academy, Nitte (Deemed to be University), Mangalore, Karnataka, India.
E-mail: panditmng@gmail.com

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Avonex group (n = 162), NEDA-3 was achieved in 33 (20.4%) at 1 year, 12 (7.6%) at 2 years and 5 (3.3%) at 4 years and none beyond 6 years. In a real world setting, data from 219 patients from the comprehensive and longitudinal investigation of Multiple sclerosis at Brigham and Womens hospital (CLIMB) study, showed that only 7.9% maintained NEDA-3 at 7 years after receiving first line injectables.[12] In contrast long-term follow up studies on patients receiving Natalizumab showed 34% to be NEDA-3 at 7 years.[8] Several observations were made that could potentially impact treatment practices. For instance, patients who relapsed during first year of treatment either clincially or radiologically after first line DMT, were at significant risk of subsequent relapses and sustained disability in the susequent 2 years of treatment.[13] Despite limitations imposed by difference in study designs and variability in the definition of NEDA-3 parameters, the superiority of second line DMTs in achieving NEDA-3 was evident. The need to devise flexible treatment options incoroporating sensitive indicators that determine treatment efficacy early in the disease course became clear. Treat to target strategies have evolved in which treatment can be escalted/switched early in the disease course.

The Four Parameter Neda (NEDA-4)

NEDA-3 essentialy measures clinical relapses, MRI evidence of disease activity and disability worsening, all of which are linked to the inflammatory phase of MS. It correlates less with the neurodegenerative process that starts early in the disease course and is ultimately responsible for disease progression.[1] Some of the obvious draw backs of NEDA-3 include the lack of inclusion of brain atrophy and cognitive dysfunction. Adding assessment parameters for cognition and tracking brain volume loss (BVL) constitutes the basis for NEDA-4.[5] Absence of clinical relapses, lack of new or enlarged T2W lesions, and disability progression in the previous 6 months and a mean annual BVL rate of <0.4% was used to define NEDA-4. It is to be noted that the authors who first proposed it[5] found gadolinium enhancing lesions in "nearly every" MRI scan with new T2 lesion or existing T2 lesion enlargement and hence excluded enhancing lesions from the initial criteria. Brain volume loss in MS correlates with brain lesion activity and clinical disability.[14,15] A meta -analysis of clinical drug trials (including both first line and secnd line DMT) that used BVL as an outcome parameter, showed that effect of treatment on BVL correlated with effect on disability progression.[16] NEDA-4 was first used in a *post hoc* study of patients on fingolomid (FREEDOM trials and extension phase).[5] NEDA-4 had significantly superior predictive value at 1 year as compared to NEDA-3, when these patients were observed for upto 6 years. In the immediate period after the 2-year trial, 19.7% of patients on fingolomid had NEDA -4 status. In the extension phase, patients who continued on 5 mgms of fingolomid daily or started the same (crossing over from the placebo arm) where re-assessed at the end of 7 years. In 45% of 246 patients still on the trial, NEDA-4 status was sustained while 70% had NEDA-3 status. In the Avonex-steroids-Azathioprine (ASA) trial,[11] among 116 patients who received intramuscular interferon-beta-1a, NEDA-4 status was evaluated based on an annual threshold BVL rate of 0.4%. Less than 5% attained NEDA-4 status at 2 years which dropped to 1% at 4 years and none there after, once again underscoring the effectiveness of second line therapy in achieving NEDA. The real challenge is to determine whether outside of the "protocol driven" randomized control trials, goals of NEDA-4 can be met. A retrospective analysis of the MS clinical and magnetic resonance Imaging outcomes in the USA (MS-MRIUS) study,[17] evaluated NEDA status in 599 patients treated with finglomid at 33 MS centers. After a median follow up of 16 months, NEDA-3 was achieved in 58.7%, while 37.2% reached NEDA-4 (included BVL ≤4%) status. This study illustrates the feasibility of assessing NEDA-4 in a clinical setting, especially when care is taken to standardize MRI parameters for quantifying BVL.

Another way of assessing NEDA-4 would be to include cognitive domain testing and quality of life measurements. The multiple sclerosis functional composite (MSFC) assesses both physical and cognitive functions and may be more sensitive particulalry in eary disease course than the standard EDSS testing. An algorithm which sensitively detects change in treatment course - Multiple sclerosis decision model (MSDM), a modified version of MSFC, was proposed by Stangler *et al*.[18] to monitor patients with MS. Apart from the 3 conventional parameters namely relapse, disability progression and MRI activity, it proposes inclusion of patient reported outcomes. MSDM includes single digit modality testing (SDMT) for evaluating cognitive functions, fatigue scale for motor or cognitive functions, the hospital anxiety and depression scale and multiple sclerosis impact scale (MSIS) for quality of life asessment. A traffic light rating was proposed where in green indicates no change in treatment, yellow flags the need for observation and short term followup examination and red indicates the need for change in therapy.

Potential biomarker that may prove useful in monitoring disease progression include neurofilament light chain (NFL) measurement.[4,19] Cerebrospinal fluid NFL at baseline predicts disease activity during 2 years of follow-up in patients with CIS and RRMS. S-NFL, determined with sensitive single-molecule array (Simoa) technology has been reported to be highly correlated to CSF levels in RRMS. Validation of the methodology and setting of thresh hold values may see the emergence of serum NFL as a predictive biomarker in the near future for inclusion in NEDA-4.

Conclusions

Treatment strategies have become bolder in recent times and the efficacy of the same has been tested against NEDA parameters. Optimally NEDA must incoroporate measures that reflect all elements of the disease including the inflammatoryand degenerative components of MS and factors that reflect disease

impact including the quality of life. The process should allow comprehensive evaluation using quick and reliable methods in a real world setting. Ideally NEDA-4 should enable a feed back about the disease progression and permit early course correction if needed, besides providing evidence of disease activity/inactivity over time.

The concept of NEDA is aspirational in nature and will continue to reform and change over time. Using combined endpoints to define the absence of disease activity is becoming increasingly common. Long term followup incorporating these parameters in a real life clinic based setting would be the real challenge and if successful would be the norm for monitoring treatment in MS.

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Conflicts of interest

There are no conflicts of interest.

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