Managing the Expanding Matrix of MS Therapies: The Orals

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## Current FDA-approved MS DMTs

<table>
<thead>
<tr>
<th>Year</th>
<th>Agent</th>
<th>Route</th>
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<tbody>
<tr>
<td>1993</td>
<td>IFN beta-1b</td>
<td>SC QOD</td>
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<td>1996</td>
<td>IFN beta-1a</td>
<td>IM QW</td>
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<td>Glatiramer Acetate</td>
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<td>2000</td>
<td>Mitoxantrone</td>
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<td>2004</td>
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<td>2010</td>
<td>Fingolimod</td>
<td>PO QD</td>
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<tr>
<td>2012</td>
<td>Teriflunomide</td>
<td>PO QD</td>
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<tr>
<td>2013</td>
<td>Dimethyl Fumarate</td>
<td>PO BID</td>
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Non-comparative Relapse Rates

Non-comparative Reduction in Sustained Disability

Integrating the Orals

• New MS patient
• Patient formerly on other DMTs
• Patient currently on DMTs
  – Those with stable disease
    • Injection fatigue
    • Risks of long-term use of parenterals (PML, t-AML, etc)
  – Those with breakthrough disease
    • For how long were they on injectable?
    • How many different ones do you use before going to more potent agents?
    • Is sequencing going to be important for these patients?
• Transitioning off of Tysabri
Orals: Impact on Clinic Practice

• Increased burden of educational component of reviewing all of these therapies
  – What information do you share?
  – To what detail?
  – Do you have help (RN educators, etc)?
  – Do you limit options that you present?
• Increased burden of insurance authorization
• Increased burden of monitoring
  – Requisite monitoring (labs, studies)
  – Compliance/Adherence issues
Selecting Appropriate Therapies for the New Patient with MS

• What is your approach?
  – All DMTs on equal footing
  – Injectables first
  – Injectables only
  – Orals only
  – Only some orals
  – Let insurance companies decide

• Pros and Cons of Orals
  – Route of administration
  – Putative mechanisms differ from parenterals
  – Side effect and safety profile
  – How long is long enough to be comfortable with safety profile of a new agent
Fingolimod

- Fingolimod is a novel, orally active, synthetic molecule
  - Rapidly phosphorylated in vivo (fingolimod-P) which acts as a sphingosine-1-phosphate agonist
  - Induces internalization of the receptor on thymocytes and lymphocytes preventing their egress from LNs and other lymphoid tissue
    - Naïve and central memory T cells are sequestered in LNs but not peripheral effector memory T cells
    - Only affects lymphocytes, not monocytes, granulocytes, eosinophils, and macrophages
- FTY-720P binds to S1P1, S1P3, S1P4, S1P5 receptors
  - Bradycardia, macular edema, decr FEV₁, etc.

Brinkmann et al, Am J Transplant 2004; 4:1019
Phase III Fingolimod Studies

- Oral Fingolimod vs. IFN B-1a in RRMS (TRANSFORMS)
- Oral Fingolimod vs. placebo in RRMS (FREEDOMS II)
- FDA-approved for RRMS 10/4/2010

In light of post-marketing cardiac events and fatalities with fingolimod, updates to the April 2012 Gilenya Prescribing Information include recommendations for:

- First dose observation
  - More parameters set
- Extended or overnight monitoring in certain circumstances
  - Cardiac co-morbidities or specific concomitant meds
- Contraindications
  - Cardiac co-morbidities or specific concomitant meds
- Re-initiation of therapy
  - Specific parameters regarding missed doses

Kappos et al. 2010;362:387-401; Cohen et al. NEJM;362:402-415
Issues in Clinical Practice: Fingolimod

• Start-up is labor-intensive
  – Pre-dose testing; vaccinations prior to initiation
  – FDO
• List of meds that prolong QT interval includes meds that many of our healthy MS patients take
  – Citalopram, escitalopram, methadone, etc
  – Overnight hospitalization is recommended
• Limited to healthy patients with few co-morbidities
  – Less favorable for diabetics, smokers, high EDSS
• Monitoring on-going basis beyond first year?
  – No clear guidelines to repeat EKG, OCTs, PFTs
• Immunocompromise is an issue
  – Long-term, exceedingly low circulating CD 4 counts of unclear significance
• Washout may be necessary for next treatment
Case History: Fingolimod
Issues in Clinical Practice: Fingolimod

• Optimum dosing may not yet be established
  – FREEDOMS 1.25 mg dosing was abandoned
  – Alternate dosing regimens are being used off-label but cannot necessarily be recommended
  – 12 mo study underway to compare 0.5 mg vs. 0.25 mg daily fingolimod with GA active comparator
  • Pts on fingolimod with higher lymphocyte counts have fewer infections
Issues in Clinical Practice: Fingolimod

• Which patient is the right fit?
  – Healthy (few co-morbidities), risk of infection needs to be a consideration

• How should fingolimod be used?
  – First-line
  – Second-line
    • Intolerance to prior agent
    • Breakthrough disease on prior agent
    • Awareness of level of immunosuppression during transition depending on prior agent
  – ? Need for washout?
    • Lymphocytes return to nl ranges 45 days; 78% of baseline at 3 months

Cohen M et al; AAN 2013 S41.002; Comi G et al, AAN 2013 P07.103; LaGanke CC et al; AAN 2013 P01.206;
Teriflunomide

• The active metabolite of leflunomide, FDA-approved for RA
• An oral immunomodulator with anti-inflammatory activity
• Inhibits pyrimidine synthesis by binding to the enzyme dihydroorotate dehydrogenase (DHO-DH)
• DHO-DH is the 4th enzyme and rate limiting step in the de novo synthesis pathway of pyrimidines (crucial for replicating DNA and RNA)
• It inhibits rapidly dividing cell populations and is non-specific to T cells
• Phase III studies TEMSO and TOWER
  – Oral teriflunomide vs. placebo in RRMS
• Phase III TENERE
  – Time to failure 14/7 mg vs. subcutaneous IFN beta-1a
• FDA-approved for use in RRMS 9/12/2012

Rammohan KW, Shoemaker J Neurology 2010 74:S47-S53; O’Connor et al. NEJM 2011;365: 1293-1303
Issues in Clinical Practice: Teriflunomide

- Pre-treatment testing
  - CBC, LFTs, TB, vaccinations

- Elevated liver enzymes/risk of liver dysfunction
  - Monthly LFTs for at least 6 months

- Teratogenic for men and women
  - Category X

- Hair thinning

- Lymphopenia

- Slow excretion, not dialyzable
  - 8-24 months after discontinuation for plasma levels to be undetectable
  - Accelerated elimination is available
    - Cholestyramine 8 gm, po q 8 hours x 11 days
    - Activated charcoal 50 gm po q 12 hours x 11 days

- Other side effects
  - GI side effects (nausea, diarrhea)
  - Hypertension
  - Polyneuropathy
Case History - Teriflunomide
Issues in Clinical Practice: Teriflunomide

• Which patient is the right fit?
  – Healthy (no liver co-morbidities), active use of contraception, mild disease*

• Pregnancy issues
  – 83 pregnancies reported in female patients
    • 70 in women exposed to TER up to 11 weeks during pregnancy
      – 26 live births, 29 induced Ab, 13 spont Ab (19%), 2 on-going; no structural/functional abnormalities
  – 22 pregnancies reported in partners of male patients
    • 19 in male partners exposed to TER
      – 16 healthy NB, 2 induced Ab, 1 spont Ab; no structural/functional abnormalities
  – Plasma level <0.02 ug/ml confers minimal risk of teratogenicity
    • Accelerated elimination protocol recommended for men and women trying to conceive
  – Effective contraception is recommended

Jung L  AAN 2014 P4.161
Considerations in Switching from Teriflunomide

- If needing to switch from teriflunomide
  - Consider elimination protocol (may need to repeat)
    - Cholestyramine 8 gm, po q 8 hours x 11 days
  - Monitor drug levels
    - <0.02 mg/L or 20 ng/ml minimal teratogenic risk, 11 half-lived, >99% drug removal

- Monitor lymphocyte counts and LFTs
- Is teriflunomide in the class of immunosuppressants that might predispose a pt to PML if NAT is used in the future?
Dimethyl Fumarate

• Oral BG-12 (dimethyl fumarate) activates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway
  – Defends against oxidative stress-induced neuronal death
  – Protects the blood brain barrier
  – Supports maintenance of myelin integrity in the CNS
• Experimental evidence suggests that BG-12 may provide anti-inflammatory and cytoprotective effects in the treatment of MS
  – Induces anti-inflammatory Th2 cytokines
  – Shown to increase IL-10 and decrease TNF-α and IL-6
  – Induces apoptosis in activated T cells
  – Induces expression of phase 2 detoxification enzymes in astroglial and microglial cells
  – Reduces the expression of adhesion molecules
• Phase III DEFINE: BG12 vs placebo in RRMS
• Phase III CONFIRM: BG12 vs placebo and GA active comparator
• FDA-approved for RRMS 3/27/2013

Issues in Clinical Practice: Dimethyl Fumarate

- Baseline testing
  - CBC, LFTs
- Twice daily may interfere with compliance
- Side effects
  - Flushing/hot flashes
  - GI upset (stomach pain, nausea, vomiting)
  - Headache
  - Decrease in lymphocyte count
- On-going monitoring
  - CBC, LFTs
- Slower titration may help with side effects
Attenuation of DMF-related GI Sxs with Montelukast

- 21 pts with DMF-related GI symptoms were enrolled
  - GI sx rating scale (GSRS- 15 Q self-adm Q)
- 10mg po daily montelukast
- GSRS scores decreased by 81% following treatment with montelukast (P <.001)
  - Symptom reduction was noted within 72 hours in 16/21 patients and has persisted for 30 days
- 8/21 patients were symptom free
- 8/21 patients had attenuation of symptoms
  - 62% reduction
- 5/21 patients had no response to montelukast

Tornatore AAN 2014 P7.251
Lymphocyte Count on BG-12

Fox et al, NEJM (2012) 367, 1087-1097
Absolute Lymphocyte Counts 6 months after Initiation of DMF

<table>
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<th>Patient</th>
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<td>546</td>
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<td>Patient 2</td>
<td>2707</td>
<td>682</td>
</tr>
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<td>Patient 3</td>
<td>2010</td>
<td>666</td>
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<tr>
<td>Patient 4</td>
<td>2475</td>
<td>731</td>
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**Lymphocyte Count on BG-12**

![Graph showing lymphocyte count over time for different treatment groups.]

**Patients at risk**

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<tr>
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<th>16</th>
<th>24</th>
<th>32</th>
<th>40</th>
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<th>72</th>
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<td>251</td>
<td>249</td>
<td>234</td>
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<tr>
<td>240 mg BID</td>
<td>357</td>
<td>343</td>
<td>330</td>
<td>330</td>
<td>311</td>
<td>296</td>
<td>280</td>
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<td>268</td>
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<td>256</td>
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<tr>
<td>240 mg TID</td>
<td>342</td>
<td>328</td>
<td>301</td>
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<td>296</td>
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<td>GA</td>
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<td>316</td>
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Fox et al, NEJM (2012) 367, 1087-1097
CD 4 Counts 6 months after Initiation of DMF

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<td>245</td>
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<td>Series2</td>
<td>1272</td>
<td>280</td>
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<td>Series3</td>
<td>1045</td>
<td>293</td>
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<tr>
<td>Series4</td>
<td>1386</td>
<td>424</td>
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# Table 3: Incidence of CTC grades for worst post-baseline lymphocyte counts

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<thead>
<tr>
<th>Category</th>
<th>Placebo (n=830)</th>
<th>BG-12 BID (n=757)</th>
<th>BG-12 TID (n=805)</th>
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<tbody>
<tr>
<td>CTC Grade 0</td>
<td>794 (96)</td>
<td>472 (62)</td>
<td>573 (71)</td>
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<tr>
<td>CTC Grade 1</td>
<td>14 (2)</td>
<td>76 (10)</td>
<td>62 (8)</td>
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<tr>
<td>CTC Grade 2</td>
<td>18 (2)</td>
<td>166 (22)</td>
<td>146 (18)</td>
</tr>
<tr>
<td>CTC Grade 3</td>
<td>4 (&lt;1)</td>
<td>42 (6)</td>
<td>24 (3)</td>
</tr>
<tr>
<td>CTC Grade 4</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Numbers in parentheses are percentages using the number of patients in the safety population with at least one post-baseline lymphocyte value (n=830, 757, and 805 in the placebo, BG-12 BID, and BG-12 TID groups, respectively) as the denominator.

Common terminology criteria

<table>
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<tr>
<th></th>
<th>Grade 1</th>
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<th>Grade 3</th>
<th>Grade 4</th>
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<td>CD4</td>
<td>&lt;LLN-500/mm³</td>
<td>&lt;500-200/mm³</td>
<td>&lt;200-50/mm³</td>
<td>&lt;50/mm³</td>
<td>death</td>
</tr>
<tr>
<td>lymphopenia</td>
<td>&lt;lln - 800/mm³</td>
<td>&lt;800-500/mm³</td>
<td>&lt;500-200/mm³</td>
<td>&lt;200/mm³</td>
<td>death</td>
</tr>
</tbody>
</table>
Issues in Clinical Practice: Dimethyl Fumarate

- **Which patient is the right fit?**
  - Potentially more broad use

- **How should dimethyl fumarate be used?**
  - First-line
  - Second-line
    - Intolerance to prior agent
    - Breakthrough disease on prior agent
  - Screen for lymphopenia
  - If needing to switch from dimethyl fumarate
    - Unclear whether/what washout is prudent
    - Follow lymphocyte counts
  - Side effects
    - bASA; montelukast
Case Study
What went wrong?

• Was it the drug we switched to?
• Was it how long we waited?
• Maybe we shouldn’t have stopped Tysabri
ENIGM: Switching from Natalizumab to Fingolimod (FTY)

• Survey-based, observational multicenter study in pts planning a switch from NAT to FTY

• Examine occurrence of MS relapse during the variable WP or during a 6-month follow-up period after the initiation of FTY

• 333 MS pts switched from NAT to FTY after a mean of 31 infusions
  – 71% were seropositive for the JC virus

• 27% of patients relapsed during the WP (mean 17 weeks)
  – 20.3% <3 mo; 31% 3-6 mo; 59% >6 mo (OR 0.23 for <3 mo 0.1-0.65 p<0.001)
  – Patients who stopped NAT because of poor tolerance/lack of efficacy had higher risk of relapse (OR 3.20; P = .004).

• 20% of patients relapsed during the first 6 months of FTY

• The occurrence of relapse during WP was the only significant predictor relapse during FTY (odds ratio, 3.80; P = .05).

• In this study, switching from NAT to FTY was associated with a risk of MS reactivation during the WP or shortly after FTY initiation

• The WP should be shorter than 3 months

Switching to FTY: Risk of Short-Term Relapse

- **Retrospective Study: Data from MSBase Registry**
  - To determine early risk of relapse after switch from NAT to FTY
  - To compare the switch experience of NAT-FTY to (IFN-β/GA)-FTY and to Rx naïve-FTY
  - To determine predictors of time to first relapse on fingolimod.

- **A total of 536 patients were followed for a median of 10 months**
  - 89 pts NAT-FTY
  - 350 pts IFN-β/GA-FTY
  - 97 pts naïve-fingolimod

- **NAT-FTY group: increase in RR on FTY vs. NAT (ARR 0.38 vs. 0.26; p = 0.002)**
  - 30% of pts with disease activity on NAT relapsed within 1st 6 mos on FTY
  - RR were generally low across all patient groups in the first 9 months on FTY (RR 0.001-0.13)

- **Independent predictors of time to first relapse on FTY**
  - # relapses in the prior 6 months (hazard ratio [HR] 1.59 per relapse; p = 0.002)
  - gap in treatment of 2-4 months compared to no gap (HR 2.10; p = 0.041).

- **Authors recommend a maximum 2-month treatment gap for switches to FTY to decrease the hazard of relapse.**

Jokubaitis VG et al, Neurology. 2014 Apr 8;82(14):1204-11
FTY is Not Able to Inhibit MS Reactivation after NAT Discontinuation

- Retrospective study in 196 MS patients who had received at least 1 NAT
- Patients were divided into two groups:
  - those switched to FTY
  - those switched to any other treatment
- 80 MS patients discontinued NAT and were followed
  - 35 pts switched to FTY after 3 or more mos
  - 44 pts switched to other treatments
    - monthly pulses of steroids, IFNbeta, glatiramer acetate, cyclophosphamide (1 patient) or none
- 31% (11/34) FTY pts developed clinical relapses and
- 41% (18/44) of “Other” pts developed clinical relapses
- No difference in risk of remaining relapse-free between grps
- Recurrence of disease activity after NAT discontinuation is a common
- FTY is not more able to inhibit disease reactivation than other treatments
  - A more aggressive approach is necessary to reduce the risk of disease reactivation
Relapses Occur When Transitioning from NAT to FTY

- Comi et al: FIRST Study 135 pts had >6 mo WP and 119 had 3-6 mo WP
  - 17% of pts relapsed in 1st mo of treatment; 6% in month 2; 4% in mo 4
- Sempere et al. 8/18 pts switched from NAT-FTY. 10/18 remained on NAT
  - 63% on FTY relapsed
  - 75% on FTY demonstrated MRI activity
- Havla et al. 32/43 pts switched from NAT-FTY and 11/43 NAT-No Rx, 24 weeks WP
  - 47% FTY relapsed vs 73% NoRx relapsed (ARR 0.8 vs. 1.8, p=0.03)
  - 20% FTY vs 70% NoRx showed Gd+ lesions on MRI after stopping NAT (p<0.05)
  - Pts switched to FTY <12 weeks after NAT had a lower post-NAT ARR compared to patients who started FTY ≥12 weeks after NAT (ARR 0.4 vs 0.9; NS)
  - Most relapses in the FTY group occurred just before or within 8 weeks after starting FTY.
Switching from NAT to DMF

- Hillman et al: 51 pts were switched from NAT to DMF for 6 months
  - 25% (13/51) relapsed (11 were women)
  - WP was not to exceed 4 weeks
- Vo et al: 40 pts switched from NAT-DMF
  - Mean WP: 18.2 weeks (2-82 wks)
  - 13% relapsed during WP (30.6 wks 2-69)
  - 15% relapsed after DMF start
    - Avg WP 14.9 wks (4-33 weeks)
    - Avg time on DMF at relapse 9 wks (1-15)
- VM experience: 45 pts switched from NAT-DMF
  - Mean WP: 6.8 weeks (1.5-12 wks)
  - 13% (6/45) relapsed
    - 1 was in WP 6 weeks
    - 3 were within 1 month of DMF Rx after WP 6 weeks
    - 2 in WP of 12 weeks
Natalizumab to Teriflunomide

• Edwards et al: retrospective review of 30 MS pts s/p ≥ 12 infusions with NAT
  – WP: within 4 weeks of last NAT infusion
  – 13% pts relapsed

• Bailey et al: retrospective review of 9 pts on NAT
  – WP: 14 mg TER started 4 wks after last NAT infusion
    • 33% pts relapsed at month 6

Edwards K et al.  CMSC 2014 DX38
Bailey RO et al.  CMSC 2014 DX53
RESTORE- Randomized NAT Treatment Interruption Study

- A randomized, partially PLC-controlled study evaluating MS disease activity during a 24-week interruption of NAT
- 175 pts were on NAT for at least 1 year (167 evaluable)
  - 45 pt randomized to NAT
  - 42 pts randomized to PLC
  - 88 pts randomized to other therapies
    - 17 pts IM IFN-β-1a; 17 pts GA; 54 pts to monthly MP
- 29% had MRI disease activity recurrence
  - 0/45 (0%) NAT
  - 19/41 (46%) PLC
  - 1/14 (7%) IM IFN-β-1a
  - 8/15 (53%) GA
  - 21/52 (40%) MP
- Relapses
  - 4% NAT pts relapsed
  - 15%-29% of patients in the other treatment arms relapsed
- MRI disease activity recurred starting at 12 weeks (n = 3 at week 12) post last NAT dose
- Relapses were reported as early as 4-8 weeks (n = 2 in weeks 4-8) post last NAT dose
- 30% (50/167) in placebo/other-therapies groups, restarted NAT early because of disease activity
RESTORE- PK PD and MR Measurements

- Monthly assessments: MRI, [NAT], alpha4-integrin saturation, lymphocyte counts, sVCAM, CD49d expression, lymphocyte subsets.
- By 4 months after the last dose of NAT all values equivalent to untreated pts
  - 77% of pts had no natalizumab activity
- Gd+ lesions did not appear until PD markers returned to levels found in untreated patients
  - the earliest lesion was reported 3 months after the last NAT dose.
- There was a relationship between alpha4-integrin saturation measured 4 wks prior to lesions and Gd+ lesion appearance
  - an increased risk of Gd+ lesions was present when saturation was <70%
- After NAT discontinuation, time to return of “untreated” alpha4-integrin saturation values is highly variable
- Alpha-4 integrin saturation is predictive of the risk of Gd+ lesion occurrence.
Figure 2. Mean serum concentration (A) and mean percentage saturation of $\alpha_4$-integrin receptors (B) over time in healthy volunteers ($n = 65$) after a single 60 min intravenous infusion of natalizumab 300 mg.
**FIGURE 2.** PK/PD Relationship During and After Natalizumab Interruption

A. **Natalizumab Concentration, μg/mL**

- Natalizumab (n=45)
- Placebo (n=42)
- IM IFNβ-1a (n=17)
- GA (n=17)
- MP (n=54)

B. **CD4+ T Cell Saturation, %**

C. **sVCAM-1, ng/mL**

*Average measurement was below the limit of detection. Arrow represents last dose before 24-week interruption period (placebo and other-therapies groups). All patients who were not rescued are included in analysis.*
PML after NAT Discontinuation

• Search of MEDLINE, FDA AE Reporting System, 2006-2012 for lab-confirmed PML, sx onset ≥ 30 days post NAT w/d

• 17 pts dev’d PML
  – Median NAT duration 47 mos (9-59)
  – 50-109 days after last NAT dose

• 11 pts (65%) received new MS Rx betw/ NAT discontinuation and PML dx
  – 50-90 days after last NAT dose

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<th>Case No.</th>
<th>Estimated Time from NTZ Discontinuation to PML Onset, Days&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Estimated Time from PML Onset to Confirmation, Days&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IRIS following NTZ Discontinuation</th>
<th>PLEX to Accelerate NTZ Clearance</th>
<th>Disease-Modifying Therapies</th>
<th>Intravenous Steroids</th>
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<td>1</td>
<td>81</td>
<td>86</td>
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<sup>a</sup> Days since NTZ discontinuation.  
<sup>b</sup> Independent IRIS.
Additional Cases of PML with Orals

• Fingolimod
  – NO prior NAT
  • Aug 2013; after 7+ mos of FTY (prior AZA x 1 mo, IFN) and steroids before and during FTY

• Dimethyl Fumarate
  – TYS-DMF switch
    • s/p 52 TYS infusions + IMVP 3gm q mo x 2 yrs, JCV(+)
    • Dec 2013 DMF was initiated during last 2 mos of TYS
    • Feb 2014 TYS d/c’d and DMF was continued as monoRx
    • Mar 2014 f/u MRI suspicious for PML
    • Apr 2014 CSF PCR (+) for JCV

• Leflunomide
  – 20 cases of PML
  – In 2 cases LEF as cause could not be ruled out

http://www.fda.gov/Drugs/DrugSafety/ucm366529.htm
Warnatz K et al. Ann Rheum Dis; 62: 50-57
Considerations in Long-Term Tysabri Use
JCV Antibody Index Stratifies PML Risk in Natalizumab-Treated MS Patients

- JCV Ab index data from JCV Ab+ MS patients enrolled in clinical studies or from postmarketing settings were used for analyses.
- JCV Ab index data were available from 71 natalizumab-treated PML patients at least 6 months prior to PML diagnosis and from 2522 non-PML JCV Ab+ patients.
- JCV Ab index was not found to be associated with duration of natalizumab treatment ($P=0.39$) or prior IS use ($P=0.43$), but was significantly associated with PML risk ($P<0.001$).
- Risk of PML in JCV Ab negative MS patients is very low (0.1 per 1000). JCV Ab+ MS patients who have low JCV Ab index have several-fold lower PML risk compared with current risk attributed to all JCV Ab+ patients.
- Utilization of JCV Ab index allows for further clinically meaningful stratification of PML risk in JCV Ab+ natalizumab-treated MS patients.

Ticho B et al. ECTRIMS 2013
Anti-JCV antibody index value was significantly higher in pre-PML patients compared with non-PML patients.

**Median (95% CI)**

- **ALL**
  - Non-PML (n=2522)
  - Pre-PML (n=71)
  - *P* < 0.0001

- **PRIOR IS**
  - Non-PML (n=176)
  - Pre-PML (n=19)
  - *P* = 0.8708

- **NO PRIOR IS**
  - Non-PML (n=2242)
  - Pre-PML (n=51)
  - *P* < 0.0001

- Difference observed only for patients with no prior IS use.

104 non-PML patients and 1 pre-PML patient were missing prior IS information and were excluded from analyses by prior IS use. IS = immunosuppressant.
PML risk can be estimated by index threshold in anti-JCV Ab+ patients (no prior IS use)

### PML risk estimates (95% CI) per 1000 patients
Based on natalizumab exposure

<table>
<thead>
<tr>
<th>Index</th>
<th>1–24 months</th>
<th>25–48 months</th>
<th>49–72 months</th>
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<td>≤0.9</td>
<td>0.1 (0–0.41)</td>
<td>0.3 (0.04–1.13)</td>
<td>0.4 (0.01–2.15)</td>
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<td>≤1.1</td>
<td>0.1 (0–0.34)</td>
<td>0.7 (0.21–1.53)</td>
<td>0.7 (0.08–2.34)</td>
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<tr>
<td>≤1.3</td>
<td>0.1 (0.01–0.39)</td>
<td>1.0 (0.48–1.98)</td>
<td>1.2 (0.31–2.94)</td>
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<tr>
<td>≤1.5</td>
<td>0.1 (0.03–0.42)</td>
<td>1.2 (0.64–2.15)</td>
<td>1.3 (0.41–2.96)</td>
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<tr>
<td>&gt;1.5</td>
<td>1.0 (0.64–1.41)</td>
<td>8.1 (6.64–9.80)</td>
<td>8.5 (6.22–11.38)</td>
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</table>

PML risk estimates for anti-JCV antibody index thresholds were calculated based on the current PML risk stratification algorithm (from September 2012) and predicted probabilities for the population at or below that particular index (0.9–1.5) and for the population above an index of 1.5. For index thresholds below 0.9, patient numbers were insufficient to allow for calculation of risk estimates.
Presence of Lipid-Specific IgM Bands May Reduce Risk of PML

- Lipid-specific IgM bands (LSMB) associate with a suboptimal response to IFN in MS. Many patients treated with NAT show these antibodies in CSF
- Multicenter European study 367 MS patients treated with NAT
- 23 patients developed a PML during natalizumab treatment
  - 1/23 had LSMB
- 66.3% of pts (228/344) that did not develop PML showed these antibodies
- Presence of LSMB conferred a protective effect vs. PML (OR=40.4, CI: 5.4-303.8, p<0.0001)
- Absence of anti JC Abs also showed a protective effect (OR=24.5, CI: 3.2-185.2, p<0.0001)
- To study the effect of the combination of the two variables, JC Ab+ pts were further classified according to LSMB status
  - 61% showed (Anti JC+, LSMB+)
  - 39% (69 patients) lacked these antibodies (Anti JC+, LSMB-)
    - 21 pts of this group developed PML
- There was no difference in risk of PML in JC+ vs JC- pts who were LSMB+ (p=1.0)
- Clear differences were seen between JC+ and JC- pts who were LSMB-
  - 90% of PML cases (OR=58.2, CI: 13.2-254, p<0.0001)
- The presence of LSMB may help to identify JC+ pts who could be at lower risk of developing PML
sVCAM levels as surrogate marker for Tysabri saturation

• RESTORE:
  – Throughout treatment interruption, good concordance was seen between serum natalizumab concentration, alpha-4 integrin saturation, and serum soluble vascular cell adhesion molecule (sVCAM) concentration
  – Binding of fluorescently labeled VCAM to circulating lymphocyte subsets increased during treatment interruption, indicating increasingly available alpha-4 integrin molecules and increased adhesion interactions

• Foley J:
  – Cross-sectional analyses revealing lower sVCAM levels in NAT dosing interval 4 weeks beyond standard
  – sVCAM levels lower in patients with hx of zoster
  – Extended cycle length reduces NAT concentration

Foley J AAN 2011 Foley AAN 2014
Alternate dosing regimen in long-term Tysabri recipients

- Risk of PML in first year and up to second year is relatively low when Tysabri saturation is still increasing and pts may report a waxing and waning “wearing off” phenomenon with each dose
- Between 12-24 months, pts generally report stabilization and this coincides with an increased risk of PML
- Continuing at q4week dosing intervals may result in over-dosing and excessive Tysabri saturation
  - Reactivation is more likely to occur sooner during Tysabri discontinuation in pts whose Tys saturation was <70% at time of discontinuation
- Many factors likely contribute to increased risk of PML with increased duration of treatment
  - Excessive Tysabri saturation may be a potential factor
sVCAM over-time (cohort 1)

Tysabri patients

Dosing interval changes

Typical Tysabri dosing = 1 month (4 weeks)
Any changes in dosing occurred primarily after 2 years of therapy
Dosing may change sVCAM levels
5 week Tysabri dosing

Tysabri patients - patients with 4 week dosing intervals

Tysabri patients - patients with a 5 week dosing interval

5 weeks

Tysabri dose

Log2 sVCAM (ng/ml)

sVCAM (ng/ml)

before

after

0

200

400

600

5 weeks

dosing
6 week Tysabri dosing

- sVCAM levels increase with increasing dosing intervals, but do not reach pre-tx levels after 6 weeks
Low Body Weight as a Potential Surrogate Risk Factor for PML

- Weight may serve as a surrogate for natalizumab drug concentration and/or lymphocyte VLA-4 receptor saturation
  - Higher saturation levels found in lower weight populations
  - Natalizumab clearance increases with body weight in a less than proportional manner such that a 43% increase in body weight resulted in a 32% increase in clearance

Foley JF AAN 2014
Considerations for long-term Natalizumab use

• No specific DMT appears to be the preferred agent if switching off NAT
• Transitioning to oral may be associated with disease reactivation
  – Shorter WP in transition may be advisable (0-8 weeks)
    • Be aware of dosing interval prior to discontinuation of TYS in considering WP
  – Monitor for PML up to 6 months after d/c
• Better risk stratification to avoid switch
  – Use of JCV IgG index
• Consider increasing dosing interval regardless of JC status
  – Weight may be a factor with dosing interval
    • Lower BMI may require less NAT