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Review article

"No evidence of disease activity": Is it an aspirational therapeutic goal in multiple sclerosis?

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ABSTRACT

'No evidence of disease activity' (NEDA) that has been identified as a potential outcome measure for the evaluation of DMTs effects. The concept has been adopted from other diseases such as cancer where treatment is intended to free the patient from the disease. Disease-free status has been substituted by NEDA in MS, since we are limited when it comes to fully evaluating the underlying disease. In general, NEDA, otherwise termed as NEDA-3, is defined by the lack of disease activity based on the absence of clinical relapses, disability progression with the expanded disability status score (EDSS), and radiological activity. Recently, brain atrophy, a highly predictive marker of disability progression, has been added as a fourth component (NEDA-4). The use of this composite allowed a more comprehensive assessment of the disease activity. Indeed, it has an important role in clinical trials as a secondary outcome in addition to primary endpoints. However, the evidence is insufficient regarding the ability of NEDA to predict future disability and treatment response. Moreover, combining different composites does not eliminate the limitation of each, therefore the use of NEDA in clinical routine is still not implemented. The aim of this review is first to report from the literature the available definitions of NEDA and its different variants, and second, evaluate the importance of its use as a surrogate marker to assess the efficacy of different DMTs.

aHSCT:	autologous hematopoietic stem cell transplantation
BVL:	brain volume loss
CSF:	cerebrospinal fluid
DMT:	disease-modifying treatment
EDSS:	expanded disability status score
IFN- β:	interferon β
MEDA:	minimal evidence of disease activity
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
NDO:	negative disability outcome
NEDA:	no evidence of disease activity
NEP:	no evidence of progression
NEPAD:	no evidence of progression or active disease
OCT:	optical coherence tomography
PBVC:	percentage of brain volume change
RRMS:	relapsing remitting multiple sclerosis
SDMT:	symbol digit modality test

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease of the central nervous system that leads to demyelination and neurodegeneration (Compston and Coles, 2002). MS diagnosis is based on the integration of the clinical presentation which relies on a comprehensive history taking and neurological examination, and paraclinical markers with the most important being magnetic resonance imaging (MRI). Indeed, imaging has become an important tool to support the diagnosis of MS, rule out other diseases, determine prognosis, and long term follow-up (Thompson et al., 2018). Based on the load and distribution of lesions, number of active lesions, as well as the extent of brain and spinal cord atrophy, the radiological pattern in MS is described as highly heterogeneous (Lucchinetti et al., 2000; Stankoff et al., 2018). Given this heterogeneity, the effectiveness of certain disease-modifying treatments (DMT) differ among patients. Currently, there are over fourteen DMTs that have been proven to improve the course of the relapsing disease and slow MS progression (Rudick et al., 2005; Trojano et al., 2011). The emergence of more effective

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DMTs widened the treatment choices for patients and posed a great challenge upon neurologists to decide on the most appropriate therapy. Generally, it is agreed to initiate treatment early and effectively as it has been shown to improve long-term outcome, with an aim of achieving complete remission. One of the main challenges remains to predict early treatment response. Therefore, it is crucial to create surrogate markers allowing the evaluation of therapeutic interventions effect; early failure or response to a certain DMT and rationalizing treatment switch.

'No evidence of disease activity' (NEDA) has been suggested as a potential outcome measure to evaluate the effect of DMTs. The concept has been adopted from other diseases such as cancer where treatment is intended to free the patient from the disease. Disease-free status has been substituted by NEDA in MS, since we are limited when it comes to fully evaluating the underlying disease (Rotstein et al., 2015). In general, NEDA, otherwise termed as NEDA-3, is defined by (1) the lack of disease activity based on the absence of clinical relapses, (2) disability progression with the expanded disability status score (EDSS), and (3) radiological activity. Recently, brain atrophy, a highly predictive marker of disability progression, has been added as a fourth component (NEDA-4). The use of this composite allowed a more comprehensive assessment of the disease activity. Indeed, it has an important role in clinical trials as a secondary outcome in addition to primary endpoints. However, the evidence is insufficient regarding the ability of NEDA to predict future disability and treatment response. Moreover, combining different composites does not eliminate the limitation of each, therefore the use of NEDA in clinical routine is still not implemented (Hegen et al., 2018).

Here, our aim was to review the literature for the available definitions of NEDA and its different variants. We also reviewed the importance of its use as a surrogate marker to assess the efficacy of different DMTs.

Methods

A search of multiple electronic databases was done in March 2019 including PubMed, MEDLINE and Cochrane Library. Keywords included "multiple sclerosis", "no evidence of disease activity", and "MRI." As a result, 413 articles were identified. Duplicates, articles not written in English, and those not including MS patients or investigating NEDA were excluded. Two of the authors screened articles by title and abstract and retained 98. Extracted data included details on subjects' characteristics, methods, outcomes, and results. Finally, articles were divided based on the NEDA version: articles evaluating only NEDA-3, and articles evaluating NEDA-4 in relation to or not NEDA-3.

NEDA-3

NEDA-3 is achieved when patients are presented with no relapses, no

Table. 1
Summary of NEDA-3 trials.

References	Trial name	NEDA type	Subjects	DMTs	Results
(Havrdova et al., 2009)	AFFIRM	1st NEDA concept *-No radiological activity* *-No clinical activity*	904 RRMS	600 on Natalizumab vs. 304 on Placebo	Over 2 years: 37% vs 7%
(Prosperini et al., 2016)	-	NEDA-3 *-Absence of relapses* *-Absence of confirmed disability worsening* *-Absence of radiological activity (MRI brain and spinal cord)*	152 RRMS	Natalizumab	Over 7 years:34%
(Cohen et al., 2016)	TRANSFORMS (extension)	NEDA *-No relapses* *-No 3-month disability progression* *-No MRI activity*	924 RRMS	628 on Fingolimod 0.5or 1.25mg vs. 296 on IFN b-1a	Year 1: 63.4% Vs 44.3%
			870 RRMS	588 continued Fingolimod 0.5or 1.25 mg vs. 282 previously on IFN b-1a, switched to fingolimod	Year 2: 69% vs 66%
(Arnold et al., 2017)	ADVANCE	NEDA *-No evidence of clinical disease activity* *-No evidence of MRI disease activity*	1012 RRMS	512 on PegIFN b-1a every 2 weeks vs. 500 on delayed treatment	Over 2 years: 37% vs 16%
(Coles et al., 2017)	CARE-MS II	NEDA *-Absence of both clinical activity* *-Absence of MRI lesion activity (absence of both new Gd-enhancing and new/enlarging T2 hyperintense lesions)*	Year 3: 393 RRMS Year 4: 387 RRMS Year 5: 367 RRMS	Alemtuzumab	Year 3: 52.9% Year 4: 54.2% Year 5: 58.2%
(Arnold et al., 2018)	ADVANCE & ATTAIN	NEDA *-No evidence of clinical disease activity* *-No evidence of MRI disease activity*	727 RRMS	374 on PegIFN b-1a every 2 weeks vs. 353 on PegIFN b-1a every 4 weeks	Over 2 years: 27.3% vs 15.9%
			692 RRMS	354 on PegIFN b-1a every 2 weeks vs. 338 on PegIFN b-1a every 4 weeks	Through year 3: 20.9% Vs 13.9%
			639 RRMS	322 on PegIFN b-1a every 2 weeks vs. 317 on PegIFN b-1a every 4 weeks	Over 4 years: 15.8% vs. 10.7%
(Havrdová et al., 2018)	OPERA I & OPERA II	NEDA *-Absence of protocol-defined relapses;* *-Absence of 12-week CDP* *-Absence of new or enlarging T2 lesions and T1 gadolinium-enhancing lesions*	1520 RRMS	761 on Ocrelizumab vs. 759 on IFN b-1a	2 years: 47.7% Vs 27.1%

IFN b-1a: interferon β-1a; Peg IFN b-1a: Pegenterferon β-1a; RRMS: Relapsing-Remitting Multiple Sclerosis patients.

disability progression, and no MRI activity. The first composite of NEDA is the absence of a relapse (interchangeably used with the terms attack and exacerbation). A relapse is defined as an acute or subacute single episode of focal neurologic symptoms reported by the patient lasting at least 24 h, with or without recovery, in the absence of fever or infection. Suggestive presentations might include unilateral optic neuritis, partial transverse myelitis, and cerebellar or brainstem syndrome. The subjective symptoms should be supported by objective clinical or para-clinical findings that reflect a single or multifocal inflammatory demyelinating event in the central nervous system. Such objective findings include abnormality on neurological exam, imaging (MRI or optical coherence tomography (OCT)) or electrophysiological testing such as visual evoked potential corresponding to the anatomic location suggested by the current or historical symptoms (Thompson et al., 2018).

The second composite of NEDA is the absence of disability progression, defined as physical disability and it's worsening over the disease course. It is most commonly evaluated using the EDSS, which has the ability to predict the level of handicap (Degenhardt et al., 2009). Progression is defined by an EDSS increase of 1.5or more if the EDSS baseline score was zero, by an increase of one if the baseline is strictly less than 5.5, and by an increase of 0.5 if the baseline is 5.5or more. The worsening in EDSS score should be sustained and confirmed in the subsequent clinical visit six months later (Prosperini et al., 2018; Rotstein et al., 2015).

The third and final composite of NEDA is the absence of radiological activity. MRI sensitivity is greater than clinical measures (Barkhof, 2002). Radiological activity was defined as occurrence of contrast-enhancing lesions on T1-weighted or new/enlarging hyperintense lesions on T2-weighted brain or spinal cord MRI (Giovannoni et al., 2015). As the need to find an outcome measure in clinical trials grows, the percentage of patients achieving NEDA-3 is being evaluated to assess the efficacy of DMTs. Table 1 reports the results of DMT trials looking at NEDA-3 as an outcome measure of absence of disease progression.

Autologous hematopoietic stem cell transplantation (aHSCT) might be an alternative treatment option that is being investigated for patients with an aggressive MS course and failing to respond to multiple treatment lines. Careful selection of MS patients who will undergo aHSCT should be done as patients with certain characteristic would benefit more and have less risk of mortality. Murano et al., showed that younger patients with a relapsing inflammatory disease course, who had previously failed no more than two DMTs, and had not reached a high level of disability, were the ideal population to undergo aHSCT (Muraro et al., 2017). In 2019, Burt et al. reported that patients with relapsing-remitting MS (RRMS) who underwent nonmyeloablative aHSCT had a prolonged time to disease progression compared with those who received DMTs. For the aHSCT group, NEDA-3 was reached by 98.1% at six months and one year, 93.3% at two years, 90.3% at three years, and 78.5% at four and five years, whereas for patients who received DMTs, NEDA-3 was maintained in 39.6% at six months, 20.8% at one year, 11.9% at two years, 5.93% at three years, and 2.97% at four and five years (Burt et al., 2019). Further investigations are still needed to assess long-term outcomes and safety of aHSCT. Sustaining long-term disease remission is hardly achievable even in patients treated with DMTs. Indeed, despite the DMTs, less than 9% of patients were able to maintain a long-term NEDA-3 (seven years follow-up) and NEDA-4 (ten years follow-up) statuses (De Stefano et al., 2015; Rotstein et al., 2015). Patients enrolled in both studies received self-injectable DMTs, hence the need of more effective DMTs such as natalizumab to ensure a greater proportion of patients reaching NEDA (34% of patients treated with natalizumab maintained a NEDA-3 status over seven years Prosperini et al., 2016) However, even though monoclonal antibodies seem to match the efficacy of aHSCT, they have been unable to achieve long-term NEDA, as aHSCT did (Soelberg Sorensen, 2016). Nonetheless, due to its high treatment-associated mortality rate, aHSCT risk-benefit profile is inferior to that of new monoclonal antibodies.

NEDA-4

In 2010, De Stefano et al. highlighted the progression of brain volume loss (BVL) throughout the course of MS independently of its subtype (De Stefano et al., 2010). BVL has also been shown to be a strong predictor of disability in MS (Fisher et al., 2002; Jacobsen et al., 2014). Since NEDA-3 is more weighted towards the inflammatory activity and addresses to a lesser extent other pathophysiological mechanisms such as diffuse damage and neurodegeneration (Ziemssen et al., 2016), it may not be sufficient to detect cognitive deterioration and thereby predict long-term disability. Adding brain volume loss to the NEDA-3 components is therefore reasonable for a better assessment of disease worsening and progression. Kappos et al. defined NEDA-4 as no evidence of relapses, new or enlarged T2 lesions and 6-month confirmed disability progression (defined as an increase in EDSS score of 1.5 points from a baseline score of 0, of 1.0 point from a baseline score of 1.0or more, or of 0.5 points from a baseline score of greater than 5.0), and a mean annual rate-BVL of less than 0.4%. Table 2 reports the results of DMT trials looking at NEDA-4 as an outcome measure of absence of disease progression.

NEDA limitations

The ability of NEDA to predict future disability was evaluated in few studies and was contradictory. Rotstein et al. (2015) showed that NEDA-3 has a positive predictive value as it allows improved early prediction of future stability than individual component. Rio et al. showed that MS patients treated with interferon-B and sustained NEDA at one year remained free of disease activity over the long-term (Río et al., 2018). Both studies showed also that early loss of NEDA status was correlated with greater risk of disability in the middle to long term. However, not all patients who were unable to sustain NEDA had a poor prognosis which could be explained by the fact that components of NEDA are not well balanced (the appearance of one new lesion is as significant as a disabling relapse) and clinical information dichotomized (appearance of a single lesion is not similar to appearance of nine new lesions). Moreover, a large prospective cohort study did not establish the ability of NEDA to predict future disability (Uher et al., 2017).

One of NEDA measures' major limitations is the frequency of evaluation. Indeed, the persistence of NEDA is highly dependent on the frequency of clinical examinations and MRIs. The more the patient is contacted, the better the chance they recall events of a relapse, and the more MRIs are acquired, the better the chances of finding new lesions and rendering the patient non-NEDA. Standardizing the frequency of clinical and imaging assessment will be an important step in harmonizing data across clinical trials and in real-life situations. In addition, the requirement of standardized MRI protocols and potentially adding image processing pipelines, would make NEDA assessment feasible only at dedicated MS centers.

NEDA has some serious limitations that need to be considered thoroughly. To understand the potentials of NEDA, it is of utmost importance to discuss the drawback of each component, as their limitation is not eliminated when combined together.

5.1 Relapse rate detection

Assessing for a relapse as an outcome measure has many limitations. An extended period of observation is required to verify whether a treatment is effective in decreasing relapse rate, as the occurrence of a relapse is rare. In different clinical trials, the time point on which NEDA is assessed varies, thereby implying that relapses on a certain treatment might be underreported (Hegen et al., 2018). Although the main definition of a relapse is clear, relapse rate also depends on its confirmation. In fact, whether the clinician confirm it by the mere presence of subjective symptoms reported by the patient without presence of objective

Table. 2
Summary of NEDA-3 vs NEDA-4 trials.

References	Trial name	NEDA type	Subjects	DMTs	Results
(Kappos et al., 2016)	FREEDOMS & FREEDOMS II	NEDA-4 - *No clinical activity* - *No radiological activity* - *Brain volume loss (BVL)*	1731 RRMS	Fingolimod	Over 2 years: 31% vs. 19.7%
(Uher et al., 2017)	-	NEDA-4 - *No clinical activity* - *No radiological activity* - *Brain volume loss (BVL)*	192 CIS & 162 RRMS	Weekly intramuscular IFN b-1a	Over 4 years: 10.1% of CIS and 3.3% of RRMS patients achieved NEDA-3 4.6% of CIS and 1% of RRMS achieved NEDA-4
(Yokote et al., 2018)	-	NEDA-4 - *No clinical activity* - *No radiological activity* - *Brain volume loss (BVL)*	22 RRMS	No treatment IFN b-1a Fingolimod Azathioprine Natalizumab	Over 2 years: 14 achieved NEDA-3 9 of whom had significant BVL and were receiving IFN-b-1a
(Goodin et al., 2019)	-	Clinical NEDA - *No clinical activity (absence of relapses or EDSS progression)* NEDA-3 - *No clinical activity* - *No radiological activity* NEDA-4 - *No clinical activity* - *No radiological activity* - *No Brain volume loss (BVL)* NDO - *death,* - *Need for wheelchair* - *EDSS ⩾6* - *Progressive MS*	245 and 371 RRMS at 16 and 21 years	IFN b-1b	Clinical NEDA predicted NDOs at 16 years. However, the addition of further components to clinical NEDA did not add any predictive capacity

CIS: Clinically isolated syndrome; IFN b-1a: interferon β-1a; IFN b-1b: interferon β-1b.

change or whether an increase in functional system or EDSS score is needed to be confirmed by a neurologist, highly impacts the rate of being classified as NEDA or not (Sorensen et al., 2011). Finally documenting the presence of a relapse does not account for the type, severity and extent of remission; all of which carry important prognostic factors and determine the time needed to reach disability or the progressive phase (Confavreux et al., 2003; Runmarker and Andersen, 1993; Weinshenker et al., 1991).

5.2 EDSS scoring

The second composite also has limitations; EDSS score is mainly driven by walking impairment (Nygaard et al., 2015; Stangel et al., 2015) and worsening in cognitive or upper extremity function will not be reflected (Damasceno et al., 2016). Moreover, EDSS does not reveal worsening in a linear way as greater changes are observed for lower scores (Hohol et al., 1999). Similarly, EDSS assessment is majorly dependent on the degree of the rater's expertise. It is therefore why most clinical trials assign training sessions to ensure consistency and also demand that only one neurologist perform the assessment of EDSS for any given patient in order to reduce measurement error (Gray and Butzkueven, 2008; Rudick et al., 2010). Finally, prolonged periods of observation are required to document disability progression. Standardization is needed to unify the definition of disability worsening (as some trial included only EDSS assessment while other included 9-HPT or neurocognitive function), and the time period after worsening required to verify this progression (the time ranged between three and twelve months).

Applying NEDA on individual patients may also present different obstacles, as the follow-up in clinical trials differs for that in a clinical setting. In clinical practice, the patients are being followed every six to twelve months depending on their status and disease stability. Therefore, EDSS assessment might not be available every three or six months. In the analysis of a clinical trial results, the duration of confirmed disability progression was defined as having no three-month disability progression (Cohen et al., 2016).

5.3 MRI measures

MRI sensitivity is known to be greater than clinical measures. Indeed, it may take several years to detect relapses or disability progression, whereas MRI has the greater ability to identify lesions especially in the early phases of the disease. However, there is no standardization in regard to either image acquirement techniques (use of pulse sequence or spatial resolution) or image analyses. High quality images and skilled neuro-radiologist (Hannoun et al., 2018) are both important factors needed to determine new/enlarging T2-lesions (Guevara et al., 2019). Multiple factors can delay or even prevent detecting new/enlarging T2-lesions including an MS patient with a high lesion load, inadequate repositioning of serial scans, inter-observer variability (Cross and Naismith, 2014), MRI field strength (1.5T *vs.* 3T), acquisition parameters (2D *vs.* 3D), and image resolution and quality (Hannoun et al., 2018). Furthermore, analyzing the images can be either done manually or semi-automatically therefore counting T2-lesions is subject to high variability. The frequency of performing MRIs is also an important issue that needs to be standardized. The more frequent assessments are performed, the more lesions are reported, and the less favorable NEDA outcome is. While infrequent MRI performance may be influenced by accidental findings or underreporting of lesion load changes (Huppertz et al., 2010; Lai et al., 1996).

There are many limitations with regards to brain atrophy assessment. Brain volume is highly affected by social factors such as consumption of alcohol and cigarette smoking as well as existing comorbidities including diabetes or vascular risk factors (Enzinger et al., 2005). Technically, it is also highly dependent on imaging techniques (as previously reported) and analysis. Indeed, nowadays there is no gold-standard software for the assessment of atrophy, multiple studies have already reported high variability between various available software for atrophy measurement (Durand-Dubief et al., 2012; Hannoun et al., 2019). Atrophy measurement is therefore not usually assessed in routine clinical practice (Weinstock-Guttman et al., 2018), but if applied, will be prone to high variability. Moreover, within a

short period of time the effect size of BVL is minimal. The concept of pseudoatrophy should also be taken into consideration; BVL is highly dependent on the time of MRI with regards to the start of DMT as it decreases considerably the first year of treatment and then stabilize to a certain degree during later periods (Jacobsen et al., 2014). NEDA-4 should therefore be tentatively assessed. It is recommended to apply a standardized MRI protocol for MS patients throughout their follow-up, in order to ensure a proper BVL measurement and limit any biases arising from image quality variabilities (Cotton et al., 2015; Simon et al., 2006; Traboulsee et al., 2016). In case of multicentric studies, standardized MRI protocols should also be implemented to reduce interference of field strength and image acquisition on the signal of the images (Vrenken et al., 2013). Consequently, comparing NEDA-4 studies should be prone to several criteria including the choice of MRI sequences, field strength, and image processing technique as well as imaging frequency (that varies in clinical trials from six to twelve months more or less).

Other definitions of NEDA and potential markers of disease progression

More advanced imaging techniques can nowadays provide better insight into neurodegenerative and inflammatory processes (Filippi et al., 2014; Mahajan and Ontaneda, 2017; Smith et al., 2017). For instance, diffusion tensor imaging was able to detect brain white matter microstructural injury in RRMS patients achieving NEDA-3 status (Harel et al., 2018), whereas magnetization transfer ratio imaging has been found to be sensitive to cortical (Button et al., 2013) and deep gray matter (Fjær et al., 2013) demyelination. Additionally, EDSS, currently and widely used in clinical practice (Çinar and Yorgun, 2018), has limited ability to detect all signs of ongoing disability progression or cognitive impairment (Balabanov et al., 2014; Cadavid et al., 2017). As a result, Wolinsky et al. (2018) added 9-hole peg test and timed 25-foot walk to NEDA-3 components thereby introducing: “No Evidence of Progression or Active Disease (NEPAD)”. Damasceno et al. even assessed cognition and brain atrophy and their contribution to the NEDA-3 status. More than half of the patients achieving NEDA-3 presented a worsening in two or more cognitive domains. Ergo, the importance of adding cognitive components to NEDA-3 components (Damasceno et al., 2016).

6.1 NEPAD: No evidence of progression or active disease

In Wolinsky et al. (2018) applied two novel outcome measures on the ORATORIO trial that included 732 PPMS patients: no evidence of progression (NEP) and NEPAD. NEP was defined as absence of confirmed clinical progression over a twelve weeks period, which included absence of: disability progression on EDSS, progression of 20% or more in both 9-hole peg test and/or timed 25-foot walk test. NEPAD however, was defined as no MRI-measured activity (absence of new or enlarging T2 lesions, and T1 gadolinium-enhancing lesions), and absence of protocol defined relapses in addition to NEP (Wolinsky et al., 2018). The 20% cut-off point for both 9-hole peg test and timed 25-foot walk was defined by Bosma et al. (2010) and later confirmed by Cadavid et al. (2017) for an optimal assessment of disease progression with the “MS Functional Composite” components.

From baseline to week 120, 29.9% of patients on Ocrelizumab achieved NEPAD versus 9.4% on placebo. Also, 70.3% patients on Ocrelizumab showed no evidence of brain MRI activity versus 26.5% subjects on placebo. Hence, MRI activity remains a dominant component in determining NEPAD outcome. NEPAD may be considered a more comprehensive and clinically meaningful endpoint especially in patients with PPMS. Further studies are required to determine if NEPAD sustained over 120 weeks will be reflected on the long term in patients with PPMS (Wolinsky et al., 2018).

6.2 MEDA: Minimal evidence of disease activity

As NEDA is considered a difficult and strict goal to achieve, minimal evidence of disease activity (MEDA) is proposed to have a more realistic goal (Gasperini et al., 2019; Prosperini et al., 2017). In a longitudinal study, Río et al. explored the impact and effect of different measures of disease activity (clinical and radiological) on 516 RRMS patients during interferon-beta therapy. MEDA was defined as having one relapse, less than three new T2-lesions or less than two gadolinium-enhancing lesions during the first year of treatment. Results showed that early significant clinical or radiological activity are predictors of long-term worsening. However, MEDA did not predict the risk of EDSS worsening during the long-term follow-up of seven years (Río et al., 2018).

6.3 NEDA-5

Multiple studies suggested the inclusion of fluid biomarkers, particularly cerebrospinal fluid (CSF) or serum neurofilament (NfL) levels to the NEDA-3 components (Bonnan et al., 2017; Giovannoni et al., 2018). CSF NfL levels at diagnosis are markers of neurodegeneration and seem to predict long-term clinical outcome in MS (Lu et al., 2018; Salzer et al., 2010). However, due to patient discomfort and various practical issues, the use of CSF biomarkers is limited as opposed to the blood and serum testing which is more accessible during clinical follow-up. Nonetheless, several studies have already shown a reasonable correlation between both CSF and serum NfL measures (Disanto et al., 2017; Håkansson et al., 2018; Kuhle et al., 2016; Novakova et al., 2017; Varhaug et al., 2018), highlighting its potential use as biomarker for disease progression (Kuhle et al., 2016). Indeed, Barro et al. demonstrated that a higher serum NfL level is associated with concurrent and future clinical (EDSS progression) and MRI measures (T2-lesion load and atrophy) of disease activity and severity (Barro et al., 2018). Regardless, due to their lower levels and a high variability, serum/CSF correlation should be further investigated in larger trials (Bergman et al., 2016; Kuhle et al., 2016).

6.4 Potential markers of disease progression

OCT was also suggested as a measure since it detects neurodegeneration and inflammation and therefore subclinical changes in MS (Lambe et al., 2018; Smith et al., 2017).

Neuropsychiatric testing was additionally found to be associated with physical disability in MS (Lynch et al., 2005). More recently, in a prospective study, 20 naïve pediatric-onset MS patients were started on natalizumab for a two year follow-up to study of efficacy and safety (Margoni et al., 2019). The main outcome of this study was based on NEDA-3-plus which included no cognition decline as a fourth component to NEDA-3. Cognitive decline was defined as a decrease of four points or more in the Symbol Digit Modality Test (SDMT) score compared to the baseline value (Margoni et al., 2019; Pardini et al., 2014). At month 24, compared to baseline, the mean SDMT value increased. However, this difference was not significant possibly due to the small sample of subjects. A decline in SDMT was only detected in two patients at months twelve and 24 (Margoni et al., 2019).

Conclusion

An increasing number of available DMTs provided patients with a slower progression of disease activity and worsening. Consequently, the definition of an appropriate treatment plan is of utmost importance to ensure patient stability. NEDA-3 clinical and radiological components have already been implemented in clinical practice and have shown some promise (Kappos et al., 2016). However, it is strongly biased towards inflammatory activity and does not take into account other underlying pathogenesis such as neurodegeneration. It is therefore important to constantly update the definition of NEDA with new markers

of disease progression, to meet the rising need to set a standardized outcome to compare different DMTs (Giovannoni et al., 2015). For instance, neurofilament considered as markers of axonal damage (Giovannoni and Nath, 2011; Lu et al., 2018), are potential prognostic biomarker for disease progression (Giovannoni and Nath, 2011; Varhaug et al., 2019). Similarly, OCT and/or neuropsychiatric testing addition to the NEDA-3 components may improve measurement of disability progression (Smith et al., 2017). Nonetheless, the predictive value of combining various measures of disease activity on the long-term outcome needs further investigation.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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