Dimethyl Fumarate and Natalizumab Update 2013

Bruce Cree, MD, PhD, MCR
Dimethyl Fumarate

*Dimethyl fumarate (BG12, Tecfidera™) was approved by the FDA for relapsing-remitting forms of MS on March 27, 2013*
Dimethyl Fumarate

Fumaric acid esters can be derived from extracts of the plant fumaria officinalis, also known as common fumitory.
Dimethyl fumarate is derived from Fumaderm, an oral therapy of fumaric acid esters approved to treat psoriasis in Germany.

Therapeutic mechanism of BG-12 in MS is speculative.

- In psoriasis patients, the beneficial effect of fumarates coincides with lymphocytopenia (40%-60%) and down-regulation of proinflammatory cytokine(s).
- Increases in an anti-inflammatory cytokine (IL-10) were noted in a small pilot study of MS patients and in an EAE model.
- Data in the EAE model suggest BG-12 activates a protective antioxidant pathway in CNS.

BG-12 Has Shown Nrf2 Pathway Activation

- Detoxification enzymes
- Antioxidant enzymes
- NADPH generating enzymes
- GSH biosynthesis enzymes
- Chaperones
- Ubiquitination/proteasome

DMF=dimethyl fumarate; MMF=monomethyl fumarate.
Fumarate: Phase II

Primary Endpoint

- Mean total number of GdE lesions from scans at Weeks 12, 16, 20, and 24 combined

**Fumarate: Relapse Rate**

![Graph showing relapse rates for different treatments.](image)

- **Placebo**: n=54
- **BG12 120 mg QD**: n=59
- **BG12 120 mg TID**: n=56
- **BG12 240 mg TID**: n=54

ARR (Weeks 0-24) for Placebo: 32%, P=NS
Fumarate: Safety and Tolerability

Oral – 240 mg three times daily (720 mg total daily dose)

- GI-related problems and flushing are the two most common AEs\(^1,2\)
  - Phase IIb (240 mg tid) – AEs more common vs placebo: headache (21%), flushing (40%), pruritus (10%), diarrhea (11%), abdominal pain (14%), nausea (16%)\(^1,2\)
  - Incidence of flushing and GI events decreased over 12 months of treatment, with notable decrease after first month\(^2\)

- Incidence of infection was not significantly different from placebo\(^2\)

- >30 years of use of fumaric acids in treatment of psoriasis (both topical and oral dosing)\(^3\)

DEFINE (BG-12/Dimethyl Fumarate) : Study Design

Randomization
1:1:1
N = 1237
MRI N = 540

Study Week
0 12 24 36 48 60 72 84 96

Placebo
BG-12 240 mg BID
BG-12 240 mg TID

EDSS/MSF/VFT
✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓

SF-36/EQ-5D
✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓ ✓

Gold R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 95]
**DEFINE: Cumulative Probability of Relapse (1° Endpoint)**

- **Hazard Ratio:**
  - BG-12 BID vs placebo = 0.51 ($P < 0.0001$)
  - BG-12 TID vs placebo = 0.50 ($P < 0.0001$)

**Number of Patients at Risk:**
- Placebo: 406, 358, 321, 282, 243, 224, 205, 190
- BG-12 BID: 410, 353, 324, 303, 288, 287, 255, 243
- BG-12 TID: 416, 348, 322, 301, 288, 270, 251, 244

Patients were censored if they withdrew from the study or switched to alternative MS medication without a relapse.

Gold R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 95]
DEFINE: Annualized Relapse Rates

Gold R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 95]
Progression of Disability: EDSS

EDSS = Expanded Disability Status Scale.

- 10.0 = Death due to MS
- 9.0–9.5 = Completely dependent
- 8.0–8.5 = Confined to bed or chair
- 7.0–7.5 = Confined to wheelchair
- 6.0–6.5 = Walking assistance is needed
- 6.0–6.5 = Increasing limitation in ability to walk
- 5.0–5.5 = Increasing limitation in ability to walk
- 4.0–4.5 = Disability is moderate
- 3.0–3.5 = Disability is mild to moderate
- 2.0–2.5 = Disability is minimal
- 1.0–1.5 = No disability
- 0 = Normal neurologic exam

Increasing disease burden
DEFINE: Time to 12-Week Confirmed Disability Progression

Number of Patients at Risk:
- Placebo: 408 375 345 319 291 285 242 224
- BG-12 BID: 409 359 333 328 304 290 278 267
- BG-12 TID: 416 360 346 325 324 291 276 265

Hazard Ratio:
- BG-12 BID vs placebo = 0.62 (P = 0.0050)
- BG-12 TID vs placebo = 0.66 (P = 0.0128)

Gold R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 95]
DEFINE: 2 Years MRI Outcomes

Gd-enhancing lesions

- Placebo (n = 165): 1.8
- BG-12 BID (n = 152): 0.1
- BG-12 TID (n = 152): 0.5

Adjusted Mean Number of New or Newly Enlarging T2 Lesions

- Placebo (n = 165): 17.0
- BG-12 BID (n = 152): 2.6
- BG-12 TID (n = 152): 4.4

90% reduction*  P < 0.0001
73% reduction*  P < 0.0001
85% reduction*  P < 0.0001
74% reduction*  P < 0.0001

Arnold DL, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [P831]
## DEFINE: Adverse Events

<table>
<thead>
<tr>
<th>AE n (%)</th>
<th>Placebo (n = 408)</th>
<th>DMF 240 mg BID (n = 410)</th>
<th>DMF 240 mg TID (n = 416)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>387 (96)</td>
<td>395 (96)</td>
<td>396 (95)</td>
</tr>
<tr>
<td>Flushing*</td>
<td>20 (5)</td>
<td>154 (38)</td>
<td>132 (32)</td>
</tr>
<tr>
<td>MS relapse</td>
<td>189 (46)</td>
<td>111 (27)</td>
<td>114 (27)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>101 (25)</td>
<td>108 (26)</td>
<td>109 (26)</td>
</tr>
<tr>
<td>Headache</td>
<td>80 (20)</td>
<td>81 (20)</td>
<td>80 (19)</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>55 (13)</td>
<td>62 (15)</td>
<td>78 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>54 (13)</td>
<td>57 (14)</td>
<td>63 (16)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>53 (13)</td>
<td>63 (15)</td>
<td>51 (12)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>53 (13)</td>
<td>55 (13)</td>
<td>54 (13)</td>
</tr>
<tr>
<td>Nausea*</td>
<td>38 (9)</td>
<td>53 (19)</td>
<td>54 (13)</td>
</tr>
<tr>
<td>Back pain</td>
<td>57 (14)</td>
<td>59 (14)</td>
<td>46 (11)</td>
</tr>
<tr>
<td>Upper abdominal pain*</td>
<td>28 (7)</td>
<td>40 (10)</td>
<td>52 (13)</td>
</tr>
<tr>
<td>Proteinuria*</td>
<td>34 (8)</td>
<td>38 (9)</td>
<td>50 (12)</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>22 (5)</td>
<td>46 (11)</td>
<td>37 (9)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>39 (10)</td>
<td>46 (11)</td>
<td>37 (9)</td>
</tr>
<tr>
<td>Influenza</td>
<td>39 (10)</td>
<td>34 (18)</td>
<td>48 (12)</td>
</tr>
<tr>
<td>Pruritus*</td>
<td>19 (5)</td>
<td>42 (10)</td>
<td>34 (8)</td>
</tr>
<tr>
<td>Vomiting*</td>
<td>24 (6)</td>
<td>40 (10)</td>
<td>30 (7)</td>
</tr>
</tbody>
</table>

*Indicates an incidence ≥ 3% higher in either BG-12 group.

Selmaj K, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [P994]
CONFIRM: A Phase 3 Trial of DMF With an Active Comparator in Patients With MS

- N = 1,417
- Ages 18-55 years
- RRMS
- EDSS 0.0 to 5.0
- 2-year study

DMF 240 mg BID
DMF 240 mg TID
Placebo
GA
20 mg/day

EDSS: Expanded Disability Status Scale; GA: glatiramer acetate.
## CONFIRM: Additional Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>DMF BID (vs Placebo)</th>
<th>DMF TID (vs Placebo)</th>
<th>GA (vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of relapse</td>
<td>-34% ($P = .002$)</td>
<td>-45% ($P &lt; .0001$)</td>
<td>-29% ($P = .0097$)</td>
</tr>
<tr>
<td>New/enlarging T2 lesions</td>
<td>-71% ($P &lt; .0001$)</td>
<td>-73% ($P &lt; .0001$)</td>
<td>-54% ($P &lt; .0001$)</td>
</tr>
<tr>
<td>New T1 hypointense lesions</td>
<td>-57% ($P &lt; .0001$)</td>
<td>-65% ($P &lt; .0001$)</td>
<td>-41% ($P = .0021$)</td>
</tr>
<tr>
<td>T1-GdE lesions</td>
<td>-74% ($P &lt; .0001$)</td>
<td>-65% ($P = .0001$)</td>
<td>-61% ($P = .0003$)</td>
</tr>
<tr>
<td>12-Wk CDP</td>
<td>-21% ($P = .2536$)</td>
<td>-24% ($P = .2041$)</td>
<td>-7% ($P = .7036$)</td>
</tr>
</tbody>
</table>

- Similar to the DEFINE trial, incidence of flushing and GI events (ie, nausea, vomiting, diarrhea) higher in DMF–treated patients vs patients on placebo, as well as vs patients on GA

CDP: confirmed disability progression.
## DMF: Integrated Efficacy Analysis of DEFINE and CONFIRM

<table>
<thead>
<tr>
<th>Endpoint (at 2 years)</th>
<th>Placebo (n = 771)</th>
<th>DMF BID (n = 769)</th>
<th>DMF TID (n = 761)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate (ARR) Reduction vs placebo</td>
<td>0.37</td>
<td>0.19*</td>
<td>0.19*</td>
</tr>
<tr>
<td>Proportion of patients relapsed HR vs placebo</td>
<td>0.57*</td>
<td>0.53*</td>
<td></td>
</tr>
<tr>
<td>Time to 12-week confirmed disability progression HR vs placebo</td>
<td>0.68*</td>
<td>0.70*</td>
<td></td>
</tr>
<tr>
<td>Time to 24-week confirmed disability progression HR vs placebo</td>
<td>0.71*</td>
<td>0.68*</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant vs placebo.

For the BG12 data I would include only the information on 240 mg twice daily. The 240 mg three time daily dose will not be used in clinical practice and is not relevant for practical educational purposes. This comment applies ot the next series of slides.

Bruce Cree, 4/12/2013
DMF significantly reduced proportion of patients relapsed and ARR by week 12

- **HR for relapse risk vs placebo:**
  - 0.68 DMF BID (P = 0.028)
  - 0.70 DMF TID (P = 0.046)

- **ARR:**
  - 0.66 DMF BID (P = 0.015)
  - 0.68 DMF TID (P = 0.030)

- Significant separation maintained thereafter

- Significant improvements in MRI parameters seen at week 24 (first post-treatment assessment) that were maintained at 2 years

ARR by Prior TX Subgroups

Adjusted ARR (95% CI)

- Placebo
- BG-12 240mg BID
- BG-12 240mg TID

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo</th>
<th>BG-12 240mg BID</th>
<th>BG-12 240mg TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>0.35</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>Any ABCR</td>
<td>0.37</td>
<td>0.22</td>
<td>0.18</td>
</tr>
<tr>
<td>1 ABCR</td>
<td>0.38</td>
<td>0.23</td>
<td>0.16</td>
</tr>
</tbody>
</table>

ABC = Avonex/Betaseron/Copaxone/Rebif

DMF: Integrated Safety Analysis from Phase II/III Studies

Safety population total N = 2,428

<table>
<thead>
<tr>
<th>Adverse events, %</th>
<th>Placebo (n = 836)</th>
<th>BG-12 BID (n = 769)</th>
<th>BG-12 TID (n = 823)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>92%</td>
<td>95%</td>
<td>93%</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>11%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Serious</td>
<td>21%</td>
<td>18%</td>
<td>15%</td>
</tr>
<tr>
<td>Serious infections</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Malignancies</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

- AEs with incidence ≥5% higher in either DMF group vs placebo:
  - Flushing and related events (hot flush, erythema)
  - Gastrointestinal events (diarrhea, nausea, abdominal pain)
  - Rash
- No opportunistic infections reported
- Overall rates of hepatic and renal events similar across groups
- In DMF groups, lymphocyte counts decreased ~25–30% over first yr, then plateaued and remained within normal limits
- Four deaths (none thought tx-related)

Ongoing Long-Term Safety and Tolerability of DMF: ENDORSE

- 5-yr extension study of DEFINE and CONFIRM
- At interim analysis, safety profile similar for those who continued DMF from parent studies, and those new to DMF
- Rate of both serious infections and hepatic AEs low (≤2%) in any tx group
- No evidence of increased risk of renal dysfunction
- Two patients developed renal cell carcinomas
  - Cause effect relationship with DMF is not known

So the most interesting observation in this study was the identification of two patients who developed renal cell carcinomas in the extension study. This may be unrelated to treatment and due to chance but needs to be mentioned.

Bruce Cree, 4/12/2013
Additional DMF Data

In the integrated analysis, compared with placebo DMF significantly:

- Reduced relapses requiring IV steroids and hospitalizations
- Led to improvements in physical and mental aspects of health and functioning, general well-being, and overall health status (QoL)

- No evidence of increased risk of fetal abnormalities or adverse pregnancy outcomes associated with gestational exposure during first trimester, although data limited

- Pregnancy class C

DMF Summary

- Compared to placebo DMF showed significant reductions with respect to the probability of experiencing a relapse, the annualized relapse rate, disability progression and accumulation of gadolinium enhancing or new T2 lesions on MRI.

- There did not appear to be substantial difference between the BID and TID treatments and the 240 mg BID formulation is now commercially available.
Who Should Use DMF?

- Newly diagnosed untreated relapsing MS patients
- Relapsing treated MS patients who wish to switch to a twice daily oral therapy
- Relapsing treated MS patients who have a sub-optimal response to treatment
- Relapsing MS patients who may be candidates for treatment with natalizumab who test positive for the JC virus
- Relapsing MS patients with concomitant medical concerns in whom the risk: benefit profile for fingolimod is of concern
Who should not take DMF?

- DMF has not been studied in patients with progressive MS or in patients who require ambulatory assistance to walk.
- Long term safety of DMF in MS is not established.
- Of note, in psoriasis, 3 patients treated with Fumaderm developed PML:
  - 2 were treated with Raptiva (efalizumab), a drug known to cause PML.
  - 1 patient had persistent low lymphocyte counts.
- Baseline and annual CBC is recommended.
Monoclonal Antibody Production

- Immunization
- Antibody-forming cells
- Fusion
- Tumor cells
- Hybridomas
- Hybridomas screened for antibody production
- Antibody-producing hybridomas cloned
- Monoclonal antibodies isolated for cultivation
Chimeric and Humanized Antibodies

Variable Murine Regions

Chimeric Antibody
IgG4 Framework

Complementarity-Determining Regions

Humanized Antibody
IgG4 Framework
SAM Inhibition: Implications for Multiple Sclerosis Therapy

- Reduced Leukocyte Infiltration and Brain Inflammation
- Leukocyte Chemoattractant signal
- α4β1 (VLA-4)
- Blood Vessel Lumen
- Endothelial Cells
- Tissue
- VCAM-1

Leukocyte

- Chemoattractant signal
- α4β1 (VLA-4)
- Blood Vessel Lumen
- Endothelial Cells
- Tissue
- VCAM-1
Annualized Relapse Rate
Pre-specified Primary Endpoint

Annualized Relapse Rate (95% CI)

Placebo: 0.81
Natalizumab: 0.26

P < 0.0001

68%
Gadolinium-Enhancing (Gd+) Lesions

Mean Number of Gd+ Lesions

Placebo

Natalizumab

P<0.0001

92%

n=315

n=627
Natalizumab PML Incidence Estimates by Treatment Epoch


Observed clinical trial rate in patients who received a mean of 17.9 monthly doses of natalizumab. The post-marketing rate is calculated as the number of PML cases since reintroduction in patients that have had at least 1 dose of natalizumab.

Incidence estimates by treatment epoch are calculated based on TYSABRI exposure through May 31, 2011 and 133 confirmed cases as of June 1, 2011. The incidence for each epoch is calculated as the number of PML cases divided by the number of patients exposed to TYSABRI (e.g. for 25 to 36 infusions all PML cases diagnosed during this period is divided by the total number of patients ever exposed to at least 25 infusions and therefore having risk of developing PML during this time). Biogen Idec, data on file.
Current Stratification of Natalizumab-Associated PML Risk

Anti-JCV Antibody Status

<table>
<thead>
<tr>
<th>Prior IS Use</th>
<th>Anti-JCV Antibody Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Natalizumab Exposure</th>
<th>Anti-JCV Antibody Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–24 mos</td>
<td></td>
</tr>
<tr>
<td>&gt; 24 mos</td>
<td></td>
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Natalizumab Exposure

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Natalizumab Exposure

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<tbody>
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<td></td>
</tr>
<tr>
<td>&gt; 24 mos</td>
<td></td>
</tr>
</tbody>
</table>

Low body mass has recently been identified as an additional potential risk factor for the development of PML.

343 cases of PML have been documented in patients treated with natalizumab as of April 1, 2013. Available at: http://chefarztfrau.de/?page_id=716

PML = progressive multifocal encephalopathy; JCV = John Cunningham virus; IS = immunosuppressant


The abstract in the notes is for a different study.

Bruce Cree, 4/12/2013
RESTORE Study: Natalizumab

● Background:
  - NTZ efficacy in RRMS based on SENTINEL and AFFIRM phase III trials
  - Associated with PML (opportunistic infection of CNS) caused by JC virus
    - Risk increases with anti-JCV antibody (+) status, prior immunosuppressant use, and duration of NTZ treatment

● RESTORE Overview:
  - Randomized study evaluating effect of 24-week NTZ treatment interruption on immune parameters and disease activity
  - Patients treated with NTZ for ≥ 12 months (N = 175) randomized (1:1:2) to:
    - NTZ
    - Placebo
    - Other immunomodulatory therapy (IM IFNβ-1a, GA, or MP; investigator determined)

Fox R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 150]
**RESTORE: Study Design**

<table>
<thead>
<tr>
<th>Screening</th>
<th>Randomized Treatment Period</th>
<th>Follow-up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Double-blind NTZ infusions</td>
<td>Open-label NTZ infusions</td>
</tr>
<tr>
<td></td>
<td>Double-blind placebo infusions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other open-label therapies IM IFNβ-1a, GA, or MP</td>
<td></td>
</tr>
</tbody>
</table>

- If patient developed evidence of MS disease activity, investigators could administer high-dose corticosteroids and/or restart NTZ as rescue treatment
  - Clinical disease activity: defined by change in overall EDSS or functional system subscale scores
  - MRI disease activity: defined as 1 new Gd+ lesion of > 0.8 cm or 2 or more new Gd+ lesions of any size
- Study not designed or powered to determine effect on development of PML

Fox R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 150]
Patients with Clinical Relapses or Meeting MRI Rescue Criteria After Randomization*

<table>
<thead>
<tr>
<th>Patients, n/n</th>
<th>Clinical Relapses&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MRIs Meeting Rescue Criteria&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>25/167 (15%)</td>
<td>48/167 (29%)</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>2/45 (4%)</td>
<td>0/45 (0%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>7/41 (17%)</td>
<td>18/41 (44%)</td>
</tr>
<tr>
<td>Other therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IM IFNβ-1a</td>
<td>4/14 (29%)</td>
<td>1/14 (7%)</td>
</tr>
<tr>
<td>GA</td>
<td>4/15 (27%)</td>
<td>8/15 (53%)</td>
</tr>
<tr>
<td>MP</td>
<td>8/52 (15%)</td>
<td>21/52 (40%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>11 relapses (44%) occurred by 16 weeks, and 14 (56%) occurred between weeks 16-28

<sup>b</sup>36 of 48 patients (75%) who met rescue criteria did so at week 16 or 20

Fox R, et al. Presented at ECTRIMS / ACTRIMS 2011; Amsterdam, Netherlands. [Abstract 150]
NTZ interruption resulted in a high rate of recurrence of MRI and clinical MS disease activity (starting clinically at ~ week 8, radiographically ~ week 12)

IM IFNβ-1a appeared to suppress MRI activity more than other open-label treatments, although this group had lower disease activity prior to start of NTZ

However, study was not designed or powered to compare efficacy of alternative immunomodulatory therapies

Monthly MP (1g IV, started 1 month after last NTZ dose) did not appear to be effective in disease suppression
Who is a good candidate for Natalizumab?

- Relapsing MS patients who have had sub-optimal responses to other disease modifying therapies and are JCV seronegative
- Relapsing MS patients who are unable to tolerate other disease modifying therapies and are JCV seronegative
- Relapsing MS patients with highly active disease who are JCV seropositive in whom the potential benefit of treatment with natalizumab outweighs the risk of PML
- The effects of natalizumab in patients with secondary progressive MS are currently under study
Who is not a good candidate for treatment with natalizumab?

- Patients who have had prior treatment with immune suppressants, e.g. azathioprine, mycophenolate mofetil, methotrexate, mitoxantrone, cyclophosphamide, etc. and who are seropositive for the JCV.

- Patients who are seropositive and have been treated with natalizumab for 2 years or more are at higher risk for PML.
Patient Decisions Regarding Natalizumab Therapy

- **UT Southwestern Study**
  - 136/469 pts treated with natalizumab discontinued tx
    - 32.4% because of concern about PML
      - Most either anti-JCV seropositive or had >24 infusions
    - 18.4%: intolerable side effects (infusion-related or infections)
    - 9.6%: lack of perceived benefit
    - 11.8%: either worsening deficits or transitioned to secondary progression

- **French Study**
  - N = 292 natalizumab-treated MS pts
    - Anti-JCV serum positivity: 150 patients (51%)
    - 112 (74.4 %) of these decided to continue natalizumab, including 23 pts (15%) with 2 known PML risk factors

Switching From Natalizumab to Fingolimod: ENIGM Study

- 36 tertiary centers in France treating 4500 natalizumab (NTZ)-treated patients
- 177 patients switched to fingolimod (FTY) after mean 36 NTZ infusions
  - 72% seropositive for JCV
  - 50% classified in highest PML risk category
- Duration of and management during a washout period (WP) evaluated

Switching From Natalizumab to Fingolimod: ENIGM Study (cont’d)

- **Results**
  - In the WP:
    - 55% pts did not receive any treatment
    - 45% received sequential MP infusions
    - Relapse rate in WP: 65%
    - Only predictive factor: WP duration ($P = 0.002$)
  - At initiation of fingolimod, EDSS had slightly worsened ($P = 0.004$)
  - 33% of patients who received FTY for >6 months had ≥1 relapse
  - 3.3% stopped FTY for efficacy or tolerance issues

MP = methylprednisolone
Additional Evaluations of Switching from Natalizumab to Fingolimod

- Fingolimod reported as most effective natalizumab exit strategy (N = 75) in single MS center (LaGanke)

**FIRST Trial**
- Patients received NTZ before baseline for:
  - >6 months (n = 135)
  - 3 to 6 months prior to baseline (n = 119)
- Patients discontinuing NTZ had higher relapse risk that was improved with fingolimod
  - Relapses in first month of fingolimod tx higher in pts with shorter previous NTZ exposure

I thought the most important study presented on fingolimod at AAN was Dr. Cohen's presentation on brain volume loss. I would include a slide from his presentation in this program. Basically what was found was that across three trials there was a significant and consistent impact of fingolimod on brain volume loss. I have attached slides from his presentation for your review.

Bruce Cree, 4/12/2013