Disclosures

Program Faculty

The program faculty reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

**Patricia K. Coyle, MD, FAAN, FANA** - Consultant/Independent Contractor: Accordant, Acorda, Bayer, Biogen, Celgene, Genentech/Roche, Genzyme/Sanofi, Novartis, Serono; Grant/Research Support: Actelion, Genentech/Roche, MedDay, Novartis

**Clyde E. Markowitz, MD** - Consultant/Independent Contractor: Teva, EMD-Serono, Bayer, Malinkrodt, Biogen, Roche/Genentech, Genzyme/Sanofi, Novartis, Celgene

Non-faculty Content Contributors

Non-faculty content contributors and/or reviewers reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

**Chad Williamson, MS, MBA, CMPP; Blair St. Amand; Lindsey Scott, PT, DPT, ATC** - Nothing to disclose

The planners, reviewers, and staff at the Consortium of Multiple Sclerosis Centers in a position to influence content have disclosed no relevant financial relationships.

Educational Objectives

- Describe the benefits of starting an optimal DMT early to achieve the new treatment goal of “no evidence of disease activity” (NEDA)
- Evaluate the short- and long-term safety, tolerability, immunologic profiles, and efficacy of available DMTs for MS
- Apply knowledge of the benefits and risks of available DMTs to select an optimal personalized MS treatment
Analyzing the Evidence to Achieve New Treatment Goals in MS

MS Definition/Demographics

• Major acquired CNS disease of young adults (short of trauma) with striking characteristics

• Young age at onset (90% between ages 15 and 50; pediatric MS 2% to 4%; 10% >age 50; <1% before age 10 or after age 60)

• Female predominance 3:1 (increasing)

• Variability; low/medium/high risk zones; largely (>90%) Caucasian (but seen in virtually all groups)

Montalban X et al. Mult Scler. 2018;24:96-120.
MS Definition/Demographics

- Lifespan shortened 6-8 years (2° complications in disabled MS, brainstem involvement, suicide)
- Significant morbidity for untreated disease (involves motor, cognitive, vocational limitations)


MS Mortality

- Manitoba data sources
  - MS (n=5,797) vs matched controls (n=28,807)
- Median survival 75.9 vs. 83.4 years
  - MS showed 2-fold increased risk of death
- Comorbidities (diabetes, ischemic heart disease, depression, anxiety, chronic lung disease) ↑ death risk in both groups
- Most common cause of death in MS related to nervous system (44% MS or related complications); circulatory diseases
  - ↑ mortality from infections, respiratory disease

**MS Phenotypes**

- Radiologically isolated syndrome (RIS) (not officially recognized)
- Clinically isolated syndrome (CIS) (categorized as high/low risk for MS based on brain MRI)
- Relapsing MS
- Primary progressive MS (PPMS)
- Secondary progressive MS (SPMS)


**MS Endophenotype**

- At risk population
- RIS
- Prodromal MS
- CIS/relapsing or PPMS

CIS = clinically isolated syndrome; PPMS = primary progressive MS; RIS = radiologically isolated syndrome
Prodromal MS

- Matched cohort study from linked health administrative/clinical databases from 4 Canadian provinces
- Compared n=14,428 MS vs n=72,059 matched controls
- Annual healthcare use (hospital admissions, physician claims, prescriptions) went up steadily from years 5 to 1 prior to CIS

CIS = clinically isolated syndrome

Prodromal MS

- Nested case-control study of conscription exams at age 18/19 of Norwegian men (1950-1995) and Norwegian MS registry
- Cognitive scores available on n=924 future MS cases, n=19,530 controls
- Cognition significantly worse in those with clinical MS onset up to 2 years post assessment
  - PPMS men with onset up to 20 years later scored significantly lower vs controls

**MS Disease Activity**

- Two modifiers; defined time frame
- Active or not active
  - Covers all phenotypes; determined by clinical relapse, or new/enlarging T2 or contrast + MRI lesion
- Progressing or not progressing
  - Covers progressive phenotypes; determined by presence/absence of gradual clinical worsening independent of relapses


**MS Natural History**

- MS starts off as CIS-relapsing MS (85%-90%)
- Relapsing MS (untreated) generally transitions to SPMS
- Progressive MS means inevitable disability

CIS = clinically isolated syndrome; SPMS = secondary progressive MS
**Early Treatment**

- Organ-specific immune mediated diseases show window of opportunity
- Minimize epitope spread
- Minimize ongoing accumulating permanent CNS damage
- Virtually all studies report better results with early vs delayed therapy
- ECTRIMS/EAN and AAN Practice Guidelines recommend treating CIS/high-risk, first-attack MS, active-relapsing MS; consider treating active SPMS, PPMS

CIS = clinically isolated syndrome; ECTRIMS/EAN = European Committee for Treatment and Research in MS/European Academy of Neurology; PPMS = primary progressive MS; SPMS = secondary progressive MS

Montalban X et al. Mult Scler. 2018;24:96-120.

**Window of Opportunity: RA**

- Meta-analysis of studies reporting DMARD-free sustained remission
  - n=18 articles out of n=836 screened (n=10 high quality)
- Strong association between symptom duration and radiographic progression, DMARD sustained remission
- Treatment guidelines endorse early therapy (≤6 months), treat to target, reassess Q3 months

DMARD = disease-modifying antirheumatic drug

Emerging Treatment Principles

- Treat early/young
  - Within 3 to 6 months of CIS
- Use shared decision-making
- Have a treat-to-target approach
  - Minimal to no evident disease activity (MEDA/NEDA)
- Emphasize wellness; identify comorbidities to be managed
  - To help CNS reserve; preserve brain

CIS = clinically isolated syndrome; MEDA = minimal evidence of disease activity; NEDA = no evidence of disease activity

Emerging Treatment Principles

- Analyze disease activity (clinical/MRI) and prognostic profile
- Follow closely both clinically and with monitoring/surveillance brain MRI
  - MRI at 6 months, then 12 months, then Q12-24 months
  - More frequently in high-risk PML patients (Q3-6 months)
- Do not be afraid to switch
  - Current ARR rates indicate 1 attack every 3-6 years

ARR = annualized relapse rate; PML = progressive multifocal leukoencephalopathy
Wellness/Health Maintenance Program

- Increasing evidence that health maintenance changes/improves CNS reserve, function, repair
- This can be considered a DMT for MS
- Components involve
  - High normal vit D levels; vit B12 >400
  - Regular aerobic exercise, weight loss
  - No smoking, limited alcohol and salt, healthy diet
  - Regular mental and social stimulation
  - Good sleep hygiene, manage stress
  - Watch blood pressure, lipids, hemoglobin A1C, bone density/prostate/health-monitoring issues

Impact of Early Therapy on Disability Pension

- Swedish MS registry treated from 2002-2012 (n=2,477)
- Analyzed time to treatment, and full-time disability pension
- Patients starting treatment within 6 months had 36% lower risk for full-time disability pension (vs more than 18 months)

NEDA

• No evidence of disease activity is composite measure
  – No relapses, confirmed EDSS worsening, new/enlarging or contrast MRI lesions
  – NEPAD (no evidence of progression or active disease) proposed for progressive MS

• NEDA provides a treat-to-target goal

• Important to look at cumulative rates

EDSS = Expanded Disability Status Scale; NEDA = no evidence of disease activity
Giovannoni G et al. MS Relat Disord. 2018;20:228-231.

NEDA

• Does not address microscopic injury or activity biomarkers
  – NEDA-4 adds brain volume loss ≤0.4% annually; proposed additions include cognition, vision, PROs, QOL, biomarkers (esp NfL protein)
  – DTI deterioration despite NEDA
  – Neurofilament light protein

• NEDA has been applied to clinical trials; proposed in clinical practice
• MEDA (minimal evidence of disease activity) allows some breakthrough activity; in RA MEDA much more likely than NEDA/remission

DTI = diffusion tensor imaging; NFL = neurofilament light; PRO = patient-reported outcomes; QOL = quality of life; RA = rheumatoid arthritis
NEDA

• In CLIMB cohort (n=219), 46% met NEDA at year 1, 7.9% at year 7
  – NEDA at year 2 (27.5%) had 78.3% PPV for no EDSS worsening at year 7
• In UCSF cohort (n=517), NEDA at year 2 (17.9%)
  – Did not predict EDSS worsening at year 10 (trend to worse score); MRI activity in first 2 years not associated with 10 year clinical worsening

EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; NEDA = no evidence of disease activity; PPV = positive predictive value


NEDA Predictors

• ↑ BBB permeability in NAWM at 6 months post treatment (measured by ↑ Ki on dynamic contrast enhanced MRI) predicted 2-year NEDA failure
• Evaluated in 35 relapsing MS patients, started on fingolimod/natalizumab
  – Those who lost NEDA at 2 years showed 51% ↑ mean Ki vs those who maintained NEDA (P=0.002)
  – >0.136 mL/100 g/min had 12.4 OR for suboptimal response
• Conclusion: BBB permeability reliably predicts suboptimal response; there is a predictive threshold for disease activity

BBB = blood-brain barrier; NAWM = normal-appearing white matter; NEDA = no evidence of disease activity.

## NEDA/MEDA

- In recent IFN-β analysis (n=516, 2 cohorts), during first year
  - MEDA (<3 new T2 or <2 contrast lesions; 1 relapse with 0 or 1-2 new T2 lesions) had little impact on long-term disability
  - NEDA did not significantly predict outcome

MEDA = minimal evidence of disease activity; NEDA = no evidence of disease activity


## Summary

- RIS not yet recognized as MS phenotype
- We should be using active vs not active, progressing vs not progressing as activity markers
- Early therapy (within 3-6 months of CIS) should be embraced
- MEDA seems more practical than NEDA, but must be defined

CIS = clinically isolated syndrome; MEDA = minimal evidence of disease activity; NEDA = no evidence of disease activity; RIS = radiologically isolated syndrome
Evaluating Current Safety/Efficacy Data of DMTs for MS

Existing and Emerging MS Therapies 2018
**Interferon Beta (IFNβ)**

- Five approved agents effective in relapsing MS
  - IFNβ-1a 30 μg IM weekly
  - IFNβ-1a 22 and 44 μg SC 3x per week
  - IFNβ-1a 125 μg SC every 2 weeks
  - IFNβ-1b 250 μg SC every other day (plus generic)
- Lengthy experience, with few safety issues
- Major AEs, flu-like symptoms, injection-site reactions; ? depression, menstrual irregularities, rare cases of microangiopathy
- Need to monitor hepatic enzymes, CBC + diff, TSH

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**IFNβ: Putative Mechanism of Action**

*IFNβ is Believed to Act at Multiple Levels*

- Increase anti-inflammatory cytokine production
- Decrease pro-inflammatory cytokine production
- Increase T suppressor cell activity
- Limit migration of T cells into CNS via decreased matrix metalloproteinase and adhesion molecule expression
- Decreased monocyte activation; antigen presentation (↓ MHC-2)
- Antiviral activity

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*References*


Glatiramer Acetate (GA)

- Two branded products (and two generics for each) currently available
  - GA 20 mg SC every day, brand and generics
  - GA 40 mg SC 3x per week, brand and generics
  - Others may be forthcoming
- Studies reported relapse rates decreased by 29% to 34% vs placebo
- Decreases new MRI lesions
- Lengthy experience, with no safety issues, best pregnancy data

GA = glatiramer acetate; MRI = magnetic resonance imaging; SC = subcutaneous

Glatiramer acetate. [prescribing information]. Kansas City, MO: TEVA Neuroscience, Inc; 2014.

Glatiramer Acetate

Putative Mechanisms of Action

- Random polymer of 4 amino acids
  - Glutamic acid, lysine, arginine, tyrosine
- Increases CD4+ and CD8+ T-regulatory cells
- May promote regulatory B cells
- Increased expression of anti-inflammatory cytokines

BDNF = brain-derived neurotrophic factor; CNS = central nervous system

Risk-Benefit Analysis and Personalized Treatment in Multiple Sclerosis

Basing Treatment Goals on the Latest Evidence

Head-to-Head Trials Show No Differences in Clinical Efficacy Between IFNβ and GA

 REGARD Study: IFNβ-1a vs GA

![Graph showing clinical efficacy comparison between IFNβ-1a and GA](image_url)

- Patients Free from Relapse (%)
  - IFNβ-1a (n=386)
  - GA (n=378)
- Annualized Relapse Rate
  - IFNβ-1a (n=386)
  - GA (n=378)

Annualized Relapse Rates for IFNβ-1a and GA in CombiRx

- Hazard Ratio = 0.94 (95% CI 0.74-1.21), P = 0.64
- Survival Distribution Function

Fingolimod

- 0.5 mg once daily
  - Requires monitored initiation
- Reduction of relapses and risk of disability progression vs placebo
- Reduction of relapse vs IFNβ
- Decreases new lesions seen on MRI, as well as rate of brain volume loss vs placebo

MRI = magnetic resonance imaging

Fingolimod. [prescribing information]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; 2012.

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Fingolimod Mechanism of Action

- Sphingosine-1-phosphate (S1P) receptor modulator
- Binds subtypes S1P 1, 3, 4, and 5
- S1P-1 receptor binding after phosphorylation results in internalization and loss of signaling function necessary for activated lymphocytes to leave lymphoid tissue and enter circulation
- Effector memory cells in tissues are not affected, thus preserving immune surveillance
- S1P receptors in glial cells allow for potential effects in CNS
- In EAE; enhanced remyelination and axonal protection when administered into the brain; unknown whether similar effects occur in MS

FTY720 = Fingolimod


Clinical Efficacy: Fingolimod

- 52% reduction in risk of relapse (70.4% vs 45.6% relapse-free x2 years)
- 30% reduction in risk of confirmed EDSS worsening at 12 weeks (17.7% vs 24.1% placebo)
- 37% reduction in risk of sustained EDSS worsening at 24 weeks (12.55% vs 19%)

EDSS = Extended Disability Status Scale

Fingolimod 0.5-mg Dose vs Placebo
Efficacy on MRI

- Reduction of mean new or increasing T2 lesions of 2.5 vs 9.8
- 50.5% of patients free of new or increasing T2 lesions vs 21.2% with placebo
- Significant reduction in change of T1 lesion volume
  - (33 mm³ vs 173 mm³)
- Reduced mean/median loss in brain volume:
  - 0.84/-0.67% per year vs -1.31/-0.98% per year, respectively


Fingolimod Safety and Tolerability

- Cardiovascular
  - First-dose observation for 6 hours
  - Caution regarding use in patients with CVD, prolonged QTc, or concomitant meds, with potential to cause cardiac arrhythmia, prolonged QT, decreased HR
  - ECG at the end of observation; new heart block, arrhythmia, or symptomatic bradycardia require further observation
- Macular edema; increased risk with diabetes or uveitis

- Hepatotoxicity
- Infections: respiratory, herpetic; must have varicella zoster virus immunity
- Avoid live virus vaccinations
- Pulmonary effects: reductions in FEV1 and DLCO
- Subsequent hypertension
- Tolerability: headache

Fingolimod Safety

- Progressive multifocal leukoencephalopathy
- Cryptococcal infections
- ?? Skin cancers
- Reports of tumefactive MS lesions in patients taking fingolimod
- Possible rebound activity following discontinuation

Teriflunomide

- Oral agent; 7- and 14-mg doses once-daily approved in the United States in 2012
- Metabolite of leflunomide, which is used to treat rheumatoid arthritis
- Most clinical benefit is seen with 14-mg dose
- Reduction in relapses, risk of disability worsening (14-mg dose only), and new MRI lesions
- Generally well-tolerated
Teriflunomide: Putative Mechanism of Action

- Inhibits dihydroorotase dehydrogenase in mitochondria
- Rate-limiting enzyme in de novo pyrimidine synthesis pathway
- Selective cytostatic effect on rapidly dividing cells, including proliferating lymphocytes
- May interfere with T cell–APC interaction, resulting in decreased T-cell activation
- Long half-life in the body: accelerated elimination protocol with cholestyramine


Clinical Efficacy: Teriflunomide

- Relapse reduction of 31% vs placebo for both doses in the TEMSO study; 36% for 14 mg dose and 22% for 7 mg dose seen in the TOWER study
- Reduction of risk of 3-month disability worsening seen for only the 14 mg dose in 30% (TEMSO) and 31% (TOWER) of patients
- In a 9-year extension of TEMSO, relapse rates ranged from 0.23 to 0.17 (all on active drug after end of initial study period)

Teriflunomide Safety and Tolerability

- Hair thinning; usually transient
- Gastrointestinal–abdominal pain, diarrhea
- Hepatotoxicity, rare fulminant hepatotoxicity with leflunomide
- Teratogenic in animal models
- Peripheral neuropathy
- Hypertension

- Potential issues in prescribing information (seen with leflunomide in RA)
  - Opportunistic infections
  - Interstitial pulmonary disease
  - Leukopenia (lymphs or PMN), thrombocytopenia
  - Hypersensitive cutaneous reactions
  - Hyperkalemia
  - Transient renal failure/uric acid nephropathy

- No new safety issues in 9-year extended follow-up


Dimethyl Fumarate

- 240 mg twice daily oral agent
- Approved in 2013
- Efficacy in reducing relapses, risk of disability, and new MRI lesions
- One study included GA reference arm, although it is not powered for direct comparison
- Initial tolerability issues are usually transient
- Lymphopenia

Dimethyl Fumarate: Putative Mechanisms of Action

- Active metabolite: monomethyl fumarate (MMF)
- Enhances release of Nrf-2 (nuclear-related factor E2 [erythroid-derived 2]) related factor from binding with Keap-1 in cytosol, allowing translocation of Nrf-2 to the nucleus
- Inhibition of NF-κβ translocation to the nucleus and its stimulation of genes related to inflammatory cytokine, chemokine, and adhesion molecule expression
- Inhibition of endothelial expression of ICAM-1, VCAM-1, and E-selectin
- Induction of Nrf-2–mediated antioxidative pathways in astrocytes and microglia, with potential neuroprotective effects

Scannevin R et al. JPET. 2012;341:274-284;

Clinical Efficacy: Dimethyl Fumarate 240 mg bid

Percent with Relapse at 2 Years

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<thead>
<tr>
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<th>DEFINE</th>
<th>CONFIRM</th>
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<tbody>
<tr>
<td>DMF</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Placebo</td>
<td>45%</td>
<td>35%</td>
</tr>
<tr>
<td>GA</td>
<td>40%</td>
<td>30%</td>
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Annualized Relapse Rate at 2 Years

<table>
<thead>
<tr>
<th></th>
<th>DEFINE</th>
<th>CONFIRM</th>
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<tbody>
<tr>
<td>DMF</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>GA</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

49% ↓ risk of relapse vs placebo in DEFINE
34% ↓ risk of relapse in CONFIRM
38% ↓ risk of 3-month disability increase in DEFINE, not significant in CONFIRM

ARR = annualized relapse rate; DMF = dimethyl fumarate; GA = glatiramer acetate
Dimethyl Fumarate: Safety and Tolerability

- GI: abdominal pain, nausea, emesis, diarrhea; transient, mitigate with titration
- Flushing, transient, mitigate by taking with meals and aspirin
- Proteinuria
- Rash/pruritus
- Severe lymphopenia 4% to 5% in clinical trials
  - Five cases of PML, three associated with significant lymphopenia

Natalizumab

- Monthly intravenous infusions
- Potent suppression of relapsing MS
- Well-tolerated in most cases
- Major risk is PML
- CNS herpes virus infections reported
- Rebound on discontinuation
- Hypersensitivity/neutralizing antibodies

PML = progressive multifocal leukoencephalopathy
Natalizumab: Putative Mechanism of Action

- Selective monoclonal antibody directed at α4β1 integrin expressed on all WBCs except neutrophils
- Blocks attachment of activated lymphocytes to VCAM-1 on endothelial cells and subsequent migration into the CNS
- May increase CD34+ progenitor cells by interfering with homing to bone marrow
- May reduce CD4+/CD8+ ratios in the CSF with long-term treatment

CNS = central nervous system; CSF = cerebral spinal fluid; WBC = white blood cells

Natalizumab: Efficacy

Annualized Relapse Rate

<table>
<thead>
<tr>
<th></th>
<th>Natalizumab</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Year 1</td>
<td>0.26</td>
<td>0.23</td>
</tr>
<tr>
<td>Year 2</td>
<td></td>
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</table>

68% relative risk reduction vs placebo

42% reduction of risk on EDSS score progression confirmed at 12 weeks

ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale
Risk of PML by Anti-JCV ab Status
In MS Patients Treated with Natalizumab

Natalizumab-associated PMS Risk

Recent Data on Anti-JCV ab Index and Natalizumab-associated PMS Risk

JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy

Kuesters G. Presented at: AAN; April 18-25, 2015; Washington, DC. Poster #P4.031.

Alemtuzumab: MOA

- Targets CD52 antigen expressed on B and T lymphocytes
- Long-lasting depletion of T cells
- B cells return within a few months (may be related to autoimmune phenomena)

Alemtuzumab: Efficacy (1)

- CARE-MS I trial RRMS, naïve to DMT
  - 55% decrease in ARR compared with IFNβ-1a 44 μg tiw
  - 78% vs 59% patients relapse-free at 2 years
  - Low occurrence of disability progression in both arms; non-significant difference
  - Reduction in new/increasing T2 and contrast-enhancing T1 lesions on MRI
  - Reduction in brain volume loss by BPF

ARR = annualized relapse rate; BPF = brain parenchymal fraction; DMT = disease-modifying therapy; MRI = magnetic resonance imaging; TIW = 3 times per week


Alemtuzumab: Efficacy (2)

- CARE-MS II trial; breakthrough RRMS
  - 49% decrease in ARR compared with IFNβ-1a 44 μg tiw
  - 65% vs 47% patients relapse-free at 2 years
  - 42% reduction in 6-month sustained disability favoring alemtuzumab
  - Reduction in new/increasing T2 and contrast-enhancing T1 lesions on MRI
  - Reduction in brain volume loss by BPF

- Observation cohort from Cambridge: 60% improvement or stabilization of disability over median 7-year follow-up

ARR = annualized relapse rate; BPF = brain parenchymal fraction; DMT = disease-modifying therapy; MRI = magnetic resonance imaging; TIW = 3 times per week

Alemtuzumab 5-Year Disability and RR

**Alemtuzumab: Safety and Tolerability**

- Infusion reactions, premedication required
- Secondary autoimmunity up to 47.7%
  - Most commonly thyroid: 39%
  - ITP: 2%
  - Rare glomerular nephropathy: 0.3%
- Infections
  - Herpes virus infections, prophylactic antiviral treatment
  - Urinary tract infections
  - Upper respiratory infections
- Possible increased risk of malignancies
  - Thyroid, melanoma, lymphoproliferative

- Tolerability
  - Headache, dizziness, paresthesias
  - GI
  - Arthralgia
  - Fatigue
- Intense REMS program
  - Monthly CBC, UA
  - Quarterly thyroid testing
  - Continue for 4 years following last dose
  - Annual skin exams
- Acute acalculous cholecystitis (8 cases), Hemophagocytic lymphohistiocytosis (HLH), 2 cases

CBC = complete blood count; GI = gastrointestinal; ITP = idiopathic thrombocytopenic purpura; UA = urinanalysis.

Ocrelizumab

- Anti-CD20 monoclonal antibody that targets mature B cells
- Phase III studies:
  - ORATORIO
    - Progressive MS
    - Ocrelizumab vs placebo
    - Significantly reduced clinical disease progression
  - OPERA I and II
    - Relapsing MS
    - Ocrelizumab vs IFNb-1a
    - Ocrelizumab reduced relapses and significantly delayed clinical disability

INF = interferon

Ocrelizumab Superior to IFNβ-1a in Reducing ARR
Phase III Results of OPERA I and II

- Compared with IFNβ-1a, ocrelizumab reduced:
  - ARR
  - 12- and 24-week CDP (by 40%)
  - T1 Gd+ lesions (by 94% to 95%)
  - New/enlarging T2 lesions (by 77% to 83%)
- Safety profile ocrelizumab:
  - Similar to IFNβ-1a
  - Most common: IRR (at first dose)

Adjusted ARR at 96 Weeks (%)

<table>
<thead>
<tr>
<th></th>
<th>OPERA I</th>
<th>OPERA II</th>
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<tbody>
<tr>
<td>ARR</td>
<td>0.292</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>0.156</td>
<td>0.155</td>
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Primary Endpoint ARR at 96 weeks

<table>
<thead>
<tr>
<th></th>
<th>IFNβ-1a</th>
<th>Ocrelizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AE</td>
<td>8.7%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Malignancies</td>
<td>n = 2</td>
<td>n = 4</td>
</tr>
<tr>
<td></td>
<td>(lymphoma)</td>
<td>(renal cancer, melanoma, breast cancer)</td>
</tr>
<tr>
<td>Deaths</td>
<td>n = 2</td>
<td>n = 1</td>
</tr>
<tr>
<td></td>
<td>(suicide, mechanical ileus)</td>
<td>(suicide)</td>
</tr>
</tbody>
</table>

AE = adverse event; ARR = annualized relapse rate; CDP = confirmed disability progression; Gd+ = gadolinium-enhancing; IFNb-1a = interferon beta; IRR = infusion-related reaction
**Ocrelizumab in Relapsing MS**

Reduction in Mean Gd+ Lesions Compared with IFNβ-1a

**OPERA I**
- Mean Number per Patient per MRI Scan*
  - IFNβ-1a 44 µg
  - Ocrelizumab 600 mg

<table>
<thead>
<tr>
<th>Week 24</th>
<th>Week 48</th>
<th>Week 96</th>
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<tbody>
<tr>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>IFNβ-1a</td>
<td>372</td>
<td>357</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>382</td>
<td>377</td>
</tr>
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91% \( P<0.0001 \) 98% \( P<0.0001 \) 95% \( P<0.0001 \)

**OPERA II**
- Mean Number per Patient per MRI Scan*
  - IFNβ-1a 44 µg
  - Ocrelizumab 600 mg

<table>
<thead>
<tr>
<th>Week 24</th>
<th>Week 48</th>
<th>Week 96</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>IFNβ-1a</td>
<td>372</td>
<td>334</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>385</td>
<td>373</td>
</tr>
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</table>

92% \( P<0.0001 \) 96% \( P<0.0001 \) 97% \( P<0.0001 \)

*Adjusted by means calculated by negative binomial regression and adjusted for baseline T1 Gd lesion (present or not), baseline EDSS (<4.0 vs ≥4.0) and geographical region (US vs ROW [Rest of World]). INF = interferon; Gd+ = gadolinium enhancing.


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**Ocrelizumab: ORATORIO Trial in PPMS**

**Phase III Study (n=732)**

Ocrelizumab 600 mg (2 x 300 mg infusions, 14 days apart) vs Placebo

- **Time to sustained disability progression (EDSS increase sust. ≥12 weeks)**
  - 24% ↓ with Ocre vs pbo \( (P=0.0321) \)

- **Time to sustained disability progression (EDSS increase sustained ≥24 weeks)**
  - 25% ↓ with Ocre vs pbo \( (P=0.0365) \)

- **Change in Timed 25-Foot Walk Test**
  - 29% ↓ with Ocre vs pbo \( (P=0.040) \)

- **Change in total volume of T2 lesions on MRI brain scans**
  - Vol of hyperintense T2 lesions 34% relative ↓ with Ocre vs pbo \( (P<0.0001) \)
  - Whole brain vol loss 17.5% relative ↓ with Ocre vs pbo \( (P=0.0206) \)

- **Adverse events (AE)**
  - Pts with AEs: 95.1% Ocre arm vs 90.0% pbo arm
  - Most common Ocre-associated AE: infusion-related reactions (38.9% Ocre vs 25.5% pbo)
  - Serious AEs: 20.4% Ocre vs 22.2% pbo

EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; Ocre = ocrelizumab; pbo = placebo

Effect of Gad+ Lesions on Efficacy of Ocrelizumab in PPMS

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Placebo (N=244)</th>
<th>Ocrelizumab (N=488)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>Events</td>
<td>n</td>
<td>Events</td>
</tr>
<tr>
<td>Overall population</td>
<td>731</td>
<td>244</td>
<td>96</td>
<td>487</td>
<td>160</td>
</tr>
<tr>
<td>TL Gd+ lesions</td>
<td>193</td>
<td>60</td>
<td>27</td>
<td>133</td>
<td>43</td>
</tr>
<tr>
<td>No TL Gd+ lesions</td>
<td>533</td>
<td>183</td>
<td>68</td>
<td>350</td>
<td>115</td>
</tr>
</tbody>
</table>

*Analyses based on ITT population; p-values based on log-rank test stratified by geographic region and age. Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression. CDP = confirmed disability progression; Gd+ = gadolinium-enhancing; EDSS = Expanded Disability Status Scale; HR = hazard ratio; ITT = intent to treat.

Ocrelizumab in PPMS

Adverse Events (>1% of patients) (PPMS)

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Placebo (n=239)</th>
<th>Ocrelizumab 600 mg (n=486)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patient with ≥1 SAE</td>
<td>53 (22.2)</td>
<td>99 (20.4)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>14 (5.9)</td>
<td>30 (6.2)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>11 (4.6)</td>
<td>19 (3.9)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>9 (3.8)</td>
<td>18 (3.7)</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, and unspecified (including cysts and polyps)</td>
<td>7 (2.9)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>3 (1.3)</td>
<td>10 (2.1)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>6 (2.5)</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>General disorders and administration-site conditions</td>
<td>3 (1.3)</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3 (1.3)</td>
<td>5 (1.0)</td>
</tr>
</tbody>
</table>

*Thirteen malignancies were reported:
- 2 (0.8%) in the placebo arm: 1 cervix adenocarcinoma in situ and 1 basal cell carcinoma
- 11 (2.3%) in the ocrelizumab arm: 4 breast cancers, 1 endometrial adenocarcinoma, 1 anaplastic lymphoma, 1 histiocytoma, 1 metastatic pancreas cancer, and 3 basal cell carcinomas

SAE = serious adverse event
Montalban X et al. ECTRIMS 2015, Abstract 228.
Ocrelizumab: Questions

- Which patients?
- ORATORIO PPMS trial only significant benefit in men?
- Cancer concern?: 6 breast cancer cases in ocrelizumab-exposed subjects vs zero in comparator groups.
- Older patients with concern for immunosenescence
- Long-term safety of continuous B cell depletion?

The Current DMT Landscape

- Multiple agents with multiple mechanisms of action
- Allow for individual optimization of DMT
- Risks with some agents increase monitoring requirements
- Potency of some newer agents may permit rapid early suppression of inflammatory disease activity in RRMS, with potential long-term benefits on MS course
- Strategies of DMT choice, sequencing, and monitoring are now important elements of MS therapy for which good data are only beginning to emerge
Balancing Risk vs Benefits of Treatment with the Patient

Thank you for joining us today!

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Your participation will help shape future CME activities.