A Practical Guide to Disease Modifying Therapy: Assessing risks and benefits of the expanding DMT repertoire

The right drug for the right person at the right time

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MS Summit June 10, 2017
Disclosures

- Dr. von Geldern: Research funding from Novartis
- Dr. Wundes: Research funding from Alkermes
Choosing a Treatment

The right drug for the right person at the right time
A *practical* guide to DMT management in MS
Goals of Disease Modifying Therapy

DMT **not a cure** but:

- Relapse rate ↓
- Relapse severity ↓
- MRI lesion burden ↓
- Accumulation of disability ↓
- Progression of brain atrophy ↓

Individual treatment response difficult to predict
Mechanism of Action

**Alemtuzumab**
- Lysis of CD52+ mononuclear cells, including CD4+ and CD8+ T cells, B cells, monocytes and some dendritic cells.

**Daclizumab**
- Enhances NK regulatory cell activity on T cells. It leads to increased lysis of activated T cells by CD56bright NK cells.

**Mitoxantrone**
- Prevents proliferation of autoimmune T cells and B cells.

**Natalizumab - IFN-β**
- Inhibits VLA-4 interactions with VCAM-1, thereby blocking the entry of VLA-4+ cells into the CNS across the BBB.

**Rituximab**
- Lysis of CD20+ B-cells.

**Fingolimod**
- Fingolimod retains T-cells and B-cells in lymph nodes by internalizing their S1P-receptors.

**Laquinimod - IFN-β**
- Downregulates MHC-II on the Macrophage (M) inhibits "antigen presentation".

**Glatiramer acetate**
- Enhances production of BDNF by neurons and other cells.

**Dimethyl fumarate**
- Enhances Nrf2, reducing oxygen radical activity.

**Anti-LINGO-1 rHgM22**
- Increases ODC remyelination of axons.
The Evolving Landscape of DMTs

**SELF-INJECTABLES**
- Interferon-beta 1a/b: Avonex®, Betaseron®, Extavia®, Rebif®
- Glatiramer acetate: Copaxone®

**INFUSIONS**
- Mitoxantrone: Novantrone®
- Natalizumab: Tysabri®

**ORAL AGENTS**
- Fingolimod: Gilenya®
- Teriflunomide: Aubagio®
- Dimethyl fumarate: Tecfidera®

**OFF-LABEL USE**
- Cyclophosphamide
- Rituximab
- Stem cell transplantation

**PHASE III**
- Cladribine
Comparing Efficacy

Limited data – not many head to head comparison trials

<table>
<thead>
<tr>
<th>Medication</th>
<th>Compared to</th>
<th>N</th>
<th>Trial name (reference)</th>
<th>ARR Relative reduction</th>
<th>ARR</th>
<th>Disability progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Interferon beta-1b</td>
<td>Interferon beta-1a i.m.</td>
<td>92 vs. 96</td>
<td>INCOMIN [63]</td>
<td>24%</td>
<td>0.5 vs. 0.7</td>
<td>44%</td>
</tr>
<tr>
<td>Interferon-beta-1a</td>
<td>Interferon-beta-1a i.m.</td>
<td>339 vs. 338</td>
<td>EVIDENCE [64]</td>
<td>16%*</td>
<td>0.54 vs. 0.64</td>
<td>13% (N.S.)</td>
</tr>
<tr>
<td>Interferon beta-1a</td>
<td>Glatiramer acetate</td>
<td>386 vs. 378</td>
<td>REGARD [65]</td>
<td>3% (N.S.)</td>
<td>0.30 vs. 0.29</td>
<td>25% (N.S.)</td>
</tr>
<tr>
<td>Interferon-beta-1b</td>
<td>Glatiramer acetate</td>
<td>899 vs. 448</td>
<td>BEYOND [66]</td>
<td>3% (N.S.)</td>
<td>0.33 vs. 0.34</td>
<td>5% (N.S.)</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Interferon-beta-1a s.c.</td>
<td>111 vs. 104</td>
<td>TENERE [31]</td>
<td>4% (N.S.)</td>
<td>0.26 vs. 0.22</td>
<td>-</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Glatiramer acetate</td>
<td>359 vs. 350</td>
<td>CONFIRM [35]</td>
<td>24% (N.S.)</td>
<td>0.22 vs. 0.29</td>
<td>17% (N.S.)</td>
</tr>
<tr>
<td><strong>Second-line</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Interferon beta-1a i.m.</td>
<td>431 vs. 435</td>
<td>TRANSFORMS [40]</td>
<td>52%*</td>
<td>0.16 vs. 0.33</td>
<td>25% (N.S.)</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Interferon beta-1a s.c.</td>
<td>376 vs. 202</td>
<td>CARE MS-1 [47]</td>
<td>55%</td>
<td>0.18 vs. 0.39</td>
<td>30% (N.S.)</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Interferon beta-1a s.c.</td>
<td>426 vs. 202</td>
<td>CARE MS-2 [48]</td>
<td>49%</td>
<td>0.26 vs. 0.52</td>
<td>42%</td>
</tr>
</tbody>
</table>

* significant difference from placebo

Torkildsen et al. 2015
Efficacy of DMTs

Network meta-analysis 39 trials (25,113 patients):
Estimates of treatment benefit against placebo
One Way to Think about Efficacy

- Alemtuzumab
- Ocrelizumab
- Natalizumab

- Fingolimod
- Daclizumab
- Dimethyl fumarate

- Teriflunomide
- Interferons
- Glatiramer acetate
First Generation Self-Injectables
# First Generation Self-Injectables

<table>
<thead>
<tr>
<th>Glatiramer acetate</th>
<th>Interferon-beta 1 agents</th>
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<tr>
<td><strong>FDA approval 1996 RRMS/CIS</strong></td>
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<tr>
<td><strong>MOA:</strong> Immune-modulator</td>
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</tr>
<tr>
<td><strong>AE:</strong> Injection site reactions, lipodystrophy, rare harmless systemic reaction</td>
<td><strong>AE:</strong> Injection site reactions, flu-like symptoms, depression</td>
</tr>
<tr>
<td><strong>Safety monitoring:</strong> none</td>
<td><strong>Safety monitoring:</strong> CBC, LFT, TSH</td>
</tr>
<tr>
<td><strong>Safest option surrounding pregnancy (category B)</strong></td>
<td><strong>High dose high frequency may be more effective</strong></td>
</tr>
</tbody>
</table>

**Copaxone®, Glatopa®**
- sc 20 mg Qday
- sc 40 mg TIW

**Avonex®, Rebif®, Plegridy®, Betaseron®, Extavia®**
- im Q 1 week
- sc TIW
- sc Q 2 weeks
- sc QOD (IFN beta 1b)
Oral agents
Teriflunomide

- FDA approved in 2012 for RRMS and CIS
- 71,000 patients on drug in 2017
- Closely related to leflunomide (for RA)
- TEMSO, TOWER (vs. placebo in RRMS)
- TENERE (vs. i.m. IFN 1a in RRMS)
- TOPIC (vs. placebo in CIS)
Teriflunomide: Mechanism of Action

oral 7 or 14 mg once daily  Aubagio®

Blocks de novo pyrimidine synthesis
→ cytostatic effect on proliferating T and B cells
Teriflunomide: Efficacy

oral 7 or 14 mg once daily

**Aubagio®**

Reduction in annualized relapse rate

**TEMSO Trial**

- Placebo: n = 363
- Teriflunomide 7 mg: n = 365
- Teriflunomide 14 mg: n = 358

-31.2% p < 0.001
-31.5% p < 0.001

Reduction in disability accumulation

**TOWER Trial**

- Placebo vs 7 mg: HR = 0.955; p = 0.762
- 14 mg vs Placebo: HR = 0.685; p = 0.044

↓ 31.5% risk on 14 mg

Miller 2017; Confavreux et al, 2014
Comparing Oral and Injectable DMTs

Retrospective Analysis of 6372 Insurance Claims:
DMF and fingolimod superior effectiveness to IFNb, GA, teriflunomide

30.4% ↓
30.5% ↓
Clinically Isolated Syndrome
Teriflunomide, IFN, Glatiramer

Teriflunomide ↓ risk of conversion to MS

IFN 1b ↓ risk of conversion to MS

Early treatment:
33% risk ↓ after 11 years

Kappos, 2016
Miller, 2014
Dimethyl fumarate (DMF)

- FDA approved in 2013
- Fumaric acid esters previously used to treat psoriasis
- 245,000 patients on drug in 04/2017
- DEFINE and CONFIRM (placebo controlled trials)

oral 240 mg twice daily  Tecfidera®
Dimethyl fumarate: Mechanism of Action

- Activates nuclear factor 2 (Nrf2) pathway (response to oxidative stress)
- Pro-inflammatory Th1 → less inflammatory Th2

oral  240 mg twice daily  Tecfidera®

Pistono et. al, 2017
Dimethyl fumarate: Efficacy

oral 240 mg twice daily  Tecfidera®

Annual Relapse Rate in first 2 years on placebo vs. year 3-7 on DMF

Proportion of patients with confirmed disability progression

Gold et. al, 2016
Fingolimod

- FDA approved in 2010
- 204,000 patients on drug in 2017
- FREEDOMS (placebo controlled trial)
- TRANSFORMS (trial against i.m. IFN)

oral 0.5mg once daily  Gilenya®
Fingolimod: Mechanism of Action

Spingosine-1-phosphate receptor modulator prevents egress of lymphocytes from lymph nodes

oral  0.5mg once daily  Gilenya®

Pistono et al, 2017
Fingolimod: Efficacy

oral  0.5mg once daily  Gilenya®

Izquierdo et al. 2017

Kappos et al. 2010
| **Fingolimod**
| **Gilenya®**
| (9/2010) |
| **Teriflunomide**
| **Aubagio®**
| (10/2012) |
| **Dimethyl fumarate**
| **Tecfidera®**
| (3/2013) |
| **Once daily** | **Once daily (7 vs 14mg)** | **Twice daily** |

**Usually well tolerated**

Diarrhea, GI symptoms, hair thinning, tingling hands/feet

Some patients poorly tolerate for flushing, GI symptoms

**Key safety**
- Heart rate
- Risk of infection
- Macula edema, esp if h/o DM or uveitis (20% instead 0.4%)
- PML cases

**Key safety**
- Boxed warning liver toxicity
- Boxed warning pregnancy
- Risk of infection, no PML
- Serious skin conditions
- Chelation therapy if needed

**Key safety**
- PML cases
- Lymphopenia

**Baseline tests:**
- Blood work
- EKG, 6h first dose monitoring
- Eye exam
- Consider skin exam, PFT

**Baseline tests:**
- Blood work
- Latent TB test

**Baseline tests:**
- Blood work

**Monitoring:**
- Blood work
- Repeat eye exam
- Occ EKG, skin exam

**Monitoring:**
- Monthly blood work for first 6 months
- Occ blood pressure

**Monitoring:**
- Blood work
<table>
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<th>Teriflunomide</th>
<th>Dimethyl fumarate</th>
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<td><strong>Gilenya®</strong>&lt;br&gt;(9/2010)</td>
<td><strong>Aubagio®</strong>&lt;br&gt;(10/2012)</td>
<td><strong>Tecfidera®</strong>&lt;br&gt;(3/2013)</td>
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<td><strong>Baseline tests:</strong>&lt;br&gt;• Blood work</td>
</tr>
<tr>
<td><strong>Monitoring:</strong>&lt;br&gt;• Blood work&lt;br&gt;• Repeat eye exam&lt;br&gt;• Occ EKG, skin exam</td>
<td><strong>Monitoring:</strong>&lt;br&gt;• Monthly blood work for first 6 months&lt;br&gt;• Occ blood pressure</td>
<td><strong>Monitoring:</strong>&lt;br&gt;• Blood work</td>
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</tbody>
</table>
Fingolimod
First Dose Observation – pivotal trials

Effect of Fingolimod on HR

DeMarco et al. MSRD 2014: Pooled data clinical trials: 2y phase III studies (Freedom/Freedom I), 1y phase III study (Transform)
**First Dose Observation**

**Populations incl patients with cardiac risks**

<table>
<thead>
<tr>
<th>On-site Set (n=1219)</th>
<th>No Cardiac Risks (n=946)</th>
<th>Cardiac Risks (n=270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline HR, bpm</td>
<td>73.5</td>
<td>68.6</td>
</tr>
<tr>
<td>Maximum mean change in HR (range)</td>
<td>-7.4 (-45.7 to 23.3)</td>
<td>-6.5 (-36.3 to 17.3)</td>
</tr>
</tbody>
</table>

**HR on the Day of Fingolimod Initiation (By Cardiac Risk)**


**Mean Sitting HR in the 6 h Following the First Dose of Fingolimod**
Attention to co-medication

OVERNIGHT monitoring needed —or-SWITCH vs HOLD during FTY initiation. No contraindication with ongoing treatment.

<table>
<thead>
<tr>
<th>Antipsychotics/ Antidepressants</th>
<th>Antibiotics/ Anti-infectives</th>
<th>Antineoplastics</th>
<th>Class IC Antiarrhythmic</th>
<th>Pain/Anesthesia</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Azithromycin</td>
<td>Arsenic Trioxide</td>
<td>Flecainide</td>
<td>Methadone</td>
<td>Anagrelide</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Ciprofloxacin</td>
<td>Vandetanib</td>
<td></td>
<td>Propofol</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td>Sevoflurane</td>
<td>Cilostazol</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Erythromycin</td>
<td></td>
<td></td>
<td>Methadone</td>
<td>Donepezil</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Fluconazole</td>
<td></td>
<td></td>
<td>Propofol</td>
<td>Droperidol</td>
</tr>
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<td>Halofantrine</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>Arsenic Trioxide</td>
<td></td>
<td>Methadone</td>
<td>Ondansetron</td>
</tr>
<tr>
<td></td>
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<td>Arsenic Trioxide</td>
<td></td>
<td>Methadone</td>
<td></td>
</tr>
</tbody>
</table>

- During initiation, switch or overnight monitoring may be required for drugs that slow HR or AV conduction: BBs [beta-adrenergic blocking agents], digoxin, and calcium channel agents
- Drugs contraindicated with fingolimod treatment: Class IA antiarrhythmics (disopyramide and quinidine) and Class III antiarrhythmics (amiodarone; dofetilide; dronedarone; ibutilide, and sotalol)
Fingolimod- low ALC and infections

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Percentage of cases if infections reporting lymphopenia (cumulative)**</th>
<th>Percentage of infections (overall)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.2 x 10^3 cells/mm^3</td>
<td>0.2-0.4 x 10^3 cells/mm^3</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>3.8%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Lower respiratory tract infections</td>
<td>2.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>3.6%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Herpes viral infections**</td>
<td>1.3%</td>
<td>1.3%</td>
</tr>
<tr>
<td>PML</td>
<td>0.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Opportunistic Infections - excluding PML and HVIs</td>
<td>0%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Patients treated continuously with fingolimod 0.5 mg with ALC<0.4 x 10^3 L for ≥60% of records

<table>
<thead>
<tr>
<th></th>
<th>&gt;2 years of FTY 0.5 mg N=358 n(OccR)</th>
<th>≤2 years of FTY 0.5mg N=1071 n(OccR)</th>
<th>OccRR (CI) &gt;2 years / ≤2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>29 (1.4)</td>
<td>14 (1.0)</td>
<td>1.47 (0.75; 3.00)</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>3 (0.1)</td>
<td>1 (0.1)</td>
<td>2.12 (0.17; 111.47)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>3 (0.1)</td>
<td>1 (0.1)</td>
<td>2.12 (0.17; 111.47)</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
<td>1.42 (0.07; 83.52)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
<td>1.42 (0.07; 83.52)</td>
</tr>
</tbody>
</table>

No increase in infections including serious or opportunistic infections in association with severity of low ALC or treatment duration

1 Novartis Safety Information, 2 Cohen ECTRIMS 2015
Fingolimod
Limited data re alternative dosing

- Novartis trial 0.5 mg qd vs 0.25 qd vs glatiramer acetate
  - poor recruitment, data available 2020/2021
- Retrospective multicenter observational data$^1$
  - n=63 qd vs n=60 qod per MD discretion for labs
  - ~3x higher risk relapse, ~2x higher risk MRI progr on qod; esp in young pt or previously on NTZ
- Retrospective multicenter$^2$
  - n=170 varies alternative dosing regimens
  - Non-statistically difference in proportion relapse-free pts

1 Zecca MJS 2017, 2 Kister et al. AAN 2017
Fingolimod
Immune response against antigens

- Patients on fingolimod vs plc were able to mount immune response\(^1\)
- Lymphocyte functions such as activation, proliferation and differentiation largely intact\(^2\)

Fingolimod- PML

PML n=13 in 204 K → Estimated risk <1:10K

• Risk factor
  – ?age: 1x 30s, 1x 40s, others older
  – ?rx duration: 1x18m, others 30-65m
  – No other obvious RF incl low ALC

• Seemingly 1-2 deaths

• Some with CSF JCV PCR viral copies <500, specifics na

• Novartis will pay for JCV PCR and offers review of MRI by Adjudication Panel (PML specialists)

• No PLEX, half-life 9 days, cleared by 6x ½ life=2m
## Fingolimod – Malignancies

<table>
<thead>
<tr>
<th>Key risks</th>
<th>Clinical trial data (Short-term (≤2-year) IRR* (95% CI) fingolimod 0.5 mg vs. placebo)</th>
<th>Post-marketing data (Reporting rate** per 1000 PTY current review period (Previous 1 year period))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell carcinoma</td>
<td>2.6 (0.9; 9.0)</td>
<td>0.5 (0.4)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0.0</td>
<td>0.16 (0.23)</td>
</tr>
</tbody>
</table>

- Basal cell carcinoma in higher rate 2% in FTY vs 1% plc in trials
  - No association with other skin cancers incl melanoma or squamous cell carcinoma
  - Alertness patients and providers

- B- and T-cell lymphoma and CNS lymphoma occurred post-marketing
  - Heterogeneous, no discernible pattern
  - NHL higher than general population adjusted for age, gender and region
## Fingolimod: Clinical Pearls

<table>
<thead>
<tr>
<th>oral</th>
<th>0.5 once daily</th>
<th>Gilenya®</th>
</tr>
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</table>

- Baseline labs with VZV status and if needed VZV vaccination before starting agent
- Pay attention to co-medications and co-morbidities
  - DM, uveitis $\rightarrow$ risk of ME↑
  - Co-meds $\rightarrow$ HR↓
- Lymphopenia not associated with infections
- Current PML rate: 13/204,000
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<td></td>
<td></td>
</tr>
<tr>
<td>• Consider skin exam, PFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring:</td>
<td>Monitoring:</td>
<td>Monitoring:</td>
</tr>
<tr>
<td>• Blood work</td>
<td>• Monthly blood work for first 6 months</td>
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</tr>
<tr>
<td>• Repeat eye exam</td>
<td>• Occ blood pressure</td>
<td></td>
</tr>
<tr>
<td>• Occ EKG, skin exam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Teriflunomide: Tolerability and Safety

- Black box warning Hepatotoxicity
  → monthly LFTs first 6 months

- Black box warning Teratogenicity
  → Birth control needed for both females and males
  → Contraindicated in females child-bearing age w/o reliable BC

- Elimination takes on average 8 months, up to 2 years
  → Expedited elimination rx: >98% elimination after 11 days
    - Pregnancy occurred or intended (incl fathering child)
    - Liver toxicity
    - Serious skin reaction or overdose
    - For pregnancy check levels and repeat if needed

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>8 g tid</td>
<td>11 days</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>4 g tid</td>
<td>11 days</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>50 g bid</td>
<td>11 days</td>
</tr>
</tbody>
</table>
Teriflunomide: Bone Marrow Suppression

- WBC ↓ 15% dose-dependent
- ALC ↓
- ANC ↓
- Platelets↓ 10% - post-marketing rare <50,000/mm3
- No cases pancytopenia or agranulocytosis (yet?, leflunomide +)

- No association to common infections, mostly nasopharyn, URI, UTI
- Rare opportunistic infections 1-2/1000 in placebo, 14 vs 7 mg
- No PML
- Tuberculosis! - 1 death due to pulmonary TB (7mg)
  - 1 GI TB (14 mg)

→ Negative quantiferon or PPD prior to initiation
→ Monitor CBC diff on top of LFTs

Pooled data clinical trials including extension studies: Singer et al, AAN meeting 2014
Teriflunomide: Skin Reactions

- Hypersensitivity/skin pooled clinical trials: 16.1% vs 14.3% plc\(^1\)
- Severe skin reactions reported
  - 7x Steven Johnson Syndrome in post-market setting
  - 24x skin exfoliation in post-market setting
  - 1 fatal TEN report in post-market setting\(^2\)

\(^1\) Leist et al. Pooled safety data 4 clinical studies (n=3044) AAN 2014. \(^2\) Gerschenfeld. MS Journal 2015, Vol. 21(11) 1476–1477

**Case Report**

Fatal toxic epidermal necrolysis in a patient on teriflunomide treatment for relapsing multiple sclerosis

- 46y F
- MS x 10y
- IFN, DMF dc’ed for tolerability

Teriflunomide
- Day 19 transient FLS x 5 days
- Day 28 fever, asthenia, stopped drug
- Day 30 respiratory failure
- Day 34 TEN suspected
- Day 39 death
Teriflunomide: Hair Thinning

- 13.9% (14mg) vs 10.0% (7mg) vs 5.1% (plc)
- Occurs usually 1st 6 months
- Mild to moderate severity
- Most resolved while staying on treatment
- Median duration 4 months all groups (1 hair cycle)
- Drug discontinuation 6% vs 2% plc

Leist et al. Pooled safety data 4 clinical studies (n=3044) AAN 2014
Teriflunomide: Clinical Pearls

oral 7 or 14 mg once daily

- Pregnancy category X (need reliable contraception)
- Rule out latent TB
- Monthly LFT monitoring x6 months
- Monitor CBCdiff
- Risk of serious skin reactions
- Expedited elimination protocol if needed

Aubagio®
<table>
<thead>
<tr>
<th><strong>Fingolimod</strong> Gilenya® (9/2010)</th>
<th><strong>Teriflunomide</strong> Aubagio® (10/2012)</th>
<th><strong>Dimethyl fumarate</strong> Tecfidera® (3/2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Once daily</strong></td>
<td><strong>Once daily (7 vs 14mg)</strong></td>
<td><strong>Twice daily</strong></td>
</tr>
<tr>
<td>Usually well tolerated</td>
<td>Diarrhea, GI symptoms, hair thinning, tingling hands/feet</td>
<td>Some patients poorly tolerate for flushing, GI symptoms</td>
</tr>
<tr>
<td><strong>Key safety</strong></td>
<td></td>
<td><strong>Key safety</strong></td>
</tr>
<tr>
<td>• Heart rate</td>
<td></td>
<td>• Boxed warning liver toxicity</td>
</tr>
<tr>
<td>• Risk of infection</td>
<td></td>
<td>• Boxed warning pregnancy</td>
</tr>
<tr>
<td>• Macula edema, esp if h/o DM or uveitis (20% instead 0.4%)</td>
<td></td>
<td>• Risk of infection, no PML</td>
</tr>
<tr>
<td>• PML cases</td>
<td></td>
<td>• Serious skin conditions</td>
</tr>
<tr>
<td><strong>Baseline tests:</strong></td>
<td></td>
<td>• Chelation therapy if needed</td>
</tr>
<tr>
<td>• Blood work</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• EKG, 6h first dose monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Eye exam</td>
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</tr>
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<td><strong>Baseline tests:</strong></td>
<td></td>
<td><strong>Baseline tests:</strong></td>
</tr>
<tr>
<td>• Blood work</td>
<td></td>
<td>• Blood work</td>
</tr>
<tr>
<td>• Latent TB test</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monitoring:</strong></td>
<td></td>
<td><strong>Baseline tests:</strong></td>
</tr>
<tr>
<td>• Monthly blood work for first 6 months</td>
<td></td>
<td>• Blood work</td>
</tr>
<tr>
<td>• Occ blood pressure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Dimethyl fumarate: Tolerability

- Prolonged uptitration
- Patient education/expectation
- Take with or after meal
- Mostly transient x 1 month
- Montelukast (Singular®) or PPI

Nausea, diarrhea, abdominal pain, vomiting
Clinical trials 40% (31% plc)
Drug discontinuation 3%
Mild to moderate in 90+
Majority last <2wk, median 1 week

NYU Initiation Protocol
- 120 mg once daily for 14 days
- 240 mg once daily for 14 days
- 240 mg twice daily

<table>
<thead>
<tr>
<th></th>
<th>Biogen Protocol</th>
<th>NYU Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients enrolled</td>
<td>124</td>
<td>205</td>
</tr>
<tr>
<td>GI Discontinuations</td>
<td>8% (10)</td>
<td>1.9% (4)</td>
</tr>
<tr>
<td>Flushing Discontinuations</td>
<td>3.2% (4)</td>
<td>0.5% (1)</td>
</tr>
<tr>
<td>Total Discontinuations</td>
<td>12% (14)</td>
<td>2.5% (5)</td>
</tr>
</tbody>
</table>

Sammarco Actrims/Ectrims 2014, Tornatore AAN 2014
Dimethyl fumarate: Tolerability

Flushing
Clinical trials 40%
Drug discontinuation 3%
Mild to moderate
Improved or resolved typically after 1m

- Prolonged uptitration
- Patient education/expectation
- Take with or after meal
- Aspirin 325 mg 30’ prior
- Anti-histamine

Severity flushing last 24 h
without

severity acute flushing
without

Dimethyl fumarate: Label Update

Recent label update: warning LFT elevation

- Clinical trials mild, transient AST/ALT elevation <3x ULN
- Post-marketing search FDA safety database: significant liver injury n=14
  - >5x ULN with concurrent bilirubin 2x ULN
  - primarily hepatocellular pattern
  - no case of liver failure, transplant or death
  - n=10 hospitalization
  - n=7 LFT elevation occurred in 1st month

Munoz et al. Multiple Sclerosis Journal Jan 2017 (epub ahead of press)
Dimethyl fumarate: Laboratory abnormalities

DMF label recommends rx interruption if ALC <0.5 for >6m

- Mean ALC ↓ by 30% 1st year
- ALC <0.5 in 4-5% x ≥1, in 2% x >6m
- Most cases of ALC <0.5 can be identified by having ALC <0.8 in 1st 6m
- ALC strongly correlated with CD4/8
- Serious infection, malignancy or non-PML opportunistic infection very rare regardless of ALC

DMF clinical trial program

- Larger percentage low ALC, up to 50%
- Larger percentage of ALC <0.5, ~ 20+% 
- Mean age higher than in trials
- No data suggest association with non-PML infections or malignancies
- Recovery after DMF discontinuation can take weeks to months; ~50% in 2 m

“Real life” cohorts

Fox et al. AAN 2017 (analysis phase II, III, IIIext)
Buck et al. AAN 2017 (multicenter observational study)
Romba et al. ECTRIMS 2015 (UW MS Center)
Dimethyl fumarate: Rare PML Cases

- PML n=5 in 245K
  - 1 death, other survival but no specifics available
  - Risk factors: low ALC, age, ?rx duration
  - Low CSF JCV viral copies: 2x 12 → ultrasensitive JCV PCR!
Challenging Clinical Scenario

- 54 y/o F diagnosed MS 2008
- BLE numbness ascending to involve whole body.
- Brain/spine MRI, CSF c/w MS
- PMH: OSA, chronic pain, depression
- Tecfidera since 6/2013, clinically and MRI stable
- Rebif 2010-2013 dc’ed for pain/mood
- Copaxone dc'ed for poor tolerance

<table>
<thead>
<tr>
<th>Date</th>
<th>ALC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb-2017</td>
<td>0.61</td>
</tr>
<tr>
<td>Aug-2016</td>
<td>0.66</td>
</tr>
<tr>
<td>Jun-2016</td>
<td>0.62</td>
</tr>
<tr>
<td>Apr-2016</td>
<td>0.51</td>
</tr>
<tr>
<td>Jan-2016</td>
<td>0.62</td>
</tr>
<tr>
<td>Sep-2015</td>
<td>0.77</td>
</tr>
<tr>
<td>Jun-2015</td>
<td>0.75</td>
</tr>
<tr>
<td>Mar-2015</td>
<td>0.84</td>
</tr>
<tr>
<td>Jan-2015</td>
<td>0.76</td>
</tr>
<tr>
<td>Jul-2014</td>
<td>0.63</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.44</td>
</tr>
</tbody>
</table>

- No infections
- JCV antibody?
Age: 34-36 y old (mean)
MS duration: 5-7 years (mean)
Relapses prior enrollment
Relapses in prior 1y: 1
Relapses in prior 3Y: 2-3
- Slower taper may help with side effects
- Montelukast (Singulair) for GI side effects
- Aspirin or anti-histamine for flushing
- Monitor lymphocyte counts and LFT
New Self-Injectable
(not related to 1st generation injectables)
Daclizumab

- FDA approved in May 2016
- REMS program required
- World wide use less than 2,500
- SELECT (placebo) and CHOICE (vs interferon)
Daclizumab: Mechanism of Action

Monoclonal antibody against CD25 IL-2 receptor on lymphocytes

Cohan, 2016
Figure 2. Patients achieving overall NEDA from Baseline–Week 96, from Baseline–Week 24 and over Weeks 24–96

Giovannoni et al., ECTRIMS, 2016

Gold et al., 2013
Daclizumab

REMS program, restricted to MS patients who failed at least 2 prior DMTs
- Monthly blood draws

Key safety concerns:
• Liver toxicity incl auto-immune hepatitis
  – 1 death in trial
  – Monthly blood work prior to next self-injection
• Immune-mediated side effects
  1. Skin (NOT injection site reaction)
     - Rash needs to be evaluated, if generalized urgent dermatology
     - pre-existing rash, dermatitis, psoriasis: 1.5-2x higher risk
  2. Lymphadenopathy
     - May require bx to r/o lymphoma, 1 lymphoma in trial
  3. Non-infectious colitis
     - 1 death d/t colitis in trial
• Infections more common compared to IFN in trials
Infusions
Natalizumab

iv  once monthly  Tysabri®

- FDA approved in 2006
- REMS program required
- 167,300 patients on drug
- AFFIRM (vs. placebo)
  SENTINEL (add on to i.m. IFN 1a)
Natalizumab: Mechanism of Action

iv once monthly  
Tysabri®

Humanized monoclonal antibody to α 4 integrin = VLA-4

- Inhibition of leukocyte adhesion to endothelium  
  → prevents extravasation of T cells and monocytes into CNS  
  → decreased CNS immunosurveillance

- Reduction of antigen presenting cells in cerebral perivascular spaces

- Mobilization of lymphoid precursors (CD34+) from bone marrow

Rice et al, 2005
Natalizumab: Immunological Effects

CD4/CD8 ratio in blood unchanged

CD4/CD8 ratio in CSF ↓

Stüve et al. 2006

iv once monthly Tysabri®
Natalizumab reduces risk of sustained progression of disability by 42% on Natalizumab.

On Natalizumab higher proportion of patients with no disease activity (clinical & MRI).
Natalizumab-related PML

- Exposure: 167,300
- PML cases: n=711 in MS (Crohn’s n=3)

- Risk factors
  - JCV antibody status
  - Prior immunosuppression
  - Natalizumab treatment duration

- Attention pitfall!
  *Do not confuse* JCV antibody testing with serum JCV PCR; latter is NOT predictive of PML risk
PML risk algorithm

Anti-JCV antibody status

Negative

1:10,000 - regardless of rx duration and prior use of IS
5 PML cases worldwide reported

0.1/1000 patients
95% CI: 0.01–0.35

<table>
<thead>
<tr>
<th>Natalizumab exposure, months</th>
<th>Patients without prior IS use, per 1000 patients (95% CI)</th>
<th>Patients with prior IS use, per 1000 patients (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Index value not available</td>
<td>Index ≤0.9</td>
</tr>
<tr>
<td>1–12</td>
<td>0.1 (0–0.4)</td>
<td>0.01 (0–0.03)</td>
</tr>
<tr>
<td>13–24</td>
<td>0.6 (0.2–1.1)</td>
<td>0.05 (0–0.1)</td>
</tr>
<tr>
<td>25–36</td>
<td>1.6 (0.9–2.5)</td>
<td>0.2 (0–0.4)</td>
</tr>
<tr>
<td>37–48</td>
<td>4.1 (2.8–5.7)</td>
<td>0.4 (0–1.0)</td>
</tr>
<tr>
<td>49–60</td>
<td>4.8 (3.2–7.0)</td>
<td>0.5 (0–1.2)</td>
</tr>
<tr>
<td>61–72</td>
<td>6.0 (3.7–9.3)</td>
<td>0.6 (0–1.5)</td>
</tr>
</tbody>
</table>

Koendgen Biogen ECTRIMS 2016
# PML risk algorithm

## Anti-JCV antibody status

- **Negative**
  - 0.1/1000 patients (95% CI: 0.01–0.35)

- **Positive**

<table>
<thead>
<tr>
<th>Natalizumab exposure, months(^a)</th>
<th>Patients without prior IS use, per 1000 patients (95% CI)</th>
<th>Patients with prior IS use, per 1000 patients (95% CI)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–12</td>
<td>Index value not available (0.1) (0–0.4)</td>
<td>Index (\leq 0.9) (0.01) (0–0.03)</td>
</tr>
<tr>
<td>13–24</td>
<td>Index (0.9) to (\leq 1.5) 0.1 (0–0.2)</td>
<td>Index (&gt;1.5) 0.2 (0–0.5)</td>
</tr>
<tr>
<td>25–36</td>
<td>Index (&gt;1.5) 0.3 (0–0.6)</td>
<td>0.9 (0.3–1.6)</td>
</tr>
<tr>
<td>37–48</td>
<td>Index (&gt;1.5) 0.8 (0.1–1.5)                2.6 (1.4–3.9)</td>
<td></td>
</tr>
<tr>
<td>49–60</td>
<td>Index (&gt;1.5) 2.0 (0.2–3.8)                6.8 (4.4–9.1)</td>
<td></td>
</tr>
<tr>
<td>61–72</td>
<td>Index (&gt;1.5) 2.4 (0.2–4.5)                7.9 (4.9–10.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Index (&gt;1.5) 3.0 (0.2–5.8)                10.0 (5.6–14.4)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Nurtalizumab exposure in months (12 months = 1 year).

\(^b\) Patients with prior IS use, per 1,000 patients (95% CI).

\(^c\) Patients with prior IS use, per 1,000 patients (95% CI) based on the highest antibody index value.

Koendgen Biogen ECTRIMS 2016
### PML risk algorithm

- **Anti-JCV antibody status**
  - Negative
  - Positive

**Disclaimer:** JCV ab index is approved by the European and Canadian regulatory agencies but not (yet?) by FDA.

#### Patients without prior IS use per 1000 patients (95% CI)

<table>
<thead>
<tr>
<th>Natalizumab exposure, months</th>
<th>Index value not available</th>
<th>Index ≤0.9</th>
<th>Index &gt;0.9 to ≤1.5</th>
<th>Index &gt;1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12</td>
<td>0.1 (0-0.4)</td>
<td>0.01 (0-0.03)</td>
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<td>3.0 (0.2-5.8)</td>
<td>10.0 (5.6-14.4)</td>
</tr>
</tbody>
</table>

- **1: 5,000**
- **1: 325**

---

Koendgen Biogen ECTRIMS 2016

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*Note: JCV ab index is approved by the European and Canadian regulatory agencies but not (yet?) by FDA.*
PML risk algorithm

Anti-JCV antibody status

- Negative
  - 0.1/1000 patients
    - 95% CI: 0.01–0.35
- Positive

- Highest PML risk!
- JCV ab index does not apply!

<table>
<thead>
<tr>
<th>Natalizumab exposure, months</th>
<th>Patients without prior IS use, per 1000 patients (95% CI)</th>
<th>Patients with prior IS use, per 1000 patients (95% CI)</th>
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</tr>
</tbody>
</table>

Koendgen Biogen ECTRIMS 2016
MRI features of PML

- Large confluent lesions subcortical
- Most commonly frontal lobe
- Hyperintense T2/FLAIR, hypointense T1
- No mass effect
- 40% spotty or rim enhancement at PML onset

Every new MRI lesion on NTZ needs to raise alarm for potential PML!
Early PML detection

A) Retrospective PML detection on MRI, B) Dong-Si Ann Clin Transl 2014, C) Biogen 2015
Proposed Algorithm

NEW and suspicious MRI lesion

Suspend dosing

- Complete MRI 3-4 weeks later
  - MRI improvement
    - Resume Dosing
  - Complete MRI 3-4 weeks after that
    - MRI improvement
      - Resume Dosing
    - Any worsening
      - JCV not detected
        - Treat as PML
      - JCV detected
        - CSF assessment
          - If strong suspicion based on MRI

- Any worsening
  - JCV not detected
    - Treat as PML
  - JCV detected
    - CSF assessment

Biogen Medical Information Services
Low viral copies reported in multiple PML cases treated with
- Natalizumab
- Fingolimod
- Dimethyl Fumarate

Viral copies detectability cut offs
- 500 copies in any regular JCV PCR testing or lab
- 10 copies in NIH and Focus lab when ordering ultrasensitive PCR

Order **ultrasensitive JCV PCR through NIH and/or Focus** when testing for possible PML associated with **ANY** DMT agent
Extended natalizumab dosing interval

Retrospective review 9 MS centers

<table>
<thead>
<tr>
<th></th>
<th>SID</th>
<th>Total EID</th>
<th>EED</th>
<th>LED</th>
<th>VED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (n)</td>
<td>1080</td>
<td>894</td>
<td>246</td>
<td>269</td>
<td>379</td>
</tr>
<tr>
<td>JC virus positive</td>
<td>50%</td>
<td>63%†</td>
<td>66%†</td>
<td>67%†</td>
<td>58%†</td>
</tr>
<tr>
<td>Median JC virus index</td>
<td>0.22 (0.99)</td>
<td>0.75 (1.25)</td>
<td>1.63* (1.36)</td>
<td>0.69 (1.22)</td>
<td>0.34* (1.06)</td>
</tr>
<tr>
<td>Prior immunosuppressives (%)</td>
<td>12</td>
<td>17</td>
<td>9</td>
<td>27†</td>
<td>15†</td>
</tr>
<tr>
<td>NTZ doses</td>
<td>27.39 (18.24)</td>
<td>40.07† (21.66)</td>
<td>51.62† (27.23)</td>
<td>33.74† (15.83)</td>
<td>37.08† (18.06)</td>
</tr>
</tbody>
</table>

- No loss of efficacy seen with extended dosing interval of 4-9 weeks
- Not sufficiently powered to evaluate impact on PML risk
  - 4 PML/standard dosing
  - 0 PML/extended dosing
Natalizumab – Other infections

• Rare non-PML opportunistic infections (each <0.1%)\(^1\)

• HSV/VZV encephalitis or meningitis n=20 post-marketing\(^2\)
  • Median 21 infusions, 2 deaths, 4 neurological/neuropsychiatric residual incomplete recovery

• Acute Retinal Necrosis (ARN) n=20 post-marketing\(^2\)
  • Fulminant retina infection by herpes virus: Acute onset VL, pain or redness 1 or 2 eyes, quickly progresses in absence of antiviral rx, retinal detachment 50-75% untreated cases

---

\(^1\) Foley et al. ECRTIMS 2016: Tygris Long-term safety (n=6500 x 5y), \(^2\) Biogen safety update March 2017
Anti-Natalizumab-antibodies

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Transient +</th>
<th>Persistent +</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFFIRM (n=625)</td>
<td>91%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>SENTINEL (n=585)</td>
<td>88%</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Consider testing anti-NTZ- ab testing if

- ongoing clinical and MRI disease activity
- infusion and hypersensitivity reactions

Confirm that persistent antibodies with repeat testing 3 m later

Calabresi et al, Neurology 2007
Reactivation ↔ Rebound

**Reactivation**
- Dosing interruption x 8m of clinical trial program d/t 2005 removal from market (n=1888)¹
  - Reoccurrence of clinical and MRI dz activity
  - Peak at 4-7 m
  - No rebound observed

**Rebound**
- Multiple reports of catastrophic and fatal MS relapses
- DMT discontinuation in middle-aged patients w/o MS relapse or MRI activity >5y
  - NTZ (18) vs 1st-line DMT (55)²
    - 2/3 of NTZ pt acute dz activity
    - 1/3 of NTZ rebound character
    - 1/3 of 1st DMT mild dz activity

¹ O’Connor et al. Neurology 2011, ² Fagius et al. Mult Scler Relat Disord 2017
Natalizumab: Clinical Pearls

- Check JCV antibody in blood regularly
- Check brain MRI regularly
- Any new neurologic symptom or new MRI lesion on natalizumab is concerning for PML
- Concerns for reactivation and rebound MS disease activity when stopping drug
Alemtuzumab

- FDA approved in 2014
- 14,000 patients on drug
- REMS program required
- 5 daily infusions
  Repeat 3 daily infusions 12 months later
Alemtuzumab: Mechanism of Action

Monoclonal antibody against CD52 on T and B lymphocytes, NK cells, eosinophils, macrophages, monocytes

Dubey et al. 2015
Alemtuzumab: Efficacy

iv treatment courses

Lemtrada®

A Sustained Disability

B Relapse

No. at Risk
Interferon beta-1a 111 91 83 76 68 65 56
Alemtuzumab, 12 mg/day 112 106 101 98 97 94 88
Alemtuzumab, 24 mg/day 110 106 102 99 96 93 89

No. at Risk
Interferon beta-1a 111 99 94 82 75 71 66
Alemtuzumab, 12 mg/day 112 107 104 101 100 96 93
Alemtuzumab, 24 mg/day 110 108 105 105 102 100 96

C EDSS Score

D Relapse Rate

No. at Risk
Interferon beta-1a 111 100 91 83 73 71 68
Alemtuzumab, 12 mg/day 112 107 103 99 99 92 88
Alemtuzumab, 24 mg/day 110 108 105 105 101 97 89

CAMMS223 Trial Investigators, 2008
Alemtuzumab

iv treatment courses Lemtrada®

REMS program, reserved for patients who failed 2 or more DMTs

Black box warnings:
- Serious, sometimes fatal auto-immune conditions, such as immune thrombocytopenia (ITP, 2%), anti-glomerular basement membrane disease
- Serious and life threatening infusion reactions
- Malignancies (thyroid, melanoma, lymphoproliferative disorders, lymphoma)

Other complications:
- Thyroid disorder (34%) incl Graves, hyperthyroidism, hypothyroidism
- Infusion reactions common (92%)
- Increased rate infections incl herpes, zoster, HPV, TB

Safety monitoring:
- Baseline and monthly blood work and urine sample for 48 months after last infusion (CBC diff, creatinine, TSH, UA)
- Baseline and yearly skin exam
- Recommended baseline and yearly HPV screening (females)
Ocrelizumab

- FDA approved in March 2017
- Anti-CD 20 B cell depleting therapy (similar to rituximab)
- OPERA I and II (vs. im IFN) for RRMS and ORATORIO (vs placebo) for PPMS
Ocrelizumab: Mechanism of Action

iv  once every 6 months  Ocrevus®

Monoclonal antibody to CD20 on B lymphocytes

Bittner et al. 2017
Ocrelizumab: Efficacy in RRMS

iv once every 6 months

Ocrelizumab: Efficacy in RRMS

B OPERA II Trial

Interferon beta-1a (N=418)

Mean no. through 96 wk, 0.42

Ocrelizumab (N=417)

Mean no. through 96 wk, 0.02

P<0.001

Disability Progression Confirmed at 24 Wk

Hazard ratio, 0.60 (95% CI, 0.43–0.84)
P=0.003

No. at Risk

Interferon beta-1a

829 785 747 705 677 644 622 600 466

Ocrelizumab

827 797 772 748 731 717 704 688 540

Hauser et al. 2017
Ocrelizumab: ORATORIO Trial for PPMS

iv once every 6 months  Ocrevus®

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ocrelizumab (N=488)</th>
<th>Placebo (N=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age — yr</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44.7±7.9</td>
<td>44.4±8.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>46.0 (20–56)</td>
<td>46.0 (18–56)</td>
</tr>
<tr>
<td><strong>Female sex — no. (%)</strong></td>
<td>237 (48.6)</td>
<td>124 (50.8)</td>
</tr>
<tr>
<td><strong>Time since onset of MS symptoms — yr†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.7±4.0</td>
<td>6.1±3.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td>6.0 (1.1–32.9)</td>
<td>5.5 (0.9–23.8)</td>
</tr>
<tr>
<td><strong>Time since diagnosis of PPMS — yr‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.9±3.2</td>
<td>2.8±3.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.6 (0.1–16.8)</td>
<td>1.3 (0.1–23.8)</td>
</tr>
<tr>
<td><strong>No previous use of disease-modifying therapy — no. (%)‡</strong></td>
<td>433 (88.7)</td>
<td>214 (87.7)</td>
</tr>
<tr>
<td><strong>Score on EDSS¶</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.7±1.2</td>
<td>4.7±1.2</td>
</tr>
<tr>
<td>Median (range)</td>
<td>4.5 (2.5–7.0)</td>
<td>4.5 (2.5–6.5)</td>
</tr>
<tr>
<td><strong>Gadolinium-enhancing lesions on T₁-weighted images — no./total no. (%)</strong></td>
<td>133/484 (27.5)</td>
<td>60/243 (24.7)</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>351/484 (72.5)</td>
<td>183/243 (75.3)</td>
</tr>
<tr>
<td><strong>No. of lesions on T₂-weighted images</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>48.7±38.2</td>
<td>48.2±39.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>42.0 (0–249.0)</td>
<td>43.0 (0–208.0)</td>
</tr>
<tr>
<td><strong>Total volume of lesions on T₂-weighted images — cm³</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>12.7±15.1</td>
<td>10.9±13.0</td>
</tr>
<tr>
<td>Median (range)</td>
<td>7.3 (0–90.3)</td>
<td>6.2 (0–81.1)</td>
</tr>
<tr>
<td><strong>Normalized brain volume — cm³</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1462.9±84.0</td>
<td>1469.9±88.7</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1462.2 (1214.3–1711.1)</td>
<td>1464.5 (1216.3–1701.7)</td>
</tr>
</tbody>
</table>

Montalban et al. 2017
Ocrelizumab: Efficacy in PPMS

iv once every 6 months Ocrevus®

Oratorio Trial (Ocrelizumab vs. placebo)

Figure 2. MRI End Points (Intention-to-Treat Population).

Montalban et al. 2017
Ocrelizumab – Infusion reactions

Majority reported during infusion
Mandatory observation x1h after infusion
Inform patients can occur for 1st 24h

- 1st infusion 2x 300 mg 2 weeks apart, all following single infusion 600mg q6m

- Premedication:
  - methylprednisolone 100 mg slow IV infusion 30 min before start OCR
  - analgesic/antipyretic and/or antihistamine 30-60 min before start OCR decreases IR
    - eg acetaminophen 1 g
    - eg diphenhydramine 50 mg po or iv

- Slow uptitration OCR infusion speed
Ocrelizumab – Infections

- Increase in infection rate, esp nasopharyngeal, URI, pneumonia, UTI
- Risk Hep B reactivation – not seen in OCR but in other anti-CD 20 agents incl fulminant hepatitis, liver failure and death
  - Baseline Hep B testing
  - Consider Hep B vaccination (per UW ID in all pts)
  - Not to be infused if active Hep B
- No opportunistic infection seen incl extension trials
Ocrelizumab – PML

• No PML cases in trials but PML risk listed in PI
• May 2017 update: PML in a patient who dc’ed NTZ 2/2017 and had OCR 4/2017
• Background
  – RTX approved 1997, indication NHL, CLL, RA, some PA (polyangiitis), >4 million patients
  – number of PML cases reported not only in hematological malignancies but also auto-immune dz
    RA n=9, SLE n=12, MS n=1
    PML risk in RA estimated 1:20,000+²

Genentech Medical Information Service, 2-Borie Semin Arthritis Rheum 2015
More malignancies in OCR compared to control groups (IFN, PLC), primarily breast CA

Thus far incidence rates malignancies and breast cancer within range of epidemiologic background

Appears that comparator groups lower than expected incidences
Ocrelizumab: Clinical Pearls

iv once every 6 months

- Infusion reactions
- Hepatitis B testing required
- Consider more extensive baseline lab screening
- Consider pneumonia/Hep B vaccination
Choosing a Treatment

No established guidelines

- Disease activity
  high lesion load, pyramidal/brainstem symptoms,
  poor recovery, short relapse interval, male, African American

- Co-morbidities

- Monitoring

- Risk tolerance

- Patient preference (injectable, frequency)

- Insurance coverage
One Way to Think about Efficacy

Alemtuzumab
Ocrelizumab
Natalizumab

Fingolimod
Daclizumab
Dimethyl fumarate

Teriflunomide
Interferons
Glatiramer acetate
Choosing a Treatment

Proposed treatment algorithm after determining disease severity by MRI and clinical measures

1. MRI Shows Aggressive Disease: Large Lesion Burden, Many Enhancing Lesions, or Black Holes
   - Yes
     - Check for serum JC virus antibodies
       - Positive
         - Fingolimod**, Dimethyl Fumarate, Alemtuzumab, Ocrelizumab*, Daclizumab*
       - Negative
         - Natalizumab, Fingolimod**, Alemtuzumab, Ocrelizumab*, Daclizumab*
   - No
     - MRI and clinical course appear less aggressive
       - Experience/Safety:
         - Glatiramer acetate, Beta-IFN
       - Oral:
         - Dimethyl Fumarate, Teriflunomide, Fingolimod**
       - Pregnancy planned
         - Teriflunomide contra-indicated during conception/pregnancy

Cross 2014
Outlook

- New derivatives:
  - Dimethyl fumarate: monomethyl fumarate
  - Fingolimod: Ozanimod, Soponimod, Ponesimod
  - Ocrelizumab: Ofatumumab

- DMTs with new mechanism: Cladribine, Laquinimod

- More options for progressive MS?
- Stem cell transplant?
- Remyelinating agents?
Trial of Minocycline in a Clinically Isolated Syndrome of Multiple Sclerosis

Table 3. Adverse Events.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Minocycline (N=72)</th>
<th>Placebo (N=70)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>62 (86.1)</td>
<td>43 (61.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>7 (9.7)</td>
<td>4 (5.7)</td>
<td>0.37</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (15.3)</td>
<td>2 (2.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (15.3)</td>
<td>5 (7.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Dental discoloration</td>
<td>6 (8.3)</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>18 (25.0)</td>
<td>15 (21.4)</td>
<td>0.61</td>
</tr>
<tr>
<td>Candida vaginitis</td>
<td>6 (8.3)</td>
<td>6 (8.6)</td>
<td>0.96</td>
</tr>
<tr>
<td>Influenza</td>
<td>4 (5.6)</td>
<td>6 (8.6)</td>
<td>0.48</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2 (2.8)</td>
<td>7 (10.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10 (13.9)</td>
<td>1 (1.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (6.9)</td>
<td>7 (10.0)</td>
<td>0.51</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (5.6)</td>
<td>5 (7.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>Serious adverse event: hospitalization</td>
<td>1 (1.4)†</td>
<td>3 (4.3)‡</td>
<td>0.30</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse event detected on laboratory testing</td>
<td>2 (2.8)∥</td>
<td>2 (2.9)∥</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Graph: Participants with Conversion to MS (Cumulative %)

Stratified log-rank test P=0.049

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Placebo</th>
<th>Minocycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>24</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th>Minocycline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>49</td>
<td>33</td>
</tr>
<tr>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>32</td>
<td>19</td>
</tr>
<tr>
<td>17</td>
<td>12</td>
</tr>
</tbody>
</table>

Metz et. al, June 2017
Comprehensive MS Care at
UW MS Center
(located at NWH campus)
206-598-3344
When to Treat

- Early treatment is better than late treatment
- Treatment is better than no treatment

Giovannoni, 2016
Vaccines and DMTs

For all DMTs except glatiramer and interferon

Live Vaccines are NOT safe:
- MMR (measles mumps rubella)
- Varicella
- Yellow fever
- Rota virus (avoid contact with recently immunized infants)
- Nasal influenza (i.m. is not live)

Vaccines may have less efficacy (esp. fingolimod, ocrelizumab)

Vaccines to consider BEFORE starting immunosuppressive DMT:
- Varicella
- Pneumococcus
- Meningococcus

### Table 1
A PML risk stratification table for disease modifying therapies.

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Treated condition predisposes to PML?</th>
<th>Latency from time of drug initiation to PML</th>
<th>Frequency/Incidence of PML</th>
<th>Year drug introduced into U.S. and European markets</th>
<th>Patients/patient-year exposure#</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I – high potential risk of PML</strong></td>
<td>No</td>
<td>Yes</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natalizumab</td>
<td>MS and Crohn's disease</td>
<td>None &lt; 8 months; &gt; 85% of cases &gt; 24 months</td>
<td>1/100–1/1000</td>
<td>U.S.- approved 2004; withdrawn Feb 2005; reintroduced Jun 2006 EUR – Apr 2006</td>
<td>161,300 patients ~527,159 PY (September 30, 2016)</td>
</tr>
<tr>
<td><strong>Class II – low potential risk of PML</strong></td>
<td>No</td>
<td>Yes</td>
<td>Low/infrequent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>MS and psoriasis</td>
<td>18–54 months</td>
<td>~1/50,000</td>
<td>U.S. – Mar 2013 Europe – Feb 2014</td>
<td>224,542 patients 308,732 PY</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>MS</td>
<td>18–54 months*</td>
<td>~1/18,000</td>
<td>U.S.- Sep 2010 EUR-Mar 2011</td>
<td>160,000 patients 368,800 PY</td>
</tr>
<tr>
<td><strong>Class III – no or very low potential risk of PML</strong></td>
<td>Yes</td>
<td>No</td>
<td>Very low or evident only with related drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Hematological malignancies, transplantation</td>
<td>Unknown; no cases with MS</td>
<td></td>
<td>U.S.- Nov 2014 EUR-Sep 2013</td>
<td>~11,000 patients 6000 PY</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Lymphoproliferative disorders, rheumatoid arthritis, ANCA-associated vasculitis, SLE</td>
<td>1/30,000</td>
<td></td>
<td>MS – unapproved indication</td>
<td>No data</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>No PML observed with teriflunomide but with related leflunomide</td>
<td></td>
<td>U.S.-Sep 2012 EUR-Aug 2013</td>
<td>68,952 patients 96,909 PY</td>
<td></td>
</tr>
<tr>
<td>Daclizumab</td>
<td>No PML observed with MS or as prophylaxis for renal transplant</td>
<td></td>
<td>U.S.-May 2016 EUR-Jul 2016</td>
<td>1516 patients 3744 PY</td>
<td></td>
</tr>
</tbody>
</table>

Legend PY - Patient year exposure.
**MS**

- **FLAIR**
  - Round, ovoid

**PML**

- **FLAIR**
  - Fingerlike towards cortex, diffuse

**T2**

- Homogenous, dark rim, edema

**MS**

- **T2**
  - Sharp borders

**PML**

- **T2**
  - Irregular borders WM

- **GM**
  - Sharp borders

Microcystic inclusions, no edema

Comma-shaped

Ovoid

Individual lesions

Clustered nodules

Ring or nodular enhancement

Patchy/irregular enhancement