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REVIEW

Therapeutic Targets for Multiple Sclerosis: Current Treatment Goals and Future Directions

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Abstract Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system, and the most common cause of nontraumatic disability in young adults. Most patients have a relapsing–remitting course, and roughly half of them will eventually enter a degenerative progressive phase, marked by gradual accrual of disability over time in the absence of relapses. Early initiation of treatment has delayed the onset of disability progression. Thus, there is increased interest in treating to target in MS, particularly targeting no evidence of disease activity. This review will describe the most common treatment goals in MS: the Rio scores, disease-free survival, and no evidence of disease activity. We will also cover how well current disease-modifying therapies achieve no evidence of disease activity, and discuss future options for improving MS treatment targets.

Key Words NEDA no evidence of disease activity · Rio score · Multiple sclerosis · Relapsing remitting multiple sclerosis · Treatment goal · Disease activity · Disease modifying therapies

Introduction

Multiple sclerosis (MS) is an autoimmune central nervous system disease that leads to progressive and permanent disability in most patients. There are approximately 400,000 people in the USA who have been diagnosed with MS [1], and the prevalence appears to be increasing. MS is a chronic disease, with a typical age of onset of between 20 and 40 years [2, 3], and is the leading cause of nontraumatic neurologic disability in young adults [4, 5]. With 15 approved disease-modifying therapies (DMTs) ranging in efficacy and safety, the best treatment approach is uncertain. Determining the optimal treatment of MS is important given its impact on society. First, the total direct medical cost of MS (including DMT) can be as high as $54,000 per year per patient, which represents a total cost of $21.6 billion to the US economy annually [6]. Second, as the disease affects individuals during their working prime, the indirect cost of absenteeism, unemployment, and underemployment in both the patient and caregivers are estimated to add another $7.1 billion to the cost of MS care in the USA. Methods to control these costs are critical. Because the annual cost increases as the person with MS develops more disability, strategies that prevent or delay the degenerative stage of the disease are the goal until a cure is found [7].

MS pathogenesis is considered to comprise 2 components: focal inflammatory demyelination and degeneration [8]. Available DMTs primarily are of benefit in controlling the inflammatory aspect of the disease; however, once the degenerative component starts, those therapies are less efficacious. In the pre-DMT era, natural history studies showed that patients with relapsing MS generally would require a cane to walk 150 m within 20 years of diagnosis [9]. In the era of DMTs, recent studies suggest that the time to reach walking issues is extended with older DMTs [10, 11]. These observations support the concept of MS as a 2-phase disease and that an early therapeutic window exists [12–14]. Therefore, the goal is to prevent the disease from causing a critical level of inflammatory injury, that begets the degenerative phase of the disease [15].

Based on large epidemiological studies and clinical trials, the optimal treatment window closes relatively early in the disease course. This window possibly closes when the patient

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reaches an Expanded Disability Status Scale (EDSS) score of 3.0 [12–14]. After which disability is no longer driven by focal inflammatory processes, even if there is still some evidence of inflammation [12]. In light of this, MS practitioners are adopting treating to target strategies beyond only monitoring clinical relapses. The most common treat to target goals are the Rio score, the modified Rio score, and no evidence of disease activity (NEDA) (Table 1). As more highly efficacious DMTs have become available, NEDA has become the favored treat to target goal. This review will describe current treatment goals for MS and then focus on the evolution of the concept of NEDA, therapeutic success of DMTs achieving NEDA, and conclude with remarks on potential future improvements of NEDA targets.

Treatment Goals for MS

The Rio Score and the Modified Rio Score

In 2008, Rio and colleagues analyzed a cohort with relapsing–remitting MS to generate potential models that could predict a poor clinical response to interferon (IFN)-β at 1 year of treatment. The model that became the Rio score consisted of magnetic resonance imaging (MRI) and clinical data. The score ranges from 0 to 3, with a patient receiving 1 point each for ≥ 3 active MRI lesions, ≥ 1 relapse, or increase of ≥ 1 points on the EDSS for at least 6 months [16]. Patients with a score of ≥ 2 at 12 months were more likely to demonstrate disability progression or relapse than those with lower scores over the next 2 years [20]. The Rio score created a method of separating patients who appeared to be poor responders to IFN-β from those who would do well, allowing physicians to better tailor the patient's care to his/her needs.

The Rio score was revisited in 2012, and improved based on additional long-term data. The new score, the modified Rio Score, once again yielded a score of 0 to 3, with 1 point each for ≥ 6 lesions on MRI, or 1 relapse, and 2 points for ≥ 2 relapses at 1 year of treatment. The 6-month confirmed disability progression criterion was no longer used because of the poor intra- and inter-rater reliability of the EDSS, particularly at lower scores [21]. In the modified Rio score, scores of 0 represented responders, and scores ≥ 2 represented nonresponders. Initially, a score of 1 was indeterminate. Therefore, patients with a modified Rio score of 1 underwent a repeat analysis after an additional 6 months. If those patients had > 1 new lesion on a MRI or a relapse, they were considered nonresponders [20]. The Rio score has shown predictive value in different ethnic cohorts and among other DMTs. One strength of the modified Rio score is the ease of use during routine clinical care. A modified Rio score ≥ 2 suggests a 60% chance of worsening disability over the following 3 years, with a positive predictive value of 83% and negative predictive of 68% [16]. Patients determined to be nonresponders based on the modified Rio score probably would benefit from changing therapy to a more efficacious agent.

Table 1 Treatment goals for multiple sclerosis (MS)

Rio score [16]	1. Evaluated at 1 year a. MRI criterion = 1; if the patient had (on the yearly MRI scan) > 2 active T2 lesions, defined as new or enlarging T2-weighted lesions, plus the number of gadolinium-enhancing T1-weighted lesions over the first year b. Relapse criterion = 1; if the patient experienced ≥ 1 relapse over the first year c. EDSS progression criterion = 1; if there was an increase in the patient's EDSS score of ≥ 1 point, sustained over at least 6 months and confirmed at the end of the follow-up period [16] 2. Score a. ≥2 represent nonresponders b. ≤1 represented responders
Modified Rio score [16]	1. At 1 year: a. MRI criterion = 1; if the patient has had > 5 new T2 lesions; b. Relapse criterion: i) =1 if the patient experienced 1 relapse ii) =2 if the patient experienced ≥ 2 relapses 2. Score a. ≥ 2 represents nonresponders b. = 0 represent responders c. = 1 indeterminate require re-examination after an additional 6 months i. Considered responder if ≤ 1 new lesion on repeat MRI and no relapse ii. Considered nonresponder if ≥ 2 new lesions or have a relapse
NEDA3 [17]	1. No clinical relapses 2. No sustained disability progression 3. No gadolinium-enhancing lesions and no new or enlarging T2-hyperintense lesions on cranial MRI
NEDA4 [18]	1. No clinical relapses 2. No sustained disability progression 3. No gadolinium-enhancing lesions and no new or enlarging T2-hyperintense lesions oncranial MRI 4. Brain volume atrophy < 0.4%
DFS [19]	1. Time to death from any cause 2. Time to evidence of MS disease activity by: a. 3-month confirmed disability worsening b. Clinical relapse c. Greater than 2 new lesions on MRI

For those who fail to meet treatment goals then escalation of therapy should be considered

MRI magnetic resonance imaging, *EDSS* Expanded Disability Status Scale, *NEDA* no evidence of disease activity, *DFS* disease-free survival

Disease-Free Survival

Owing to its origins from oncology literature, the use of disease-free survival (DFS) in MS has been limited to a subset of autologous hematopoietic stem cell transplant (AHSCT)

trials in MS. In MS, DFS is defined as the time until the patient either dies from any cause or has evidence of MS disease activity. Evidence of MS disease activity can occur in 3 separate ways in DFS: 3-month confirmed disability worsening after 6 months of treatment, a clinical relapse, or > 2 new lesions on MRI. The most notable study using DFS would be HALT-MS, which explored the uses of high-dose immunosuppressive therapy that consisted of carmustine, etoposide, cytarabine, melphalan, and rabbit antithymocyte globulin as conditioning agents before an AHSCT. With that regimen, 78.4% were event-free at 3 years [19]. DFS has not been widely adopted is MS pharmaceutical clinical trials, in favor of NEDA.

NEDA

The NEDA concept first entered MS literature as a post-hoc analysis carried out by Havrdova et al. of the AFFIRM Trial [22]. In this analysis, 37% of patients in the natalizumab arm had freedom from both clinical and radiographic signs of disease activity. The authors called this combination the absence of disease activity, or disease activity-free. Eventually, the term disease activity-free evolved into what is now known as NEDA3 owing to it consisting of 3 parts [23]: absence of relapses, confirmed disability worsening measured by EDSS, and MRI lesion activity [22]. The NEDA3 has been utilized in post-hoc and prespecified analysis of trials conducted after the AFFRIM trial.

A potential weakness of NEDA3 was its stronger focus on the inflammatory components of the disease. While confirmed progression on EDSS accounts for some degenerative component of the disease, it is largely driven by walking disability and has limited ability to capture cognitive disability. Moreover, NEDA3 is not sensitive enough to capture subtle changes of inflammation and neurodegeneration that underlie disability. For example, half of those who meet NEDA3 still had cognitive decline at 2 years [24]. NEDA4 attempts to address this concern by adding brain volume loss as a surrogate for subtle pathophysiological processes contributing to disability progression. Some studies show that brain volume loss > 0.4%/year is a good long-term predictor of disability and cognitive function [25]. NEDA4 is starting to see more widespread use in clinical trials, but until brain volume loss (BVL) can be routinely measured in MS MRI sequences, NEDA3 will remain the treat to target goal in clinical practice [26].

Comparing Modified Rio Score, DFS, and NEDA

Advocates for using the less restrictive modified Rio score over NEDA point out that while any accumulation of new lesions on MRI is suboptimal, the of number of new lesions that indicates need for a treatment change is uncertain [27]. For example, a 15-year follow-up study of one of the initial IFN-β trials failed to prove that individuals who had ≥ 2 new T2 lesions on MRI had higher odds of worst disability progression quartile [28]. Advocates of the modified Rio score also argue that adhering to NEDA either through escalating therapies or adopting highly efficacious therapies first line, may expose patients to unnecessary risks and side effects without clear benefit [10, 27]. Also, NEDA3 criteria require EDSS monitoring not routinely done owing to time constraints. However, even with a modified Rio score of 0, there was an approximately 24% chance of demonstrating disability worsening [16]. With the newer highly efficacious therapies that can better suppress inflammation, modified Rio score is no longer sufficient as a treatment target as it allows for some disease activity during the critical treatment window.

As a treatment goal, DFS is in some ways a stricter endpoint goal and in other ways not. To fail DFS, a patient requires 2 new MRI lesions *versus* 1 required by NEDA. What makes DFS specifically stricter is that once someone has failed, that is it. NEDA, however, can be defined by any window of time. Sometimes NEDA can be used in a continue survival analysis. However, NEDA can also be measured in short time periods. In some trials, NEDA rates are published by year. Therefore, a patient can fail to meet NEDA criteria one year, but then meet it the following. Therefore, owing to the survival analysis nature of DFS, it can be considered a higher benchmark of disease suppression. However, use of DFS is mainly limited to AHSCT research, and has not been studied as much as modified Rio score or NEDA in everyday clinic use.

Advocates of NEDA argue that any evidence of disease suggests suboptimal treatment. In many smaller studies, individual MRI lesions do not appear to correlate with relapses and progressions; however, in a recent large scale meta-analysis, 61% of the variance of disability progression over a 2-year period, could be explained by accrual of T2 lesions [26]. This supports the concept that focal inflammation drives relapse and disease progression in the earliest stage of the disease [12]. By not stopping the focal inflammation early in the disease course, NEDA advocates believe that the therapeutic window could be missed. Furthermore, long-term studies exploring NEDA in MS have demonstrated that achieving NEDA for the first 2 years of treatment predicts lower odds of disability at 7 to 8 years [25, 29]. One study that failed to show benefit of NEDA at 2 years had patients with a mean disease duration of 7 years, which may have been past the therapeutic window, again suggesting the importance of achieving disease control within the critical time window. While critics point out that there are studies that suggest that NEDA is not predictive of progression, those studies are felt to be underpowered or suffer from methodological flaws [30]. Another criticism of NEDA is that it does not represent a cure and can lead to a false sense of security [31] as NEDA misses several factors that suggest ongoing disease activity like

meningeal inflammation, iron deposition in gray matter, atrophy of the brain and spinal cord, and changes in normal-appearing white matter that can only be detected with advanced imaging. Some studies suggest disability accrual may be a function of age, which NEDA3 fails to account for [32]. The criticisms regarding NEDA suggest that it does not capture enough information, but we feel an evolving definition of NEDA as new clinical metrics are explored will only improve treatment targets. In the meantime, we advocate for using NEDA3 to the full extent possible in clinical practice, rather than a less strict goal represented by modified Rio score.

Full adoption of NEDA as it currently is defined may be difficult to achieve in clinical practice. The most common reason for failure to maintain NEDA is radiographic activity, and is closely followed by clinical activity. Only a minority of patients fail as a result of clinical disease progression. This oversensitivity to the active inflammatory stage of the disease is one of the biggest criticisms of NEDA. If the changes that correlate best with long-term disability like brain and spinal cord atrophy are not considered, then missing known markers of disability may make NEDA a sensitive target for the inflammatory stage of the disease but not the degenerative stage. Further complicating targeting NEDA is that even in ideal clinical trial settings NEDA is achieved only 47.9% of the time. In a real-world cohort mimicking clinical practice, only 20.4% to 40% of patients maintained NEDA for 2 years. At long-term follow-up ranging from 7 to 10 years, > 90% of patients have lost NEDA status [29, 33]. Constantly changing therapy to chase the goal of NEDA may lead to endless escalation of therapy and progressively more toxic DMT side effects for an unachievable, and still not fully proven, long-term goal However, once again, these failures may not necessarily be a failure of NEDA as a treat to target goal, but a failure of current DMTs and missing the optimal treatment window.

Rate of Achieving NEDA with Current Therapies

There are increasing studies examining the rate of achieving NEDA for the available DMTs. Beginning with the AFFRIM trial, NEDA has been analyzed in almost every new pivotal DMT trial. Over the next few paragraphs, we will review the various DMTS and the rate of achieving NEDA in their respective trials. This information is summarized in Table 2 but is not intended as a cross-trial comparison. A more detailed review of DMT is contained in another article in this issue.

Natalizumab is a highly effective therapy and paved the way to discuss NEDA as a treatment target. In a post-hoc analysis, roughly 37% of patients achieved NEDA *versus* 7% on a true placebo. At the 8-year follow-up of the AFFRIM trial, those who were NEDA-positive in the first 2 years had significantly lower annual relapse rates, lower rates of confirmed EDSS progression, and higher rates of confirmed EDSS improvement than those who were NEDA-negative. Moreover, for those with highly active disease or breakthrough disease in IFN-1β, natalizumab achieved NEDA3 rates of 67% to 75% at 2 years [43]. The use of natalizumab appears to increase the odds of 2-year NEDA, leading to long-term benefit.

Another highly effective infusion therapy is alemtuzumab. In Care-MS1 and Care-MS2, patients on alemtuzumab achieved NEDA rates of 39% and 32%, respectively [19]. Moreover, recent data suggest that alemtuzumab can improve pre-existing disability [44]. Ocrelizumab is the most recent infusion to be approved. In OPERA I and OPERA II [40], 47% of patients achieved NEDA at 2 years. Fingolimod was the first oral therapy to be approved for the treatment for MS. Post-hoc analysis from the FREEDOMS trials demonstrates that fingolimod achieves NEDA3 in 33% of patients and NEDA4 in 19.7% of patients [18, 45]. Among patients who had either highly active disease and treatment naïve or had breakthrough disease and were on IFN-1β, fingolimod was able to induce NEDA3 in 42% to 67% of patients [43]. Another oral therapy increasingly used as first-line therapy is dimethyl fumarate. In post-hoc analysis, dimethyl fumarate achieved NEDA in 18% to 28% of patients [17, 46]. The last oral therapy available is teriflunomide, which demonstrated a 23% rate of NEDA in treated patients in post-hoc analysis from TESMO [17]. The last DMT to explore NEDA during its pivotal trial is daclizumab, where patients achieved NEDA rates of 24% to 39% in post-hoc analysis [41, 42].

For the platform-injectable therapies for MS, NEDA had not been conceptualized during their respective pivotal trials. Therefore, NEDA has mainly been measured in post-hoc analyses, serving as a comparator to more efficacious therapy. From the CONFIRM and COMBIRX trials, glatiramer acetate achieved NEDA rates in only 12% and 19% of patients, respectively [35, 46]. IFNs achieved NEDA rates of 13% to 29.2% [34, 35, 40, 47]. Pegylated IFN-β1a, specifically compared with placebo in a post-hoc analysis of the ADVANCE trial, achieved a NEDA rate of 33.9% [36].

Cladribine, was not approved in 2011 owing to safety concerns, but with long-term follow-up from CLARITY, the medication has been submitted for approval and is undergoing review by the European Medicines Agency. In the CLARITY trial, roughly 44% to 46% of patients achieved NEDA [37].

Autologous hematopoietic stem cells have been studied for the last 20 years for the treatment of MS. Multiple stem-cell trials demonstrated rates of DFS in the range of 60% to 80%, which is profoundly better than any conventional therapy [19, 38, 39, 48], but the overall number of participants remains small. In the HALT MS trial, 78.4% were event-free at 3 years [19]. At this time, the optimal hematopoietic stem cell transplant (HSCT) technique has not been determined, and trials have been limited to noncomparator cohort studies. While

Table 2 Rates of achieving no evidence of disease activity (NEDA) in trails of disease-modifying therapy (DMT)*

Trial	NEDA type	Duration of NEDA evaluated (y)	Treatment NEDA (%)	Comparator NEDA (%)
AFFIRM [22]	DAF	2	Natalizumab (37)	Placebo (7)
FREEDOMS [17]	NEDA3	2	Fingolimod (33)	Placebo (13)
FREEDOMS [17]	NEDA4	2	Fingolimod (19.7)	Placebo (5.3)
CARE MS 1 [34]	DAF	2	Alemtuzumab (39)	IFN-β1a (27)
CARE MS 1 [34]	DAF	2	Alemtuzumab (32)	IFN-β1a (14)
Define [17]	NEDA3	2	Dimethyl fumarate (28)	Placebo (15)
CONFRIM [17]	NEDA3	2	Dimethyl fumarate (18)	Glatiramer acetate (12)
TESMO [17]	NEDA3	2	Teriflunomide (23)	Placebo (14)
CombiRx [35]	NEDA3	3	Interferon + glatiramer acetate (33)	IFN-β1a (21) Glatiramer acetate (19)
ADVANCE [36]	NEDA3	1	Pegylated IFN-β1a (33.9)	Placebo (15.1)
CLARITY [37]	NEDA3	2	Cladribine (44)	Placebo (16)
Canadian HSCT phase 2 trial [38]	NEDA3	3	HSCT (69.6)	None
HALT-MS [19]	DFS	3	HSCT (78.4)	None
Northwestern HSCT [39]	DAF/NEDA3	2	HSCT (80)	None
OPERA I [40]	NEDA3	2	Ocrelizumab (47.9)	IFN-β1a (29.2)
OPERA II [40]	NEDA3	2	Ocrelizumab (47.5)	IFN-β1a (25.1)
DECIDE [41]	NEDA3	2	Daclizumab (24.3)	IFN-β1a (13.8)
SELECT [42]	NEDA3	2	Daclizumab (39)	IFN-β1a (11)

*Not intended to compare across trials

DAF disease activity free, *IFN* interferon, *HSCT* hematopoietic stem cell transplant, *DFS* disease-free survival

HSCT appears promising for MS, the treatment still comes with a high mortality rate of 1% to 5% [49]. Furthermore, HSCT has not been compared with newer, highly efficacious DMT, although a trial to accomplish this task has been proposed [48]. When comparison trials have been performed for other autoimmune diseases, HSCT was found to be no more effective than standard therapy with significantly higher toxicity [50]. Without a well-designed randomized control trial to compare the 2 therapies, HSCT will remain reserved for the most active and aggressive cases not controlled with the conventional therapies through clinical trials [51].

Treatment Strategies to Achieve NEDA

Determining the best treatment strategy in MS is difficult owing to its heterogeneity, chronicity, lack of understanding of the underlying process causing disease progression, and lack of treatments specifically targeting the mechanisms that underlie progression. The best treatment strategy during this crucial time window is an area of controversy, with some MS experts favoring an escalation approach and others favoring the initial use of highly effective agents.

The escalation approach to MS is the traditional treatment paradigm. By starting with the safest, albeit least efficacious, medications, neurologists focus on minimizing long-term safety risks. For the patients that breakthrough on the lower efficacious drugs, then their treatment is escalated to a more potent and potentially more toxic therapy. This escalation strategy can continue until the patients achieve disease remission, suffer intolerable side effects, or have adverse safety events. A criticism of this method is that the therapeutic window appears to close early in the disease, and a patient may no longer be in the ideal window to affect the progressive disease process by the time highly efficacious agents are started. To mitigate this risk, some proponents of escalation therapy recommended starting with a second-line or even a third-line therapy, especially in those with risk factors that portend to a more aggressive disease course [14].

The concept of using highly effective agents as initial therapy is becoming increasingly popular in the MS world. Neurologists point to the field of rheumatology, where the concept of escalation has been replaced by early aggressive treatment with highly efficacious therapy [52]. To most MS specialists, this would mean starting with therapies that would be considered second- and third-line like fingolimod, dimethyl fumarate, natalizumab, or ocrelizumab. However, some call for an even more aggressive approach or a true induction approach by using potent therapies like mitoxantrone, alemtuzumab, HSCT, or, potentially, cladribine. They argue that by achieving strong disease control early on, the courses of several rheumatologic conditions have been changed leading to improved quality of life and less radiographic evidence of disease [53]. After starting with these induction agents, treatment would either continue depending on the agent or potentially de-escalating therapy once disease suppression is achieved. In general, the induction and highly efficacious therapies have rare but potentially serious safety concerns. Consequently, most neurologists have reserved using the most aggressive therapeutic strategies to those with the most aggressive disease [54]. Clear treatment targets and biomarkers that help identify those who truly need the most aggressive approach are sorely lacking and prevent complete adoption of this initial treatment strategy.

Some MS centers have a hybrid approach. Using currently available tools to identify those with risk factors of aggressive MS (multiple enhancing lesions, presence of brainstem and spinal cord disease, frequent relapses with incomplete recovery) are identified and treated with more efficacious therapies from the start. For those without such factors, a more conservative, traditional escalation strategy is employed to avoid serious safety risks. This strategy still misses many patients who may not show worrisome signs until a few years into their disease course. While some factors like age, sex, location of prior relapses are known at diagnosis, other risk factors like poor relapse recovery, number and severity of relapses in the earlier years of the disease, and time to the second event can only be determined retrospectively. By waiting for the disease to declare itself, we may be missing the window of treatment and allowing patients to suffer permanent neurologic impairment prior to reaching appropriate therapy [54, 55]. This in itself argues towards the more aggressive approach of early use of highly efficacious therapies.

Treating to the target of NEDA can be used with any treatment strategy. However, we feel that the early use of highly efficacious therapies (i.e., fingolimod, natalizumab, and ocrelizumab) strategy balances the benefits of increased rates of achieving NEDA when compared with the escalation approach, while avoiding some of the serious side effects of the more toxic therapies (i.e., mitoxantrone, alemtuzumab, cladribine). HSCT may have a role in the future, but at this time is limited to clinical trials. In time, robust biomarkers of disease activity and predictors of disease progression may better settle the debate on escalation approach, early use of highly efficacious therapies approach, and most aggressive approach.

How to Improve Our Therapy Target

As mentioned previously, NEDA3 does not capture subtle inflammatory and neurodegenerative processes that underlie disability progression. NEDA4 has already been proposed but remains limited to research until imaging metrics for brain atrophy becomes widely available [56]. Other surrogates have been proposed, but more studies are needed to define cut-offs and validate the metrics. These include neuropsychiatric measures, evoked potentials, optical coherence tomography (OCT), laboratory testing, and advanced radiographic tests.

The easiest improvements would be those that can be implemented in routine clinical care, which can improve wide adoption of NEDA as a treatment target. The Multiple Sclerosis Functional Composite (MSFC) score, formal neuropsychiatric testing, or self-administered questionnaires are potential candidates. First, MSFC components of the timed 25-foot walk, the 9-hole peg test, and the paced auditory serial addition test can be easily implemented in the clinic by trained intake staff [57, 58] The MSFC metrics have been demonstrated to be associated with disability [59], which has led to a proposed addition to NEDA [60]. Implementing neuropsychiatric testing in clinical practice can address the problem of under-recognition of cognitive dysfunction, which is associated with radiographic measures of atrophy and physical disability [61, 62]. Several self-administered questionnaires like MS Neuropsychological Screening Questionnaire or the Multiple Sclerosis Impact Scale are shorter screening methods [59, 63] that can be utilized and may be completed by the patient prior to the appointment at home or while waiting in the office.

Other potential additions to NEDA would be evoked potentials, OCT, laboratory biomarkers, and advanced MRI metrics. One study showed that a combination of evoked potentials can predict disability at 6 years [64]. OCT can reliably examine and quantifiably measure the thickness of the retinal nerve fiber layers. The rate of atrophy of ganglion cell plus inner plexiform layer has been shown to correlate with whole brain and gray matter atrophy [65–67]. The retinal nerve fiber layer measurement has also been shown to be associated with disability and walking speed [67–69]. Overall, OCT may provide another method of detecting subtle subclinical changes in MS. The most promising laboratory biomarkers are the light subunit of neurofilaments and antimyelin oligodendrocyte glycoprotein, which correlate to axonal damage and predict a more aggressive course that could suggest the need for more efficacious therapeutic strategies [70]. Advanced MRI metrics

to detect changes in normal-appearing white matter that may be correlated to disability have also been proposed but are not yet validated for NEDA use.

Of the above discussed metrics, adding OCT and/or neuropsychiatric testing to NEDA3 as a treatment goal are the most practical, and may improve measurement of disability progression. Some MS centers are already incorporating these metrics in routine clinical care, which can provide future insight on the utility of these metrics as a treatment target.

Conclusions

At this time, there are 15 approved treatments for MS. The therapies have varying levels of efficacy and safety. There is not yet consensus on the best treatment strategy or treatment target. The modified Rio score is easy to implement and does not require special training but allows disease activity during the optimal treatment window, and therefore misses the opportunity to prevent disability progression. NEDA3 is becoming increasingly favored as more highly efficacious therapies become approved. The more recent therapies used NEDA as a target in the pivotal trials which can allow for better comparisons of treatment efficacy. However, NEDA3 is harder to implement in routine clinical practice. More studies are required to optimize NEDA elements. The potential metrics that can be more readily implemented included neuropsychiatric testing, OCT and brain atrophy, but as these are not widely available, remain restricted to specialized MS centers or research. As more tools are being developed to measure disease and disability, the focus should be on how to incorporate new metrics into NEDA so that as a treatment target it can be widely adopted, guide treatment decisions and optimize treatment windows, and can truly achieve the primary goal of disability prevention in MS care.

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