MS: A Clinical Overview, with Gaps in Evidence

Patricia K. Coyle, MD
Professor and Vice Chair (Clinical Affairs)
Director, MS Comprehensive Care Center
Stony Brook University Medical Center, Stony Brook, NY

November 1, 2017
Disclosures

• **Consultant:** Accordant, Acorda, Bayer, Biogen, Celgene, Genentech/Roche, Genzyme/Sanofi, Novartis, Serono

• **Research:** Actelion, Alkermes, Genentech/Roche, MedDay, NINDS, Novartis, Opexa

Stony Brook Medicine
MS Overview

• Background
• Phenotypes
• Therapeutic arenas
• Current disease modifying therapies
• Gaps
MS Background

- Major acquired CNS disease of young adults
- Characteristic features
  - low, medium, high risk zones
  - female predominance (currently 3:1)
  - young person’s disease (90% have onset between ages 15 to 50; pediatric onset 2% to 5%; <1% under age 10, or over age 60)
  - marked disease variability
MS Background

- over 90% are Caucasians (but diverse groups can be affected)
- MS is on the rise (among women)
Clinical Phenotypes

• 85% to 90% begin with intermittent attacks, stable in between
  • clinically isolated syndrome (CIS) represents first attack
  • relapsing MS

• 10% to 15% show slow worsening from onset
  • primary progressive MS (PPMS)
  • older age at onset, equal sex ratio, progressive myelopathy

Neurology 2014; 83:278
Clinical Phenotypes

- Secondary progressive MS (SPMS)
  - relapsing MS can transition to progressive MS, typically at midlife
MS Endophenotype

- At risk (pre-disease state)
- Radiologically isolated syndrome (RIS)
  - asymptomatic MS
- Prodromal MS
- CIS
- MS

Lancet Neurol 2017; 16:413, 445
MS Therapeutic Arenas

• Preserve/improve CNS reserve (wellness, health maintenance, vascular comorbidity control)
• Symptom management
• Acute relapse management
• Disease modifying therapies (DMT)
Current DMTs

- Needle injectables
  - interferon betas (5 distinct agents)
  - glatiramer acetate (3 agents)
- Orals
  - fingolimod
  - teriflunomide
  - dimethyl fumarate
Current DMTs

• Monoclonals
  • natalizumab
  • daclizumab
  • alemtuzumab
  • ocrelizumab

• Mitoxantrone
  • chemotherapy agent (anthracenedione)
  • rarely if ever used currently
MS Gaps

• No cure

• Very limited progressive MS therapies
  • all DMTs approved for relapsing forms of MS
  • only a single DMT approved for PPMS

• No CNS repair therapies

• No biomarkers to choose DMT

• No definitive early biomarker to determine DMT response (suboptimal responder)
MS Gaps

• Unclear role of aggressive (induction/high efficacy) therapy vs. escalation therapy
Key Questions

• How critical is early treatment?
  • Can it ever “cure” MS?
• Can we prevent relapsing MS from transitioning to SPMS?
• When (if ever) should we stop DMTs?
• Is there any role for combination strategies?
Learn More

www.pcori.org
info@pcori.org

twitter
#PCORI2017

YouTube
Thank You!

Patricia K. Coyle, MD
Professor and Vice Chair (Clinical Affairs)
Director, MS Comprehensive Care Center
Stony Brook University Medical Center, Stony Brook, NY
November 1, 2017
Comparing Multiple Sclerosis Therapeutic Strategies: TRaditional vs. Early Aggressive Therapy for Multiple Sclerosis (TREAT-MS) Trial

Ellen M. Mowry, M.D., M.C.R.

Associate Professor of Neurology and Epidemiology, Johns Hopkins University
Co-PI, TREAT-MS Trial

November 1, 2017
Rationale for the TREAT-MS Trial

• There are multiple effective FDA-approved therapies for relapsing-remitting MS; none is approved for the later, neurodegenerative phase of the illness
  • These have different levels of efficacy; some are first-line, while others are higher-efficacy but may carry greater risks of serious adverse events

• Pivotal clinical trials for approved MS therapies have shown no to modest differences in disability accrual during the very short trial periods

• Whether a more aggressive treatment strategy early in MS prevents longer-term disability is not clear
TREAT-MS: Study Aims

• **Aim 1.** To evaluate, independently among patients deemed at higher risk vs. lower risk for disability accumulation, whether an “early aggressive” therapy approach, versus starting with a traditional therapy, influences the intermediate-term risk of disability progression.

• **Aim 2.** To evaluate if, among patients deemed at lower risk for disability accumulation who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy therapy versus a new first-line therapy have different intermediate-term risk of disability accumulation.
TREAT-MS: Study Population

- 900 participants will be aged 18-60 years and will meet current criteria for relapsing-remitting MS.

- Participants must qualify for at least one higher-efficacy therapy based on inclusion/exclusion criteria.

- 40 sites throughout the United States will enroll participants (mix of university and practice setting).

- Participants will be followed for up to 52 months.
TREAT-MS: Randomization Scheme

Informed Consent and Screening

- Patient has “high risk” disability indicators
  - Patient randomized to first-line therapy
    - If breakthrough disease after >6 months...
      - Patient may change to another therapy (type and timing determined by patient and neurologist)
  - Patient randomized to higher-efficacy therapy

- Patient has “low risk” disability indicators
  - Patient randomized to first-line therapy
    - If breakthrough disease after >6 months...
      - Patient randomized to higher-efficacy therapy
  - Patient randomized to first-line therapy
    - If breakthrough disease after >6 months...
      - Patient may change to another therapy (type/timing determined by patient and neurologist)
TREAT-MS: Outcomes

• **Primary Outcome**: Risk of sustained disability progression (defined by the “Expanded Disability Status Scale-Plus”)

• **Secondary Outcomes**: patient-reported disability, health-related quality of life, social status; clinical performance metrics (MS Functional Composite, Symbol Digit Modalities Test); clinically significant adverse events

• **Tertiary Outcomes**: loss of brain tissue on magnetic resonance imaging and optical coherence tomography; inflammatory activity; use of symptomatic medications/interventions
Engagement: Examples

• The Study Advisory Committee (SAC) includes patients, partner, stakeholder organizations, & payers

• Recruitment strategies & planning and dissemination strategies will involve the same groups; a patient will serve on Data Safety Monitoring Board

Study Advisory Committee Activities

Prior to trial

✓ Decide on criteria for inclusion in disability risk strata (higher vs. lower risk)
✓ Determine which medications are classified as higher-efficacy vs. lower-efficacy
✓ Establish recommendations for maximally-tolerated disease activity as guideline for patients/clinicians who have breakthrough disease
✓ Establish study windows for scheduling visits
✓ Establish which medications will be considered “symptomatic” therapies for tertiary outcome
✓ Establish final criteria for sustained progression of disability as primary endpoint

During trial

✓ If a new therapy is approved, determine if it is classified as higher-efficacy vs. lower-efficacy
✓ Determine if newly-available medications require any modification of eligibility criteria
Conclusions

• In this pragmatic, randomized controlled trial, we hope to identify if specific treatment strategies in the relapsing-remitting phase of MS can prevent, delay, or reduce intermediate- to longer-term disability accrual

  **Relevant because higher-efficacy therapies carry greater risks of serious adverse events**

• Great autonomy for the patient/physician team will be maintained, and the trial will be guided by the SAC.

• This study will help inform and transform how we treat people with MS.
Learn More

info@pcori.org

#PCORI2017
Questions?
Thank You!

ELLEN M. MOWRY, M.D., M.C.R.
Associate Professor of Neurology and Epidemiology, Johns Hopkins University
Co-PI,* TREAT-MS trial
November 1, 2017

*with Scott Newsome, D.O.
Tele-Exercise And Multiple Sclerosis (TEAMS): A Comparative Effectiveness Trial Between a Clinic- and Home-Based Teleexercise Intervention for Adults with Multiple Sclerosis (MS) Living in Geographically Isolated Communities in the Deep South

James H. Rimmer, PhD

University of Alabama/Lakeshore Foundation Endowed Chair in Health Promotion and Rehabilitation Sciences

www.teamsstudy.org

11/1/17
• Seeks to determine if our evidence-based rehabilitation and exercise program produces similar health outcomes when delivered in clinic or at home, using preloaded tablets and an Interactive Voice Response (IVR) system.

• Primary Outcomes
  • Decreased fatigue
  • Decreased pain
  • Increased physical activity
  • Improved quality of life
• Recruiting 820 individuals diagnosed with MS
• 38 clinic locations across Alabama, Mississippi, and Tennessee
  • Rolling out 8 sites initially
CAM Intervention

- 4 Functional Levels
- 2 Levels for Self-reported Osteoporosis
• 6 Functional Levels
  • TEAMS 1 and TEAMS 2: Floor & standing exercises
  • TEAMS 3: Floor, chair, and supported standing exercises
  • TEAMS 4: Chair exercises
  • TEAMS 3-OP & 4-OP: Self-reported Osteoporosis
• Characteristics of Functional Levels
  • Modifications and challenges
  • Varied repetitions, pose hold times, and dual-tasking exercises
  • Equipment is specific to each exercise level

• Exercise Videos for At-home (TeleCAM) Group
  • Actors have all been diagnosed with MS
  • Adjustable tablet stand for exercising at home
Community Engagement

- Self-help group meetings
- Pharmaceutical patient and medical professional events
- MS Coalition symposiums, walks, and educational events
- Consortium of MS Centers, iConquerMS, NARCOMS, Antidote, & REACHnet
- Neurologists, PCPs, nurse practitioners, infusion centers, & case managers of local hospitals
- Therapist intervention training at each clinic
Recent Updates

Breastfeeding with a Spinal Cord Injury
Oct 08, 2017
A mother with spinal cord injury shares her story about breastfeeding her newborn.
Learn More

www.pcori.org
info@pcori.org
twitter
#PCORI2017

www.teaMSstudy.org
Thank You!

James H. Rimmer, PhD
UAB/Lakeshore Foundation Endowed Chair in Health Promotion and Rehabilitation Sciences

11/1/17
Studies of Disease Modifying Therapies

• Discontinuation of Disease Modifying Therapies (DMTs) in Multiple Sclerosis (MS)
  • John Corboy, MD, MA | University of Colorado Denver

• Comparing Two Oral Medicines to Improve Patient Experiences with Relapsing-Remitting Multiple Sclerosis
  • Silvia Rossi, MD, PhD | Fondazione IRCCS Istituto Neurologico Carlo Besta

• Rituximab in Multiple Sclerosis: A Comparative Study on Effectiveness, Safety, and Patient-Reported Outcomes
  • Fredrik Piehl, MD, PhD | Karolinska Institute

• Determining the Effectiveness of Early Intensive versus Escalation Approaches for the Treatment of Relapsing-Remitting Multiple Sclerosis (DELIVER-MS)
  • Daniel Ontaneda, MD | Cleveland Clinic Foundation

• A Pragmatic Trial to Evaluate the Intermediate-Term Effects of Early, Aggressive versus Escalation Therapy in People with Multiple Sclerosis
  • Ellen M. Mowry, MD | Johns Hopkins University
Studies of Treatments for Symptoms of MS

• Improving the Quality of Care for Pain and Depression in Persons with Multiple Sclerosis
  • Dawn Marie Ehde, PhD | University of Washington

• Randomized, Double-Blind, Crossover, Placebo-Controlled Trial of Amantadine, Modafinil, and Methylphenidate for Treatment of Fatigue in Multiple Sclerosis
  • Bardia Nourbakhsh, MD | Johns Hopkins University

• A Randomized Controlled Trial of Telephone-Delivered Cognitive Behavioral Therapy, Modafinil, and Combination Therapy of Both Interventions for Fatigue in Multiple Sclerosis
  • Tiffany Braley, MD, MS | University of Michigan
Studies of Telerehabilitation

• Comparing Clinic- and Home-Based Exercise Programs to Help Adults with Multiple Sclerosis
  • James Rimmer, BS, MA, PhD | University of Alabama at Birmingham

• Comparing the Effectiveness of Fatigue Management Programs for People with MS
  • Matthew A. Plow, PhD | Case Western Reserve University

• Comparative Effectiveness of an Exercise Intervention Delivered via Telerehabilitation and Conventional Mode of Delivery
  • Deborah A. Backus, PhD, PT | Shepherd Center
Amplifying the voices of people with MS

Cyndi Zagieboylo
President and CEO
National MS Society
National MS Society

Vision
A world free of MS

Mission
People affected by MS can live their best lives as we stop MS in its tracks, restore what has been lost and end MS forever
What we see in social media

- **36.2%** symptoms: 180,110 mentions
- **17.2%** diagnosis: 85,611 mentions
- **5.8%** medication: 28,701 mentions
- **28.0%** wellness: 139,384 mentions
- **8.3%** providers: 41,059 mentions
- **4.6%** insurance: 22,641 mentions
Top MS Symptoms That People Talk About

- Pain
- Emotional Changes
  - Walking/Balance
- Cognition
- Fatigue
- Vision
- Speech/Swallowing
- Numbness
- Spasticity
- Dizziness/Vertigo

Thousands
Learn More

www.pcori.org  www.nationalmssociety.org
info@pcori.org  #PCORI2017