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OPINION ARTICLE

REVISED Evidence of disease control: a realistic concept beyond NEDA in the treatment of multiple sclerosis [version 2; referees: 2 approved]

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## Abstract

Although no evidence of disease activity (NEDA) permits evaluation of response to treatment in the systematic follow-up of patients with multiple sclerosis (MS), its ability to accomplish detection of surreptitious activity of disease is limited, thus being unable to prevent patients from falling into a non-reversible progressive phase of disease. A protocol of evaluation based on the use of validated biomarkers that is conducted at an early stage of disease would permit the capture of abnormal neuroimmunological phenomena and lead towards intervention with modifying therapy before tissue damage has been reached.

**Open Peer Review**

**Referee Status:** ✔ ✔

|  | Invited Referees | |
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|  | **1** | **2** |
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| **version 1** published 25 Apr 2017 | ✔ report | ✔ report |

1 **Hans Lassmann** , Medical University of Vienna, Austria

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**Author roles: Londoño AC**: Conceptualization, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Mora CA**: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing

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**REVISED** **Amendments from Version 1**

Our main focus of interest, while writing this manuscript, entailed the importance of documenting the non-evident activity of disease in MS which remains hidden to clinical and imaging-related tools when applying the NEDA composite, independently of the specific treatment given to prevent tissue damage. Evidence of disease control (EDC) aims to following up patients with a strong basis on analysis of biomarkers that could reflect the current stage of inflammation and neurodegeneration in opposition to a blind –and prolonged- follow-up process characterized by awaiting a clinical relapse, an increment in the EDSS score and/or the presence of new abnormal MRI imaging findings.

Finally, in relation to our proposed idea of developing a protocol of evaluation based on the use of validated biomarkers at an early stage of disease aiming at modifying therapy before tissue damage has been reached, we implemented Table 1 and a new closing paragraph in this new version of the manuscript that refer to the dynamic interaction of networks leading to the molecular expression of MS in the preclinical and disease states and spreading from the initial clinical assessment to the application of systems biology in MS. This implemented material led to the addition of four new citations in the references section of the manuscript.

**See referee reports**

## Introduction

Immunomodulatory therapies used in the treatment of patients with the clinical isolated syndrome (CIS) of multiple sclerosis (MS) and early relapsing remitting multiple sclerosis (RRMS), as well as the autologous hematopoietic stem cell transplant (aHSCT) used in the treatment of the catastrophic form of the disease, have accomplished a reduction in clinical relapses, a halting in progression toward neurological disability and have demonstrated a reduction of disease activity in MRI scans. This progress has led to the emergence of the 'no evidence of disease activity' (NEDA) composite which evaluates the response to these therapies in clinical studies, but its systematic application and utility in the clinical setting have not been established[1]. NEDA could be considered not only a goal of therapy, but also as an indicator of prognosis and a tool that measures the effect of the medication currently being used[2]. We propose a more aggressive approach that challenges the current application of NEDA.

## Fragility of the NEDA composite

In a cohort of 219 patients with either CIS or RRMS, 60 of 218 (27.5%) maintained NEDA status at 2 years, whereas only 17 of 216 (7.9%) had NEDA at 7 years. NEDA status at 2 years had a positive predictive value of 78.3% for no progression of disease at 7 years, demonstrating that it may be optimal in terms of

prognostic value in the long term[1]. This study disclosed a dissociation between clinical and MRI-followed disease activity, with a more prevalent loss of NEDA status determined by MRI changes at onset, followed by clinical relapses without presence of new lesions or changes in the previously existing lesions at later stages. The loss of NEDA status due to changes in expanded disability status scale (EDSS), which is a method of rating impairment in neurological functions excluding cognition, was infrequent in comparison to the determination provided by the clinical relapse and imaging-based biomarkers[1]. These findings support a decrement in the inflammatory activity of disease as duration of disease increases, and the possibility of recruitment of additional neuronal pathways and/or a cortical remodeling that could compensate for the loss of function[3]. Also, cognitive impairment may affect more than 82% of the patients with MS from early stages of the disease, affecting cognitive performance and quality of life[3]. Damasceno *et al.* proposed that NEDA should also take into consideration other important measures of the patients' neurological condition, such as their cognitive status and the volumetric analysis of the brain, converting NEDA into a completely effective tool for therapy evaluation. In their cohort of 42 patients with RRMS treated either with beta-interferon or glatiramer acetate, NEDA status was accomplished in only 30.8% of patients, with worsening of more than two cognitive domains in 58.3% of the NEDA group, and with evidence of cortical thinning and higher thalamus volume decrease in patients with MRI activity[4]. Studies using drugs known to produce a better therapeutic effect in multiple sclerosis, such as natalizumab and alemtuzumab, have disclosed loss of the NEDA status after 2 years of initiation of therapy in 37% and 39% of the treated patients, respectively[4]. Currently, aHSCT is the only therapeutic approach that has accomplished NEDA status after 3 years in 75% of patients[5]. Giovannoni has recently discussed the adaptation of NEDA to the type of the therapeutic regime, and has considered three scenarios. These include a) no treatment, b) maintenance/escalation of disease-modifying therapy, and c) use of induction therapies (such as alemtuzumab, cladribine and aHSCT) establishing a baseline according to the pharmacodynamics of each drug available[2].

Although progression of disease, which reflects the neurodegenerative component of MS, is expected to be reflected by the EDSS score in the actual concept of NEDA, evidence has shown that the T25FW (timed 25-foot walk) test gave better documentation of clinical progression[1]. Considering the use of NEDA, Dadalti Fragoso discussed the difficulties encountered when using EDSS to objectively document patient functionality in different areas. Clinical manifestations such as fatigue or sensitivity to heat are not considered, there is an inconvenient variability among evaluators with differences up to 2.0 points for EDSS and 3.0 points

for functional system evaluation, and there is the disadvantage of having the patient, and not the evaluator, reporting the ability to walk 500 m or 300 meters[6]. These studies have shown that, in a high percentage of patients, activity of disease was present at baseline and could not be detected by NEDA thus resulting in a delayed therapeutic intervention and irreparable damage of the central nervous system (CNS).

### Background activity beyond the surveillance of NEDA
The term 'minimal evident disease activity' (MEDA) has been applied to MS patients who have been apparently stable in comparison to patients with higher level of activity in the short to intermediate term[2]. Thus, beyond documenting NEDA we mostly need to achieve documentation of the unnoticed surreptitious activity of disease which remains despite treatment. The determination of biomarkers of inflammation and neurodegeneration in body fluids, combined with the use of non-conventional MRI with the ability to detect changes in the normal appearing brain tissue, could assist in the detection of a sequence of cellular and molecular events, inside and out of the CNS, that occur before fulfilling the current definition of NEDA composite. Multiple biomarkers have been identified in MS, but their validation and clinical application have not been established[7,8]. Teunissen recently discussed the use of biomarkers for MS such as N-acetylaspartate (representing mitochondrial dysfunction and/or neuro-axonal loss), chitinase 3 like-protein 1 (meaning reactive astrogliosis and microglial activity), neurofilament light chain (related to axonal loss) and glial fibrillary acidic protein (representing astrocytic cytoskeleton injury). They have been validated in at least two independent cohorts, and evaluation of their expression could be a useful tool at the time of diagnosis of MS, and during follow-up after the administration of disease modifying therapy[9].

Bonnan *et al.* have recently suggested that NEDA cannot predict sustained remission or complete recovery of disease, and proposed a 'disease free status score' be established, based on whether or not there is biological activity of disease, by measuring the level of biomarkers in CSF[10]. Taking into consideration that, at present, there are no therapeutic agents available that would be able to offer a cure for MS, a disease free status score could create confusion on top of becoming a non-realistic concept. We support the concept that the methodology used to determine the stage of disease should be based on the measuring of the level of biomarkers involved in the inflammatory and neurodegenerative events of disease, not only by CSF analysis but also with non-invasive available tools such as PET-CT and non-conventional MRI to evaluate the normal appearing brain tissue[11–16].

### Goals and conclusion
In the systematic evaluation of the patient with MS, the primary goal should be the monitoring of evidence of disease control with biomarkers in order to:
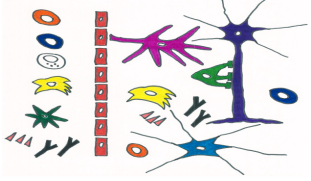
1. Prevent clinical relapses

2. Confirm absence of changes suggestive of progression of the disease in pre-existing lesions, including checking for presence of new lesions or atrophy detected by MRI; and

3. Prevent progression toward disability

By supporting a pro-active management of disease, avoiding brain tissue injury instead of controlling existing inflammation and/or neurodegeneration, this approach is promoting a personalized management of disease[17].

Early treatment of patients with CIS has led to the identification of a therapeutic window that, with current interventions, would be able to slow down progression toward higher scores in EDSS evaluation[3]. Taking into consideration the recent significant attention given to novel monoclonal antibody therapies (including alemtuzumab, rituximab, ocrelizumab, daclizumab)[18–21] and stem cell therapies (aHSCT)[22], our most immediate goal should involve searching for strategic interventions to control both inflammation and neurodegeneration, hopefully reaching a stage of prolonged remission in selected patients. Taking into consideration that NEDA status is currently able to switch on red flags only when tissue damage has already occurred in the CNS, we believe that 'evidence of disease control' will be accomplished through a better defined, convincing and more realistic monitoring of validated biomarkers.

The current clinical-pathological method of analysis of diseases is evolving toward a holistic approach that characterizes human disease focused on the total integration of its composing parts (genetics, genomics, biochemical, cellular informatics, physiology, clinics, etc) the interactions of which are multiple, dynamic and interdependent[23]. These components include a group of networks, the disruption of which will furnish relevant biological information able to transform disease classification, not from phenotype but from molecular presentation, allowing preclinical diagnosis, and individualizing therapy[24]. The study of MS pathogenesis from the perspective of biological systems interaction will permit the understanding of its complexity [see Table 1][23]. Thus, ongoing characterization of biomarkers in the study of patients with MS is becoming an assertive step in the right direction.

**Table 1. From clinical assessment to application of systems biology in MS.**

| Networks | BASED ON |
|---|---|
| **NEDA status**[25]<br>• NEDA 1–3<br>• NEDA 4<br>• NEDA 5<br>• NEDA 6<br>• NEDA 7<br>• NEDA 8 | Clinical event, EDSS, MRI<br>Brain atrophy<br>Cognitive impairment<br>CSF neurofilament level<br>Patients related outcome<br>Oligoclonal bands |
| **BIOMARKERS**[7,8]<br>Related to cells, structures, metabolic pathways, and inflammatory and degenerative cascades. | OCB, NAA, Glutamate, IL-12, IL-23, Enolase, NfL, CXCL13, IL-8, ATP break down products, GFAP, MMP9, MMP3, Th17, Th1/Th17, Chitinase 3, IFN-ϒ, TNF-α, Fetuin-A, Osteopontin, PET (microglia), non-conventional MRI. Others. |
| **NEURO-IMMUNO-PATHOLOGY**<br> | Tissue damage resulting from interaction of neurons, glial cells, immune system cells (B & T-cell lymphocytes, macrophages, dendritic cells), cytokines and antibodies in the CNS |
| **GENETIC DETERMINANTS**[8]<br> | HLA-DRB1*1501:<br>• risk for MS<br>• early disease onset.<br>• risk for progression from RRMS to SPMS<br><br>HLA-DPB1* 0501 & HLA-DPB1* 0301:<br>• risk for opticospinal MS.<br><br>HLA-DRB1* 1501 & HLA-DQB1* 0301:<br>• worst brain atrophy measures.<br><br>DR3 & DR4 haplotypes:<br>• risk for MS.<br><br>TOB1 gen:<br>• early conversion from CIS to CDMS.<br><br>ApoEε4:<br>• greater risk for mental disorders.<br><br>Pharmacogenomics |
| **GUT-IMMUNE-BRAIN AXIS**[26]<br>The gut-associated lymphoid tissue system (GALT) is located in the intestinal lamina propria, near the epithelium, and consists of:<br><br>Organized cellular complexes<br>• Peyer's patches<br>• solitary lymphoid follicles<br><br>Dispersed cells<br>• T and B cells, macrophages, and dendritic cells | The human intestinal flora (microbiota) interaction with GALT could be considered harmless, beneficial or pathogenic depending on the anti-inflammatory or pro-inflammatory state that could result from this interaction. In the later, it could influence immunity and inflammation in the pathophysiology of MS. |

The table shows the dynamic interaction of networks leading to the molecular expression of MS in the preclinical state and through disease span.

**Abbreviations in the table: EDSS**: Expanded Disability Status Scale; **OCB**: oligoclonal bands; **NAA**: N-Acetyl aspartate; **IL**: interleukin; **NfL**: light chain sub-unit of neurofilaments; **CXCL13**: C-X-C Motif Chemokine Ligand 13; **ATP**: adenosine triphosphate; **GFAP**: glial fibrillary acidic protein; **MMP**: matrix metalloproteinase; **Th17**: IL-17 secreting T-lymphocyte; **IFN-ϒ**: interferon gamma; **TNF**α: tumor necrosis factor α; **CIS**: clinical isolated syndrome; **CDMS**: clinical definitive multiple sclerosis

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# Open Peer Review

## Current Referee Status: ✔ ✔

**Version 1**

Referee Report 24 May 2017

✔   **Declan Chard** (iD)

Institute of Neurology, University College London, London, WC1N 3BG, UK

With a view to preventing disability by optimising treatment decisions, there has been growing interest in the concept of 'no evidence of disease activity' (NEDA) outcomes. In their opinion article Londoño and Moro consider the complexities of NEDA definitions and the role of such scores in clinical practice.

They authors remind us that the definition of NEDA as a marker of treatment failure and predictor of future clinical outcomes is subject to debate. While considering definitions of NEDA, it is perhaps also worth mentioning the work of Rio and colleagues (Multiple Sclerosis. 2009 Jul;15(7):848–53.), which suggests that radiological evidence of disease activity does not necessarily translate into a significantly increased short-term risk of clinical disease activity.

The authors consider the limitations of using EDSS scores as a marker of clinical progression, to which could perhaps be added the difficulties determining if an episode of symptoms is due to inflammation (Tallantyre *et al.* 2015[1]) They also highlight that MRI measures of lesion accrual or brain atrophy may still overlook clinically relevant disease activity, and that fluid biomarkers may also provide relevant indicators of evolving pathology.

On reviewing the work of Rotstein *et al.* (2015)[2] the authors note that 'loss of NEDA status due to changes in expanded disability status scale (EDSS), which is a method of rating impairment in neurological functions excluding cognition, was infrequent.' While less frequent than relapses, the figures for people with established MS shown in Table 2 (if I have read these correctly) suggest that by 7 years about 20% of those with evidence of clinical activity had progression without relapses (74% had evidence of either progression or relapse, 59% had had a relapse, implying that 15% had progression without a relapse).

The authors 'support the concept that the methodology used to determine the stage of disease should be based on the measuring of the level of biomarkers involved in the inflammatory and neurodegenerative events of disease'. This touches on an interesting line of thought on differentiating MS subtypes, which clinically can be difficult (and I am not aware of any biomarkers that substantially improve on this on a person-by-person basis), and how this relates to definitions of NEDA or ongoing clinically relevant disease activity. With regard to clinical outcomes, while NEDA definitions include both relapses and disability progression, the two may not be closely linked (Vukusic and Confavreux 2007[3]). As such, predictors of the risk of future relapses and risk of non-relapse associated progression may differ, and similarly composite scores designed to predict these outcomes may not necessarily be the same, or applicable to all MS subtypes equally. It would be interesting to hear more of the authors' thoughts on this.

In the abstract, the authors state that 'A protocol of evaluation based on the use of validated biomarkers that is conducted at an early stage of disease would permit the capture of abnormal neuroimmunological phenomena and lead towards intervention with modifying therapy before tissue damage has been reached.' However, there are perhaps some qualifications to this if a biomarker protocol is going to be useful in clinical practice, for example that the biomarkers used need to be (alone or in combination) reliable markers of disease activity at the level of individual people with MS, and that the pathological processes they reflect can be effectively targeted by treatments.

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**Is the topic of the opinion article discussed accurately in the context of the current literature?**
Yes

**Are all factual statements correct and adequately supported by citations?**
Partly

**Are arguments sufficiently supported by evidence from the published literature?**
Yes

**Are the conclusions drawn balanced and justified on the basis of the presented arguments?**
Yes

*Competing Interests:* Declan Chard has received research support from the MS Society of Great Britain and Northern Ireland, and the National Institute for Health Research University College London Hospitals Biomedical Research Centre. He has received honoraria (paid to his employer) from Ismar Healthcare NV, Swiss MS Society, Excemed (previously Serono Symposia International Foundation), Merck, Bayer and Teva for faculty-led education work; Teva for advisory board work; meeting expenses from Merck, Teva, Novartis, the MS Trust and National MS Society; and has previously held stock in GlaxoSmithKline.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 12 Jun 2017

**Carlos Mora**, Georgetown University Hospital, Washington DC, USA

We strongly appreciate the comments and input provided by the reviewers of the first version of our article. With especial interest in the comments and questions posed by reviewer 2 (Dr Chard) we acknowledge the work of Rio and colleagues (Multiple Sclerosis. 2009 Jul;15(7):848-53) and we take into consideration the fact that although the mentioned study was limited to the effect of one

disease modifying agent (IFNb given in four different commercially available preparations) on patients with the relapsing-remitting form of disease [RRMS] it showed that progression in at least two of the three variables analyzed (relapses, increase of disability or MRI activity) after 12 months would correlate with risk of progression of disease in the following years. However, this conclusion cannot be extrapolated to other groups of patients with RRMS who have happened to be treated with other disease modifying agents taking into consideration the different mode of action of these immune-modulators. In relation to the comment on our citation of Rotstein and colleagues (JAMA Neurol. 2015;72(2):152–158. 25531931 10.1001/jamaneurol.2014.3537) we extended the content of the sentence in the text reflecting that the loss of NEDA status due to changes in EDSS was infrequent in comparison to the level of determination provided by the clinical relapsing and imaging-related biomarkers.

As for the invitation to comment on how the different MS sub-types may correlate to definitions of NEDA or ongoing clinically relevant disease activity we concur with the fact that although NEDA definitions include both relapses and disability progression, the two may not be closely linked and, therefore, a different set of biomarkers ought to be validated to determine forthcoming inflammation and/or neurodegeneration. On the other hand, differentiation of sub-types of disease (especially in reference to inflammatory vs. degenerative pathologic processes) will be feasible with the forthcoming application of biomarkers in the MS related clinical practice. NEDA may not be a useful tool for the evaluation of patients with PPMS taking into consideration that this sub-type of MS is characterized by on-going disability and minimal inflammatory activity in MRI. At present, with the development of new medications for the treatment of PPMS, it would be essential to count with measurable biomarkers which would allow the determination of an objective response to therapies.

***Competing Interests:*** No competing interests to disclose

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Referee Report 02 May 2017

✔ **Hans Lassmann**

Center for Brain Research, Medical University of Vienna, Vienna, Austria

This opinion article deals with a highly relevant topic, the validity of the concept of no evidence for disease activity "NEDA" in multiple sclerosis.  Prevention of disease progression may possibly be achieved in patients, when treatment completely blocks ongoing disease activity and NEDA has been suggested as a tool to check, whether this is achieved in individual patients. However, clinical detection of disease activity, as suggested in the NEDA concept is far from being complete. Thus, this opinion article suggests to supplement current NEDA criteria with additional para-clinical markers. Such potential biomarkers are non-conventional new MRI sequences, magnetic resonance spectroscopy (N-acetyl aspartate) for evaluation of mitochondrial injury and biochemical markers such as chitinase 3, neurofilament or glial fibrillary acidic protein in the cerebrospinal fluid.  Whether these additional markers will increase the reliability of NEDA criteria, will have to be established in prospective clinical studies. However, so far none of them are perfect para-clinical predictors of disease activity and currently no tools are available to monitor major pathological substrates of disease progression in MS, such as for instance the dynamic development of demyelinating lesions in the cortex, the expansion of pre-existing white matter lesions or the presence of more subtle changes within the normal appearing white and grey matter of the MS brain.

**Is the topic of the opinion article discussed accurately in the context of the current literature?**
Yes

**Are all factual statements correct and adequately supported by citations?**
Yes

**Are arguments sufficiently supported by evidence from the published literature?**
Yes

**Are the conclusions drawn balanced and justified on the basis of the presented arguments?**
Yes

*Competing Interests:* No competing interests were disclosed.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**