Recent Advances in Neurology: Multiple Sclerosis
Emerging Therapies

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Updates on Approved Therapies

**Immunopathogenesis of the MS Lesion**

Figure courtesy of Dhib-Jalbut S, 2008

**PreCISe 5-year Follow-up: Early Treatment with GA Reduces CDMS Risk**

- 42% reduction in the number of new T2 lesions per year ($p < 0.0001$)
- 59% reduction in T2 lesion volume from baseline ($p < 0.0001$)
- 23% less loss of brain volume (atrophy) from baseline ($p = 0.021$)

*Adjusted for treatment exposure; Number of scans: early (654), delayed (671)

Long-Term Follow-up for IM IFNβ-1a

Odds ratios (ORs) were calculated for early disease activity as a predictor of EDSS progression (≥ 4.5-point change of EDSS over 15 years).
During the 2-year trial, early disease activity in treated patients predicted EDSS progression:
- ≥ 2 GdE lesions: OR = 8.96, p < 0.001
- ≥ 2 relapses: OR = 4.44, p = 0.010
- ≥ 3 new T2 lesions: OR = 2.89, p = 0.080

In patients originally in the placebo arm, early MRI indicators and relapses did not significantly predict long-term EDSS outcomes.


Estimated Incidence of PML by Natalizumab Treatment Epoch

85 cases of PML have been documented in patients treated with natalizumab as of January 19, 2011.

Natalizumab Suspension Is Associated with MS Disease Activity

Natalizumab Suspension Is Associated with MS Disease Activity

Study rationale:
- PML risk increases markedly with exposure to natalizumab treatment
- Consequences of treatment suspension are unknown

Patient groups:
- 68 natalizumab-treated patients who underwent treatment interruption (NAT-INT)
- 16 patients who maintained treatment (NAT-MAINT)

Results (6 months after NAT-INT)


West T and Ores A Annals Neurology 2010;68:395-9

Presence of Anti-JCV Antibody Affects Incidence of PML

Estimated risk of PML in JCV seronegative individuals is <1:10,000
Implications for JCV seronegative individuals:
1) ongoing use with annual monitoring for seroconversion
2) first line use of natalizumab

West T and Ores A Annals Neurology 2010;68:395-9

**Emerging MS Therapies**

**Teriflunomide: TEMSO Study**

**Phase 3 Trial Design**

- 108-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study

- Oral teriflunomide 14 mg once daily
- Oral teriflunomide 7 mg once daily
- Placebo once daily

Percent Completing Study: 73.3%
- 74.9%
- 71.3%

1088 patients (1:1:1)

Randomization Week 24 Week 48 Week 72 Week 108 Clinic Visits

**Clinical 2 Year Outcomes**

- Annualized Relapse Rate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Annualized Relapse Rate</th>
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<tr>
<td>Placebo</td>
<td>.539</td>
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<tr>
<td>7 mg Teriflunomide</td>
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<tr>
<td>14 mg Teriflunomide</td>
<td>.369</td>
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*O’Connor P et al. ECTRIMS 2010 Göteborg, Sweden [Abstract 79]*
Teriflunomide: TEMSO Efficacy Clinical 2 Year Outcomes

12 week confirmed EDSS change

Percent Confirmed Progression

Placebo 7 mg Teriflunomide 14 mg Teriflunomide

23.7% \( p = 0.0835 \)

29.8% \( p = 0.0279 \)

O’Connor P et al. ECTRIMS 2010 Göteborg, Sweden

Teriflunomide Phase III Study (TEMSO): Total Lesion Volume

Key MRI endpoint: burden of disease (total lesion volume)

Mean ± SE Change from Baseline

Placebo 7 mg teriflunomide 14 mg teriflunomide

*relative change from placebo


Teriflunomide: TEMSO MRI 2 year Outcomes

Number Gad Lesions

Number of Gadolinium Enhancing Lesions

Placebo 7 mg Teriflunomide 14 mg Teriflunomide

1.331 0.570 0.261

57.2% \( p < .001 \)

80.4% \( p < .001 \)

Wolinsky J et al. ECTRIMS 2010 Göteborg, Sweden P982

Teriflunomide: TEMSO Safety and Discontinuations

Percent AE

Placebo 7 mg Teriflunomide 14 mg Teriflunomide

Any AE 87.5% 89.1% 90.8%

Serious AE 12.8% 14.1% 15.9%

Discontinuation AE 8.1% 9.8% 10.9%

Serious Hepatic disorders 2.5% 1.9% 2.5%

ALT > 3 X Upper Limit Nml 6.7% 6.3% 6.7%

Serious Infections 2.2% 1.6% 2.5%

\( N = 1,088 \) patients randomized to teriflunomide (7 mg or 14 mg daily) or placebo

73.2% of patients completed treatment

ALT, alanine aminotransferase

O’Connor P et al. ECTRIMS 2010 Göteborg, Sweden [Abstract 79]
**Teriflunomide: TEMSO Conclusions**

- Teriflunomide significantly reduced the annualized relapse rate
- 14 mg Teriflunomide significantly reduced the proportion of patients experiencing 12 week sustained change in EDSS
- Teriflunomide reduced accumulation of brain MRI lesions in a dose dependent manner
- Teriflunomide was well tolerated and reasonably safe
  - Caveat: Teriflunomide is a teratogen (women and men)
  - Following discontinuation serum concentration becomes safe after 2 years due to biliary recirculation
  - Therefore requires cholestyramine and activated charcoal washout
- Cross-trial comparison suggests teriflunomide’s efficacy is similar to that of interferons and glatiramer acetate (caveats apply)

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**Ofatumumab**

**Ofatumumab: Phase II trial**

- Ofatumumab is a humanized anti-CD20 monoclonal antibody that binds to B cells and causes cell death
- 24 week, phase II, multicenter, randomized, placebo-controlled, dose finding study in International Panel criteria MS
- 2:1 randomization with increasing doses of ofatumumab 100mg, 300mg, 700mg following verification of safety at lower doses
- MRI at weeks -4, baseline, 8, 12, 16, 20, 24

**Ofatumumab Phase 2 Trial Design**

24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study
- IV ofatumumab 700 mg (N=7)
- IV ofatumumab 300 mg (N=11)
- IV ofatumumab 100 mg (N=8)
- Placebo (N=12)

Sorensen S et al. ECTRIMS 2010 Göteborg, Sweden
**Ofatumumab Phase II Study: T1 Gd-Enhancing Lesions**

- Similar MRI results were found for cumulative total number of Gad lesions and T2 lesions
- No safety signals, well tolerated
- Peripheral B cells were depleted at all doses
- Dose dependent B cell repletion observed at 24 weeks:
  - B cells reduced by 78% (100mg), 95% (300 mg), 98% (700mg)

**Ocrelizumab**

- The anti-CD20 monoclonal antibody rituximab selectively depletes CD20+ B-cells and demonstrates effect in RRMS
  - Phase I (Bar-Or, Ann Neurol 2008)
  - Phase II (Hauser, N Engl J Med 2008)
- Ocrelizumab is a recombinant humanised anti-CD20 antibody designed to selectively target CD20+ B-cells that binds to part of the a epitope targeted by rituximab
- This Phase II trial evaluated efficacy, by brain MRI lesions, and safety of 2 doses of ocrelizumab in patients with RRMS vs placebo and vs once weekly 30 mcg INFβ-1a
Ocrelizumab
Phase 2 Trial Design

48-week, randomized, double-blind, placebo-controlled with active comparator, parallel-group, multicenter study

- IV ocrelizumab 2000 mg (N=54)
- IV ocrelizumab 600 mg (N=54)
- IM IFN β-1a 30 mcg (N=55)
- Placebo (N=55)

218 patients

Week -4       Baseline   4        8       12        16       20       24/26          48

Sorensen S et al. ECTRIMS 2010 Göteborg, Sweden

*Humanized anti-CD20 mAb IFN β-1a arm was open-label; all efficacy comparisons were exploratory


↓ 89–96%, P < 0.0001 for both ocrelizumab doses vs placebo

Ocrelizumab: Clinical Results

ARR

0.24 (n=54) 0.24 (n=54) 0.24 (n=54) 0.24 (n=54)

0.0 0.2 0.4 0.6 0.8 1.0

0-24 weeks

Placebo OCR 600 mg OCR 2000 mg IFN beta-1a

Kappos L et al. ECTRIMS 2010 Göteborg, Sweden

Ocrelizumab: Safety

- No imbalance in AEs was observed across the treatment groups
- No imbalance in the number of infections was observed between ocrelizumab and placebo
- There were 7 serious AEs: 1 in placebo, 1 in 600 mg, 3 in 2000 mg, 2 in IFN beta-1a
- There were 2 serious events considered to be infection related: 1 in 2000 mg ocrelizumab, 1 in placebo
- No opportunistic infections were reported
- Higher incidence of IRRs observed in ocrelizumab groups for Cycle 1 Day 1 infusion (34.5% in 600 mg, 43.6% in 2000 mg); IRR rates were not different to placebo for the Cycle 1 Day 15 infusion
- There was 1 death in the 2000 mg ocrelizumab dose group at Week 14, disease onset Week 12
  - Systemic inflammatory response syndrome (SIRS) with disseminated intravascular coagulopathy and multi-organ dysfunction syndrome
  - No signs of viral infection found prior to and during hospitalisation, and in autopsy specimen
  - At Day 11 of hospitalisation, the patient had developed bacterial pneumonia
  - Immediate cause of death: transtentorial haemorrhage due to brain oedema

Kappos L et al. ECTRIMS 2010 Göteborg, Sweden
Alemtuzumab

Background and Mechanism of Action

- Alemtuzumab is a monoclonal humanized antibody directed against CD52 antigen (anti-CD52 Antibody)
- CD52 is a cell surface glycoprotein. The function of the CD52 antigen is unknown
  - Present on >95% of T cells and B cells (not plasma cells), monocytes, and eosinophils
- Alemtuzumab binding to CD52 causes:
  - Targeted depletion of CD52-expressing cells within 2 days
  - Depletion of B cells, T cells, monocytes
    - Long-term depletion of CD4+ (median 61 months in SPMS trial) and CD8+ T cells (30 months), resulting in prolonged lymphopenia and reduced inflammation in the CNS


Relapses Disability

ARR=annualized relapse rate.

CAMMS223 Trial Results: Co-Primary Endpoints

- 74% reduction in ARR vs IFNβ-1a (0.36 for IFNβ-1a and 0.10 for alemtuzumab)
- 71% reduction in sustained disability vs IFNβ-1a

Alemtuzumab: CAMMS223 Open Label Follow-up

- Open label extension study
- Participants in the 3 year Phase II trial of alemtuzumab in early, active RRMS were followed for up to 60 months
  - 55% (122/222) of alemtuzumab treated patients were evaluated at month 48 and 59.6% (133/223) were evaluated at 60 months
  - 32% (36/111) of interferon treated patients were evaluated at month 48 and 35.1% (39/111) were evaluated at 60 months
- Disability and relapse assessments were performed by an investigator masked as to initial or current treatment

N.B.: ~15% of patients followed to month 48 used alternate MS therapy. No explanation was provided as to why more subjects were evaluated at month 60 than at month 48. Original cohort: IFNβ-1a N=111, Alemtuzumab N=223. Wynn D et al. ECTRIMS 2010 Göteborg, Sweden P426, Coles et al ECTRIMS 2010 Göteborg, Sweden
Alemtuzumab: CAMMS223
60 Month Outcomes

Annualized Relapse Rate (ARR) (months 0-60)

- IFNB-1a: 0.35 (N=39)
- Alemtuzumab (all cycles): 0.11 (N=133)

Mean Change in EDSS at 60 months

- IFNB-1a: 0.00
- Alemtuzumab: 0.06 (N=133)

Note: ~15% of patients followed to month 48 used alternate MS therapy.
Original cohort: IFNβ-1a N=111, Alemtuzumab N=223 (161 subjects received 2 cycles, 61 received 3 cycles).

Laquinimod
Two Phase III Studies

ORAL LAQUINIMOD 0.6 mg OD: 500 RRMS PATIENTS
24/30 MONTHS OF DOUBLE-BLIND TREATMENT
ORAL MATCHING PLACEBO: 500 RRMS PATIENTS
ENDPOINTS: RELAPSES, EDSS, MRI (T1/T2/BLACK HOLES, BRAIN VOLUME), MSFC
NB: Clinical endpoints (relapse rate and disability progression) were met.

ORAL LAQUINIMOD 0.5 mg OD: 400 RRMS PATIENTS
AVONEX® 30mcg/WEEK: 400 PATIENTS
ORAL MATCHING PLACEBO: 400 RRMS PATIENTS
24 MONTHS OF TREATMENT, DOUBLE-BLIND FOR ORAL, RATER-BLINDED FOR AVONEX®
ENDPOINTS: RELAPSES, EDSS, MRI (T1/T2/BLACK HOLES, BRAIN VOLUME), Multiple Sclerosis Functional Composite (MSFC)

Chronic Cerebro-Spinal Venous Insufficiency (CCSVI) Hypothesis

1: CNS reflux of venous blood due to stenosing lesion
2: Erythrocytes enter brain parenchyma
3: Iron deposition in the brain
4: Toxic reaction to iron
5: Iron deposition and neuronal damage
6: MS demyelination and neuronal damage

Arguments for CCSVI

- CCSVI criteria met in 67–80% of MS patients vs 18–28% of controls
- Iron concentration ↑ in brains of MS-CCSVI patients
- Reduced visibility of brain parenchyma venous vasculature in MS-CCSVI patients
- Reported improvements in MRI variables and function in CCSVI patients who had minimally invasive endovascular treatment
- Calls for new studies to further test CCSVI hypothesis and treatments

Arguments against CCSVI

- Apparent CCSVI may be an artifact of flawed study methods
- Findings that directly challenge the hypothesis:
  - No evidence of venous reflux in MS patients with intracranial venous stenosis
  - No differences between MS patients and controls in proximal internal jugular vein (IJV) stenosis or flow in IJV and vertebral veins
  - Little or no evidence of CCSVI at disease onset in MS patients based on Doppler criteria
  - No relationships between CCSVI and lesion burden
- Any venous abnormalities observed in MS patients may be a result rather than a cause of the disease process

What will MS Therapy look like in 2012?

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<th>Safety</th>
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