Research Updates in MS Research

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University of Washington Multiple Sclerosis Center

MS Summit June 11, 2016
Dr. von Geldern has nothing to disclose.
This talk does mention off label use of medications.
These are exciting times!

A lot of research is happening in the field of MS right now.
Many clinical trials in MS

1616 studies in multiple sclerosis listed on clinicaltrials.gov in May 2016
470 are currently open (recruiting)

44 trials had results posted to clinicaltrials.gov
From June 2015 to May 2016 (since the last Summit)
Highlights
Recent Findings and Developments

- Risk and Life Style Factors
- Disease Modifying Therapies
- Remyelination and Repair
- Symptom Management
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Risk and Life Style Factors

Coffee Consumption May Decrease MS Risk

Two large case control studies:
California study: > 948mL coffee daily 31% lower risk for MS compared with no coffee
Swedish study: > 6 cups a day associated with 30% lower risk for MS

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<th>OR</th>
<th>OR[1]</th>
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<td>0.05</td>
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<td>0.70 (0.49 to 0.99)</td>
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<tr>
<td>7+</td>
<td>74/128</td>
<td>0.80</td>
<td>0.01</td>
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<td>p for trend</td>
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</table>

A K Hedström et al. JNNP 3 March 2016
Risk and Life Style Factors

Vitamin D Deficiency in Pregnancy Linked to MS Risk

Finnish Case Control Study:
Maternal Vitamin D deficiency during early pregnancy associated with increased risk of MS in offspring

Figure 2. Multivariate Relative Risk for Multiple Sclerosis in Offspring by Maternal 25-Hydroxyvitamin D Level Adequacy During Pregnancy

Adjusted for sex, gestational age, and season at time of sample collection. 
*P* = .006 for the relative risk in the <12.02 category vs the 12.02 to <20.03 category.
Risk and Life Style Factors

Smoking Cessation Decreases Risk of Conversion to Secondary Progressive MS

A Kaplan-Meier plot with the age at conversion to secondary progressive (SP) disease for smokers at diagnosis who quit smoking completely (n = 118) and smokers at diagnosis who smoked continuously (n = 332).

Ramanujam R et al: JAMA Neurology, 1 October 2015
Smoking Cessation Decelerates Brain Volume Loss in MS

Observational retrospective study of 254 patients with relapsing MS:
148 continued to smoke, 106 stopped smoking.

Phase I: baseline to year 4 (both groups continued to smoke)
Phase II: year 4 to year 6 (one group continued to smoke, other group stopped)

Annual brain volume loss for smokers: -0.54 in phase I and -0.51 in phase II (p=0.036)
Annual brain volume loss for quitters: -0.55 in phase I and -0.38 in phase II (p<0.0001)
Comparison between smokers and quitters: -0.38 vs -0.51, p<0.0001
Risk and Life Style Factors

Diet Mimicking Fasting Reduces Autoimmunity and MS Symptoms and Promotes Regeneration in Mice

Periodic 3-day cycles of fasting:
- ↓ clinical severity in all mice, completely reversed symptoms in 20%
- ↓ pro-inflammatory cytokines, TH1 and TH17 cells, antigen-presenting cells
- ↑ corticosterone, regulatory T cells
- ↑ oligodendrocyte precursor cell regeneration, remyelination

Preliminary data suggesting that an FMD or a chronic ketogenic diet are safe, feasible, and potentially effective in the treatment of relapsing-remitting multiple sclerosis (RRMS) patients

Choi et al., 2016, Cell Reports, June 7, 2016
Risk and Life Style Factors

GEMS (Genes and Environment in MS)

2632 first-degree relatives of people with MS

NIH (NINDS) and Harvard (Brigham and Women’s Hospital)
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Disease Modifying Therapies

FDA News Release

FDA approves Zinbryta to treat multiple sclerosis

For Immediate Release

May 27, 2016
Disease Modifying Therapies

**Ocrelizumab: OPERA I and II**

Humanized monoclonal antibody targeting B cells (CD20)

Two identical randomized (1:1) controlled trials, 821/835 patients with RRMS

Ocrelizumab 600mg iv every 24 weeks vs IFN 1a 44µg SC TIW x 96 weeks

Primary Endpoint: **Significant reduction in annual relapse rate**

![Graph showing significant reduction in ARR compared with IFN β-1a](image-url)
Disease Modifying Therapies

Ocrelizumab: OPERA I and II

Secondary and exploratory endpoints:
- ↓ Gd enhancing lesions 94% / 95% (OPERA I / OPERA II)
- ↓ new/enlarging T2 lesions 77% / 83%
- ↓ new T1 hypointense 57% / 64%
- ↓ brain volume loss 23% / 24%

No evidence of disease activity (NEDA):
**Ocrelizumab achieves better NEDA than IFN**
47.9% / 47.5% vs 29.2% / 25.1%
= 64% / 89% increase of NEDA

Hauser ECTRIMS 2015 and AAN 2016; Arnold AAN 2016; Traboulsee, AAN 2016
Positive effect on disability

Confirmed disability progression (CDP):
12 week CDP 9.8% vs 15.2% (40% risk reduction)
24 weeks CDP 7.6% vs 12% (40% risk reduction)

Higher proportion of OCR-treated patients with improved/stable disability:
92.3% / 87.5% vs 86.1% / 80.4%

Significantly fewer patients with worsened disability:
7.7% / 12.5% vs 13.9% / 19.6%
= 44% / 42% reduction in worsened disability
Disease Modifying Therapies

**Ocrelizumab: ORATORIO**

Monoclonal antibody targeting B cells (CD20)

Randomized (2:1) placebo-controlled trial; 732 patients with primary progressive MS

Ocrelizumab 300mg x 2 (2 weeks apart) iv every 24 weeks vs placebo for >120 weeks

Significant reduction in disability progression
Disease Modifying Therapies

Ocrelizumab: ORATORIO
Monoclonal antibody targeting B cells (CD20)

- Timed 25 foot walk progression ↓ 29%
- Rate of brain volume loss ↓ 17.5%
- T2 lesion volume -3.4% vs +7.4%

Adverse events: similar in both groups
Malignancies higher?
More infusion reactions with first infusion (28%)
Minocycline

- Immunomodulatory and neuroprotective properties
- Effective in animal models of MS (as a single agent and in combination with IFN beta or glatiramer acetate)

No statistically significant effect when added to sc IFN beta 1a
Disease Modifying Therapies

Minocycline

Reduces the Relative Risk of Multiple Sclerosis in People Experiencing Their First Demyelinating Event

Randomized double-blind placebo-controlled trial
143 patients with clinically isolated syndrome
Minocycline 100mg BID vs placebo x 2 years

At 6 months conversion to MS:
61.4% placebo vs. 34.0% minocycline
Absolute risk reduction 27.4%
Relative risk reduction was 44.6%
Number needed to treat 4 (p= 0.002)

At 12 months:
Absolute risk reduction 25.1%
Relative risk reduction 37.6%
number needed to treat 4 (p=0.002)

Metz et al. ECTRIMS 2015
Disease Modifying Therapies

Autologous hematopoietic stem cell transplantation

Curing multiple sclerosis

Stem cells are starting to prove their value as medical treatments

Miraculous' results from new MS treatment

Breakthrough treatment for MS patient

Doctors in Sheffield say patients with multiple sclerosis (MS) are showing "remarkable" improvements after receiving a treatment usually associated with cancer.

Steven Stacey was diagnosed with MS in 2013 and within a year went from being an able-bodied athlete to needing a wheelchair and losing sensation in much of his body.

He said, "I went from running marathons to needing 24-hour acute
Disease Modifying Therapies

Autologous hematopoietic stem cell transplantation

“Conclusion: ... auto-HSCT... will be astoundingly effective when used on appropriately selected patients”

Bakhuraysah et al. Stem Cell Research & Therapy, 2016
Disease Modifying Therapies

Autologous hematopoietic stem cell transplantation

NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs.
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Remyelination and Repair

**Anti-Lingo-1: RENEW Study**

Human monoclonal antibody against LINGO-1
CNS specific membrane glycoprotein, suppressor of oligodendrocyte differentiation and myelination

Phase 2 placebo-controlled clinical trial of 82 patients with first episode optic neuritis
Anti-LINGO-1 100mg/kg iv every 4 weeks for 20 weeks

Anti-LINGO-1 treated
↑ VEP latency
consistent with
↑ remyelination
Remyelination and Repair

Anti-Lingo: RENEW

Subgroups analysis showed greater improvement in:

- Older patients (> 33 years)
- Earlier treatment (<25 days from onset)
- More severe baseline visual acuity impairment
- Primary progressive MS

Aktas et al. ECTRIMS 2015
Remyelination and Repair

High Dose Biotin: Pilot Study
Co-enzyme for acetylCoA carboxylase

Uncontrolled non-blinded pilot study
23 patients with primary and secondary progressive MS
High doses of biotin (100–300 mg/day) for 2 to 36 months (mean=9.2)

4 patients visual acuity improved, 2 patients VEP improved
16/18 patients with spinal cord involvement clinical improvement

Sedel et al. Multiple Sclerosis and Related Disorders, 2015
Randomized double-blind placebo-controlled trial
150 patients with secondary or primary progressive MS
300 mg biotin po a day x 48 weeks
Preplanned 12 month extension phase (placebo switched to biotin)

EDSS and TW25 improved 12.6% at 9 and 12 months
Mean change in EDSS maintained over 24 months (p=0.014)
Clinical global impression of change improved at 12 months

Side effects: Low TSH
Remyelination and Repair

High dose Biotin (MD 1003): MS-ON trial

Randomized, double-blind, multicenter, placebo-controlled (2:1) trial
92 MS patients with visual loss related to relapsing or progressive optic neuritis
Decreased visual acuity for at least 6 months following relapse or progressive ON

Biotin 300 mg po a day x 24 weeks, 24 week extension phase (all biotin)

No significant difference in improvement of visual acuity (trend only)
Prospectively defined subgroup analyses: benefit in progressive optic neuropathy
On biotin ↑ mean 2.75 letters, on placebo ↓ mean -1.45 letters
Extension those initially on placebo stopped worsening after switch to biotin

Tourbah et al. AAN 2016
Phase 2 clinical trial: 50 MS patients with chronic optic neuropathy
4mg clemastine BID vs placebo for 3 months, then 2 months cross over

- Reduction of VEP latency delay of 1.9 ms (95% CI [0.66, 3.1]; p=0.003) primary endpoint
- Trend for improvement of low contrast visual acuity (p=0.089) secondary endpoint
- Side effect: Mild increase in fatigue (p= 0.017)
Lipoic Acid for Secondary Progressive MS

Double-blind, placebo-controlled randomized trial 51 patients with SPMS
Lipoic acid 1200 mg po a day x 2 years

Less brain atrophy (p= 0.004), no effect on EDSS (p= 0.77)
Trend toward improved 25 foot walk (p=0.056) and T2 lesion volume change (p= 0.057)

Spain R et al., AAN 2016
Remyelination and Repair

Autologous Mesenchymal Stem Cell-Derived Neural Progenitor Cells (MSC-NPs)

Open label, phase 1 clinical trial with 20 patients with progressive MS Intrathecal MSC-NPs every 3 months x3

Preliminary data: 62% of patients functional neurological improvement

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<th>Study subject number</th>
<th>EDSS baseline</th>
<th>EDSS 3 mo. FU</th>
<th>EDSS 6 mo. FU</th>
<th>% Improvement of T25FW (≥20% considered significant)</th>
<th>Assistive Device</th>
<th>Other Area of Improvement</th>
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<td>Scooter</td>
<td>58% improvement on SHPT at 3 mo FU (≥20% considered significant)</td>
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<td>13%</td>
<td>Bilateral canes</td>
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Side effects:
Mild headache 53%; moderate/severe headache 12%; fever 18%

Sadiq et al., AAN 2016
Remyelination and Repair

**Sobetirome: Animal Study**

Thyroid hormone analog
Induces differentiation of oligodendrocyte progenitor cells

Lysolecithin mouse model of demyelination
Sobetirome (5 mg/kg) injections vs T3 vs placebo

MRI and pathology showed less demyelination and more remyelination in T3 and Sobetirome-treated mice

No systemic hyperthyroidism in Sobetirome

Bourdette D et al. ECTRIMS 2015 and ACTRIMS 2016
Remyelination and Repair

ABT-555: Several Animal Studies

- Immune modulation
- Neuroprotection
- Remyelination
- Neuroregeneration

in

Rat optic nerve crush model
Rat optic neuritis model
Rat spinal cord rargetet EAE
Mouse disseminated EAE

Human monoclonal antibody to RGMa
repulsive guidance molecule, inhibitor or neurite outgrowth

Mueller et al. ECTRIMS 2015
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Symptom Management

Suicide Risk in MS Patients

Cross-sectional observational study of 34 patients with MS

Prevalence of suicide ideations was 11.8%

Significant factors associated with suicide ideations: not married, not Caucasian, living alone, depression, changes in appetite, sadness, loss of pleasure, greater frequency of MS relapses – but not disability

Take home message: Screening for suicide risk is important (BDI-FS)
Symptom Management

Delivery of mindfulness training via phone

Feasibility pilot study of 25 patients with MS
6 week program of group phone sessions
Compared to 10 patients who did not complete program

Improved cognition and sleep quality
Reduced fatigue and depression

Frontario A et al. CMSC 2016
Summary

- There are several promising agents for progressive MS
- There is a lot we can do today for MS patients
- There is a lot more to be learned...
Life After New Diagnosis (LAND)
How individuals cope in their first year after being diagnosed with MS.

Living with chronic pain
Coping with chronic pain through focus groups, interviews and on-line surveys.

MS Care
Collaborative care to improve pain and depression care.

Power over Pain (POP)
Multiple psychology pain management strategies to understand if, how, and why they are helpful to patients with pain.

GetSMART
Impact of an exercise intervention on cognitive functioning.

ENHANCE: Mindfulness and neurofeedback

Promoting Resilience in Adults Aging with MS: Intervention to promote healthy aging with MS.

Enhance Wellness:
Benefits of a health and wellness program for older adults with physical disabilities, including MS.
Physical Modalities to reduce erythema caused by Plegridy
Pilot study of warm and cold compress to reduce injection site erythema due to peginterferon-beta-1a

Mirabegron and behavioral modification for overactive bladder in MS
Randomized controlled double-blind trial of behavioral modification with or without mirabegron for effect on overactive bladder symptoms in people with Multiple Sclerosis.

Laughter therapy for mood in central nervous system disorders
Single-arm prospective investigation of the effects of laughter therapy on mood, stress, and self-efficacy in people with central nervous system disorders.

Impact of Tecfidera on the Gut Microbiome
Pilot study measuring the impact of Tecfidera on the Gut Microbiota: Does a change in the gut flora correlate with gastrointestinal disturbances following therapy initiation?

ESTEEM
Multicenter, Global, Observational Study to Collect Information on Safety and to Document the Drug Utilization of Tecfidera™ (Dimethyl Fumarate) When Used in Routine Medical Practice in the Treatment of Multiple Sclerosis
ASSESS
Evaluating Safety and Efficacy of Two Doses of Fingolimod versus Copaxone
12-month, Randomized, Rater- and Dose-blinded Study to Compare the Efficacy and Safety of Fingolimod 0.25 mg and 0.5 mg Administered Orally Once Daily With Glatiramer Acetate 20 mg Administered Subcutaneously Once Daily in Patients With Relapsing-remitting Multiple Sclerosis

IM22
Intravenous Infusion Study of rHIgM22 in Patients with MS Immediately Following a Relapse
Double-Blind, Placebo-Controlled, Single Ascending Dose Intravenous Infusion Study of rHIgM22 in Patients with Multiple Sclerosis Immediately Following a Relapse

ESTEEM
Multicenter, Global, Observational Study to Collect Information on Safety and to Document the Drug Utilization of Tecfidera When Used in Routine Medical Practice in the Treatment of Multiple Sclerosis

EVOLVE-MS
Study of ALKS 8700 in Adults with Relapsing Remitting Multiple Sclerosis
Phase 3 Open Label Study to Evaluate the Long-term Safety and Tolerability of ALKS 8700 (a monomethyl fumarate molecule) in Adults with Relapsing Remitting Multiple Sclerosis
CONCERTO
Multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled study followed by an active treatment period, to evaluate the efficacy, safety and tolerability of two doses of oral administration of laquinimod (0.6 mg/day or 1.2 mg/day) in subjects with relapsing remitting multiple sclerosis (RRMS).

EXPAND

SYNERGY
Study to assess the efficacy, safety, tolerability, and pharmacokinetics of BIIB033 in subjects with relapsing forms of multiple sclerosis when used concurrently with Avonex.

CENSUM
Phase 1 randomized study of MEDI-551 in subjects with relapsing-remitting multiple sclerosis.

TCELNA
Phase 2 double-blind, placebo controlled multi-center study to evaluate the efficacy and safety of Tcelna™ in subjects with secondary progressive multiple sclerosis.
VACCINEX

LOW DOSE FINGOLIMOD
12-month, randomized, rater- and dose-blinded study to compare the efficacy and safety of fingolimod 0.25 mg and 0.5 mg administered orally once daily with glatiramer acetate 20 mg administered subcutaneously once daily in patients with relapsing-remitting multiple sclerosis.

RESPOND
Multicenter, open-label, 12-month observational study evaluating the clinical effectiveness and impact on patient-reported outcomes of oral Tecfidera delayed-release capsules in patients with relapsing forms of multiple sclerosis after suboptimal response to glatiramer acetate.

IMAGING DEMYELINATION
Quantitative imaging of white and gray matter demyelination in multiple sclerosis using macromolecular proton fraction mapping.

SPRINT MS
Randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability and activity of Ibudilast (MN-166) in subjects with progressive multiple sclerosis.
Thank You

Team at the UW MS Center