THE 12TH ANNUAL LINDA MORGANTE

Multiple Sclerosis Nurse Leadership Program

2021

EVOLUTION OF PRECISION MEDICINE: TREAT TO TARGET APPROACHES

Cheryl Blaschuk NP, MSCN
Medical College of Wisconsin
Department of Neurology

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New Treatment Paradigms in MS: What We Know

- MS: autoimmune demyelinating disease of CNS
- Most common nontraumatic disability of young adults
- Most patients have RRMS
- Approximately one-half of RRMS patients → SPMS (↑ disability and ↓ or ⊘ relapses)
- Early treatment = delayed onset of disability

CNS = central nervous system; MS = multiple sclerosis: RRMS = relapsing-remitting MS; SPMS = secondary progressive MS

New Treatment Paradigms in MS

- American Academy of Neurology (AAN)
  - PRACTICE GUIDELINE RECOMMENDATIONS SUMMARY: *Disease-Modifying Therapies for Adults With Multiple Sclerosis*
  - Guideline detail as published in April 2018
  - https://www.aan.com/Guidelines/home/GuidelineDetail/898

- Therapeutic Targets for Multiple Sclerosis: Current Treatment Goals and Future Directions
  - Smith AL et al. *Neurotherapeutics*. 2017;14(4):952-60.

Most Common Treat to Target Goals in MS

- Rio score
- Disease-free survival
- No evidence of disease activity (NEDA)

Smith AL et al. *Neurotherapeutics*. 2017;14(4):952-60.

Treat to Target Goals: Rio Score and Modified Rio Score

- Developed in 2008 by Rio J et al to score treatment response
  - 0-3 score
  - MRI lesions ≥3, relapse ≥1, EDSS ≥1 sustained 6 months
  - Patients w/ score of ≥2 at 12 months = greater chance of disease progression or relapse
- Modified in 2012
  - 0-3
  - MRI lesions: ≥6 = 1, relapse ≥1 = 1, then relapse ≥2/y = 2
  - Score 0 = responder, 1= indeterminate (re-evaluate at 6 months), ≥3 = nonresponder
  - EDSS was removed due to poor intra- and interreliability
    - ≥2 = 60% chance of worsening at 3 years and probably benefit Δ DMTs

Hyun JW et al. *PLoS One*. 2015;10(5):e0129243.

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging

Treat to Target Goals: Disease-Free Survival

- From oncology literature
- Applied only to autologous hematopoietic stem cell transplant
- HALT-MS trial: high-dose immunosuppression
- 78.4% were event free at 3 years
- Not widely adopted in clinical trials

Smith AL et al. *Neurotherapeutics*. 2017;14(4):952-60.

Treat to Target Goals: NEDA 3 and 4

- Came out of the AFFIRM trial for natulizumab
- NEDA 3: Absence of relapses, CDW with EDSS, no Gad-enhancing lesions, and no new enlarging T2 lesions
- Stronger focus on inflammatory aspects of MS
- NEDA 3 drawback: DSS – primarily walking and no cognitive measurement; not sensitive to capture subtle changes inflammatory or neurodegeneration, which underlie disability
- NEDA 4: BVL >0.4% is predictor of disability and cognitive dysfunction
- NEDA 4 drawback: routine BVL measurement is not consistent

Guevara C et al. *Front Neurol*. 2019;10:788.

BVL = brain volume loss; CDW = confirmed disability worsening; Gad = gadolinium

Assessing Response to Therapy

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New Treatment Paradigms in MS: Assessing Response to Therapy

- Utilize treat to target to evaluate response to DMT
- Understand mechanism of action (MoA)

New Treatment Paradigms: Consideration for Switching Therapy

- 1 or more relapses, 2 or more new MRI lesions (Gad or new T2), or increased disability over past 12 months
- Monitor MRI and relapses and understand when DMTs become most effective (eg, how long have they been on DMT and how is their adherence?
- Evaluate degree of disease activity, adherence, adverse event (AE) profiles, and MoA

https://www.aan.com/Guidelines/home/GuidelineDetail/898. Accessed May 18, 2021.

New Treatment Paradigms: Consideration for Switching Therapy (cont)

- Evaluate for injection discomfort and/or injection fatigue
- Evaluate for AEs and manage
  - If AEs affect adherence, consider change
- Evaluate labs if persistently abnormal
- Evaluate patients' risk tolerance re: PML and JCV index over 0.9 or new conversion to JCV+

https://www.aan.com/Guidelines/home/GuidelineDetail/898. Accessed May 18, 2021.

JCV = John Cunningham virus;
PML =progressive multifocal leukoencephalopathy

New Treatment Paradigms: Consideration for Switching Therapy (cont)

- Understand long-term safety data re: risk of malignancy and infections
- Natalizumab infusion reactions: check antibodies if + or persistent
- Counsel patients re: stopping natalizumab and risk of significant relapses. Wait no more than 8-12 weeks after stopping natalizumab to start new therapy
- Discontinue DMT in context of pregnancy and do not initiate DMTs if pregnant. Pregnancy is well tolerated by MS female

New Treatment Paradigms

PRECISION MEDICINE IN MS

Framework for Developing New Taxonomy of Disease: Toward Precision Medicine

Describe and define diseases based on intrinsic biology + traditional physical "signs and symptoms"

Go beyond description and be directly linked to a deeper understanding of disease mechanisms, pathogenesis, and treatments

Highly dynamic when used as research tool, continuously incorporating newly emerging disease information

Chitnis T et al. *Mult Scler*. 2020;26(5):522-32.

Precision Medicine Approach: Challenges

- Precision diagnosis
- Predicting treatment response
- Personalized monitoring to progressively update this prediction

Gafson A et al. *Mult Scler J*. 2017;23(3):362-9.

Precision Medicine: Biomarkers

- Brain MRI: key in diagnosis, prognosis, and early treatment response
- Lesion counts (T2), active inflammation with Gad (T1)
- Brain volume: ↑ evidence of its usefulness in monitoring
- CSF CHI3L1 and NF-L promising prognostic and biomarkers in CIS → MS and disability development
- CD62L and IgM oligoclonal bands: may play a role in risk of PMS with natalizumab patients

Comabella M et al. *Curr Opin Neurol. 2016;*29(3):254-62.

CIS = clinically isolated syndrome; CSF = cerebrospinal fluid; Ig = immunoglobulin; PMS = progressive MS

Precision Medicine: What Needs to Be Done?

- Large representative data sets
- Agreement on outcomes meaningful to patients
- Validated models predictive of behavior of individual patients
- Decision criteria agreed on by all stakeholders
- Wide access to tools and approaches for personalization

Gafson A et al. *Mult Scler J*. 2017;23(3):362-9.

New Treatment Paradigms in MS: Conclusion

- Treat to target: Evaluate DMT's efficacy using primarily NEDA 3
- Switching therapies: With 18+ therapies, it is more important to routinely evaluate response to DMTs—not only disease mechanisms, pathogenesis, and MoA—but when to make a change
- Precision medicine: Right patient, right drug, and right time
  - Will require coordinated effort in MS community

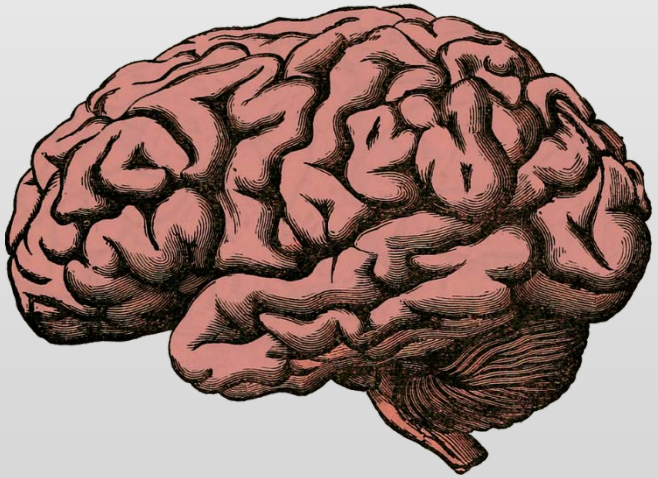
Why Do We Treat Early?

TIME

IS

BRAIN

=



Thank you for your time and attention

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