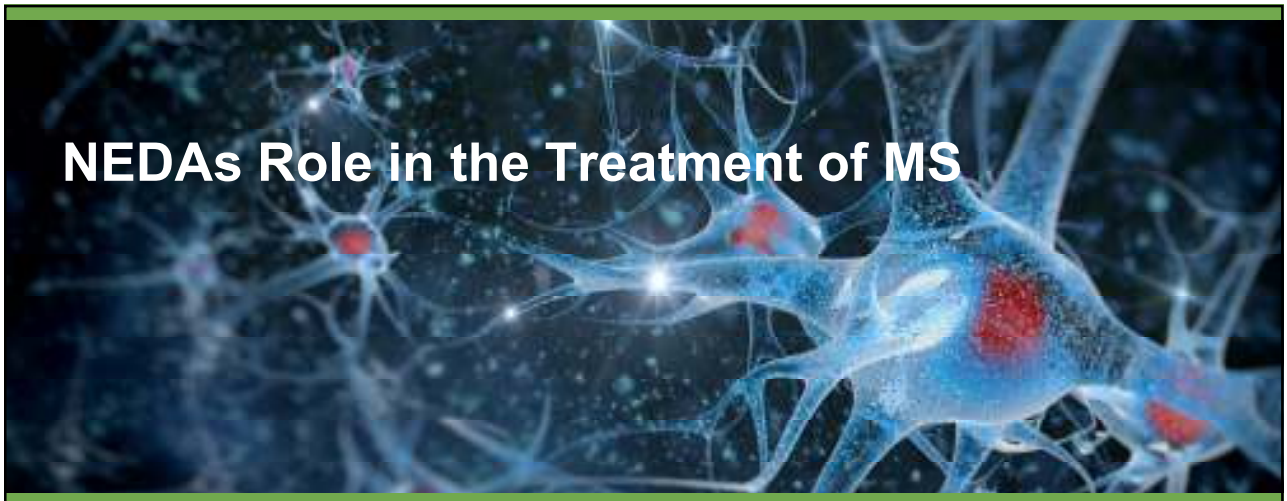


gmsa
Global Multiple Sclerosis Academy

Introduction

- This interview will discuss:
  - The utility of NEDA-3 in MS treatment
  - NEDA-4 and other considerations to improve MS treatment monitoring
  - The potential role of cladribine in the management of MS

NEDA-3

- No Evidence of Disease Activity or NEDA is a composite of:
  - No relapses
  - No disability progression as determined by EDSS (Expanded Disability Status Scale)
  - No MRI activity (new or enlarging T2 lesions or Gd-enhancing lesions)
- Combines radiological and clinical outcomes
- Important goal for treating individual patients with relapsing disease

Stangel M et al. Ther Adv Neurol Disord. 2015; 8(1): 3–13.

Current Agents in terms of NEDA-3

- No head-to-head trials have been conducted in the context of NEDA-3 with available agents in MS
- It is therefore difficult to compare current agents in terms of NEDA-3
- Currently approved agents are within the estimated range of 20-40% effectivity in the context of NEDA-3

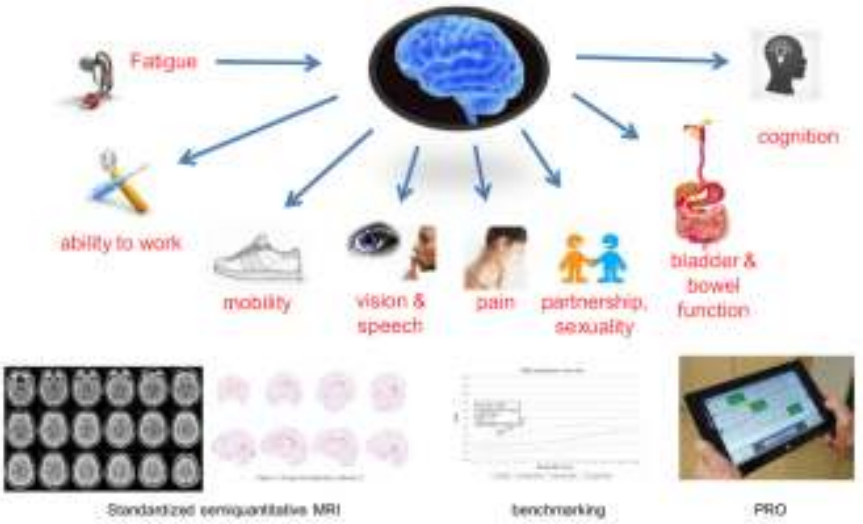
NEDAs Role in the Treatment of MS

NEDA-4

- Recent addition of brain atrophy measures to NEDA-3
- Can be useful in forecasting study outcomes but not clinical practice
- There are difficulties in the standardization and quantification of brain atrophy measures
  - However these are useful in motivating patients and designing algorithms
  - Could also improve adherence
  - Allow for further integration of neuropsychological effects and other patient reported outcomes

Ziemssen T et al. J Neurol. 2015 Dec 24. [Epub ahead of print]

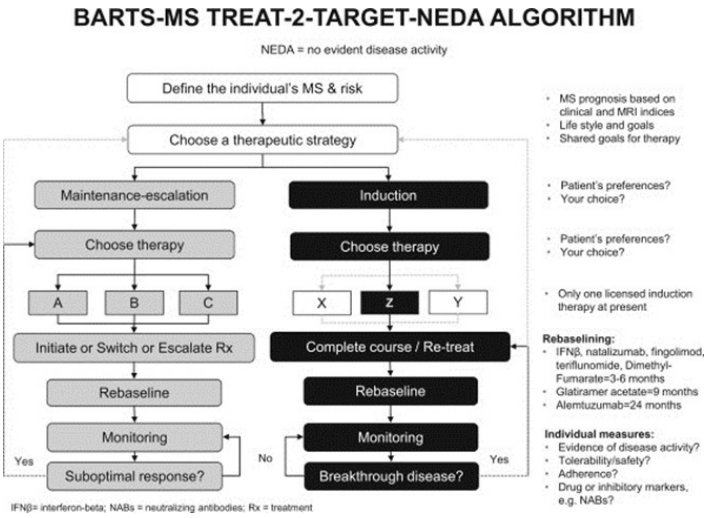
Other Considerations for Monitoring MS Treatment



Ziemssen T et al. J Neurol. 2015 Dec 24. [Epub ahead of print]

NEDAs Role in the Treatment of MS

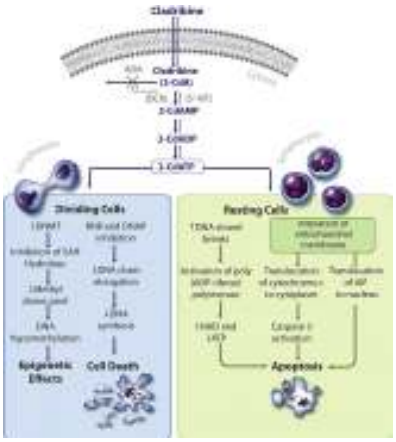
Treatment Algorithm for Implementing NEDA



Giovannoni G et al. Mult Scler Relat Disord. 2015;4(4):329-33.

Cladribine in the Management of MS

- Has a unique benefit-risk profile
- Interferes by selectively reducing the number of T and B cells
  - Affects nucleoside pools in lymphocytes



Sigal D et al. Blood. 2010; 116(6).

NEDAs Role in the Treatment of MS

Cladribine Efficacy Data

Trial	Design	Arms	Primary Endpoint	Result of the primary endpoint	Key secondary endpoints and their results
CLARITY[1]	Randomized, double-blind, placebo-controlled study involving 1,326 patients with RRMS over 96 weeks	3.5 mg/kg, 5.25 mg/kg vs. placebo	Annualized Relapse Rate	57.6% relative reduction in 3.5 mg/kg group; 54.5% relative reduction in 5.25 mg/kg group	30.9% and 29.6% higher relapse-free rate, and 33% and 31% reductions in EDSS progression in 3.5 and 5.25 mg/kg groups, respectively. Reduced Gd-enhanced T1-weighted lesions, active T2-weighted lesions and combined unique lesions in treated groups
ORACLE MS[2]	Randomized, double-blind, placebo-controlled study involving 617 patients with Clinically Isolated Syndrome over 96 weeks	3.5 mg/kg, 5.25 mg/kg vs. placebo	Time to conversion to MS by Poser criteria	67% relative reduction in 3.5 mg/kg group; 62% relative reduction in 5.25 mg/kg group	50% and 57% reductions in the time to conversion to McDonald MS in 3.5 and 5.25 mg/kg groups, respectively. Lower median numbers of new or persisting Gd-enhanced T1-weighted lesions, new or enlarging T2- weighted lesions, and combined unique active lesions in treated groups

1. Giovannoni G et al. N Engl J Med. 2010;362:416-426.
2. Leist T et al. Lancet Neurol. 2014;13:257-267.

Conclusions and Perspectives

- NEDA-3 represents an achievable treatment goal in MS treatment
- Use of brain atrophy measures (NEDA-4) needs to be further standardized
- NEDA can be used to design treatment algorithms for individual patients with MS
- Neuropsychological parameters and other patient reported outcomes continue to evolve as outcome measures for MS treatment
- Given the plethora of agents available for the treatment of MS, risk-benefit profiles of each agent can be considered in individual patients
- The oral agent cladribine can be potentially useful as an induction agent in the treatment of MS

NEDAs Role in the Treatment of MS

NEDAs Role in the Treatment of MS