Track Two

Disease Modifying Therapy Safety Update

-Eric Williamson, MD
Consulting: Bayer, Biogen, Celgene, Genentech, EMD Serono, Teva and Novartis in the past

Current research support: Actelion, Alexion
DMT Safety Update Topics:

1. Progressive Multifocal Leukoencephalopathy (PML) and Disease Modifying Therapies (DMTs)
2. Infections other than PML with DMTs
3. Malignancy/autoimmune concerns
4. Vaccinations
Overview for Managing PML concerns with DMTs

1. PML – known risks
2. Risk mitigation
3. Early detection of PML
4. Restoring immune function, Treating PML/IRIS
PML in “At Risk Groups”

Immunologically healthy persons

Abnl Immunity

HIV/AIDS

1,200,000 HIV Infected

• 9,800,000 cancer survivors
• 2,100,000 RA treated with immunotherapy
• 200,000 organ transplants
• >100,000 bone marrow transplants

Until recently HIV-PML represented 80-90% of all PML cases
## PML Risk with DMTs

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Conditions Predisposing to PML</th>
<th>Latency from Time of Drug Initiation to PML</th>
<th>Incidence of PML</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I Agents - High Potential</strong></td>
<td><strong>NO</strong></td>
<td><strong>YES</strong></td>
<td><strong>HIGH</strong></td>
</tr>
<tr>
<td>Natalizumab</td>
<td>MS and Crohn’s disease</td>
<td>None &lt;8 months; 85% of cases &gt;24 months</td>
<td>&gt;1/100 with 3 risk factors; 4.2/1000 overall</td>
</tr>
<tr>
<td><strong>Class II – Low Risk</strong></td>
<td><strong>NO</strong></td>
<td><strong>YES</strong></td>
<td><strong>Low - Infrequent</strong></td>
</tr>
<tr>
<td>Fingolimod (19* as of 2/18); * 2/19 with prior natalizumab exp</td>
<td>MS</td>
<td>18-84 months</td>
<td>1/12,000</td>
</tr>
<tr>
<td>Dimethyl fumarate (5 as of 2/18)</td>
<td>MS and Psoriasis</td>
<td>18-54 months</td>
<td>1/50,000</td>
</tr>
<tr>
<td><strong>Class III-No or Very Low Risk</strong></td>
<td><strong>YES</strong></td>
<td><strong>NO</strong></td>
<td><strong>Very Low</strong></td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Hematological malignancies, transplantation</td>
<td></td>
<td>Unknown – no cases with MS</td>
</tr>
<tr>
<td>Ocrelizumab (Rituximab as proxy)</td>
<td>Rituximab: LPD, RA, ANCA vasculitis, SLE</td>
<td>None</td>
<td>Unknown – 1 case with MS after natalizumab</td>
</tr>
<tr>
<td>Teriflunomide (Leflunomide as proxy)</td>
<td>Leflunomide: RA</td>
<td></td>
<td>Unknown – 1 case with MS after natalizumab</td>
</tr>
</tbody>
</table>
PML Risk with Natalizumab

- Roughly 800 cases/≈200K patients exposed
- Overall incidence ≈4/1000
- Duration of natalizumab prior to PML months to years
  - 14% had 1-24 doses
  - 86% > 24 doses

- Factors associated with increased risk include:
  - Prior immunosuppressive therapy
  - Longer treatment duration
  - Positive JCV antibody status
Cumulative Natalizumab PML Risk by Treatment Duration

Figure 3. Global Cumulative Natalizumab PML Risk Estimates by Treatment Duration: As of February 28, 2017
### TABLE 2. PML Risk Estimates by Index Threshold in Anti-JCV Antibody–Positive Patients with No Prior IS Use

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Index</th>
<th>PML Risk Estimates per 1,000 Anti-JCV Antibody–Positive Patients by Natalizumab Treatment Duration, No Prior IS Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–24 Months (99% CI)</td>
</tr>
<tr>
<td>≤0.9</td>
<td>0.1 (0–0.15)</td>
</tr>
<tr>
<td>≤1.1</td>
<td>0.1 (0–0.23)</td>
</tr>
<tr>
<td>≤1.3</td>
<td>0.1 (0–0.28)</td>
</tr>
<tr>
<td>≤1.5</td>
<td>0.1 (0–0.30)</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>1.0 (0.84–1.07)</td>
</tr>
<tr>
<td>No index</td>
<td>0.6 (0.42–0.88)</td>
</tr>
</tbody>
</table>

PML risk estimates across anti-JCV antibody index thresholds were calculated based on the PML risk stratification algorithm (from September 2012) and predicted probabilities shown in Table 1 for the anti-JCV antibody–positive population at or below respective index thresholds from 0.9 to 1.5. For index thresholds at or below 0.7, PML patient numbers were insufficient to allow for calculation of risk estimates.

*Based on existing PML risk stratification algorithm using September 2012 data for the anti-JCV antibody positive group with no prior IS use.

CI = confidence interval; IS = immunosuppressant; JCV = JC virus; PML = progressive multifocal leukoencephalopathy.

Data from Biogen

**Label changes**

1) Duration of therapy >2 years, November 2009
2) Prior use of immunosuppressive, July 2010
3) JCV Antibody assay, January 2012

Change in Rate of Natalizumab PML Incidence
There are three kinds of lies: lies, damn lies and statistics.
PML after Natalizumab Discontinuation

Data as of August 29, 2014
494 Confirmed cases
419/481 detected prior to or <1 month after last dose
62 (13%) detected >1 month after drug discontinuation

>15 cases of fingolimod associated PML as of 2018 (and additional cases attributed to prior natalizumab)

Mean age 53 years with 5 patients <50 years old
14/15 with >2 years of fingolimod exposure

2/15 with confounding medical conditions
- Cancer treated with chemotherapy
- Ulcerative colitis treated with immunosuppressive agents

2/15 with some natalizumab exposure
- 1 patient had natalizumab for 10 months discontinued for 7 months then fingolimod for 38 months before PML
- 1 patient had fingolimod for 4 years and 6 months before discontinuation and the initiation of natalizumab

4 had lymphocyte counts <200 cells/µL

Berger J et al Neurology 2018
5 confirmed cases of PML with DMF; reportedly none since institution of discontinuation of DMF if JCV Ab+ and lymphocyte count <500

4 cases with no natalizumab; 1 case received 76 months of natalizumab followed by 2 month washout (natalizumab not considered to be confounder by Biogen)

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Duration of Therapy</th>
<th>ALCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>F</td>
<td>54 months</td>
<td>0.28 x 10^9/L to 0.58 x 10^9/L for &gt;3.5 years</td>
</tr>
<tr>
<td>64</td>
<td>M</td>
<td>26 months</td>
<td>0.3 x 10^9/L to 0.53 x 10^9/L for &gt;18 months</td>
</tr>
<tr>
<td>59</td>
<td>M</td>
<td>18 months</td>
<td>&lt;0.5 x 10^9/L for &gt;12 months</td>
</tr>
<tr>
<td>61</td>
<td>F</td>
<td>22 months</td>
<td>Start at 1.0 x 10^9/L and dropped to 0.6 x 10^9/L at 13, 17, and 20 months after initiating DMF</td>
</tr>
<tr>
<td>63</td>
<td>F</td>
<td>41 months</td>
<td>Start at 1.4 x 10^9/L and dropped to 0.6 x10^9/L at 18 months; 0.3 x 10^9/L at 40 months and 0.5 x 10^9/L at 41 months</td>
</tr>
</tbody>
</table>
PML with Rituximab and Ocrelizumab in MS

Ocrelizumab:
- 4 MS patients reported following first dosing of ocrelizumab (Apr 2017-2nd quarter of 2018) after natalizumab
- 1 MS patient receiving ocrelizumab (Mar 2018) with progressive clinical symptoms that started Dec 2017 at the time of discontinuing fingolimod

Rituximab:
- Analysis for risk in MS population difficult as RTX typically used for diseases that predispose in themselves to PML (B cell malignancies, RA, Sjogren’s)
- Use for neurological disorders (CIDP, MG, MS, paraneoplastic disorder) rarely, if ever, associated with PML

*1 MS patient with natalizumab-PML treated with RTX subsequently – no clinical worsening and CSF JCV DNA undetectable in absence of B cells
Maintain a high index of suspicion for PML in the presence of new neurological symptoms

A new positive, or increasing JCV antibody index should be a concern

Screening MRIs should be performed regularly
Radiographically Isolated PML

23 year old man with MS on natalizumab for 24 months shows new lesion. One month later he is recognized to have inappropriate behavior on routine visit.

- 8% of natalizumab associated PML is RIS at diagnosis
- Survival better with NTL-RIS
  - 95% RIS vs 74.6% symptomatic
  - RIS functional outcome better
PLEX clears natalizumab and desaturates α4 integrin
  Recommendation of 3x 1.5 volume PLEX over 5-8 days$^1$

Retrospective Italian study of 219 NTZ-PML$^2$
  184 (84%) underwent PLEX
  No improvement in mortality or morbidity

PLEX → Immune Reconstitution Inflammatory Syndrome
  >80% of both groups developed IRIS
    27.5d in PLEX+ vs. 45d in PLEX-
  IRIS predictor of worse outcome
Clinical worsening
MRI progression
  - Extension of lesions
  - Contrast enhancement
  - Brain edema
Intense perivascular inflammatory infiltrates

Martinez JV et al: Neurology 2006; 67:1692-4
No proven benefit of PML treatments to date

Suggested therapies for symptomatic IRIS
- 1 g IVMP for 3-5 days followed by oral taper over 6-8 weeks\(^1\)
- 1 g IVMP for 5 days followed by oral taper over 2 weeks\(^2\)
  - If symptoms during or after taper worsen, re-treatment with the same dose or IVMP 2 g for 5 days with subsequent taper

Corticosteroids may be “double-edged sword”
2. Infections other than PML with DMTs
In the Cambridge cohort of alemtuzumab, 13% experienced reactivated VZV.

Figure 1. Incidence of Infections over Time

SC IFNB-1a = subcutaneous interferon beta-1a
The incidence of VZV from clinical trials reveal no significant difference between fingolimod and natalizumab, DMF, or RTX.

Alemtuzumab was associated with a significant increased risk in comparison to other DMTs.
**Mitigating the Risk of VZV Infection**

**CDC recommends Varicella vaccination for:**
- Children
- Adults without immunity: 2 doses, 4+ weeks apart
  - Evidence of immunity includes:
    - U.S.-born before 1980 (minus pregnant women and healthcare Ws)
    - Documented receipt of 2 doses varicella vaccine at least 4 wks apart
    - Diagnosis or verified history of varicella or herpes zoster
    - Lab evidence of immunity or disease

**CDC recommends Zoster vaccination via:**
- 2 doses of recombinant zoster vaccine (RZV - Shingrix) 2–6 months apart to adults 50 years or older regardless of past episode of herpes zoster OR receipt of live zoster vaccine (ZVL - Zostavax)
  - if previously received ZVL, admin RZV at least 2 months after ZVL

*RZV is preferred and the VA formulary option!!!
Mitigating the Risk of VZV Infection

High rates of reactivated VZV in immediate aftermath of alemtuzumab warrant:
- Pretreatment vaccination (6 weeks before administration)
- Prophylactic acyclovir (200 mg bid started with each treatment course and continued for ≥ 2 months)

Vaccinating before fingolimod is in label if VZV-:
- Pretreatment vaccination (6 weeks before administration)

*Prophylaxis/vaccination with other immunosuppressive DMTs may also be reasonable
Alemtuzumab effects rapid and sustained depletion of mature lymphocytes

Hematological changes after treatment with 20 mg alemtuzumab/day for 5 consecutive days

T lymphocytes that repopulate after alemtuzumab treatment have a Th2 phenotype (anti-inflammatory) vs the Th1 phenotype (pro-inflammatory)
No Correlation of Infectious Risk with Lymphopenia with Alemtuzumab

![Graph showing no correlation of infectious risk with lymphopenia with Alemtuzumab. The graph displays the total lymphocytes log absolute count over months, with data points indicating no significant correlation.](image-url)
Infections Reported with Alemtuzumab

- Infections in general: 71% alemtuzumab v 53% IFNβ1a
- Serious infections: 3% alemtuzumab v 1% IFNβ1a
- 23% had infections within 4 months of treatment cycle
  - 8% respiratory tract infections, 11% UTI
- Herpes infections developed in 16% of alemtuzumab v 3% of IFNβ1a
  - HPV associated cervical cancer occurs in 2%
- Listeria monocytogenes has occurred from 3d to 8 mo after
- Active and latent TB in 0.3%
- Fungal infections (oral and vaginal candidiasis) in 12% v 3% IFNβ1a
- Other infections
  - Nocardia, both cerebral and pulmonary
  - PML - 1 fatal case, after natalizumab treatment
  - Spirochetal givingivitis
  - Pyogenic granuloma
  - Cytomegalovirus
- Hepatitis B and C carriers at risk for irreversible liver damage

https://www.lemtradahcp.com/
Listeria monocytogenes & Alemtuzumab

- Listeria first reported with alemtuzumab in 2008
- From licensing through May 15, 2017: 32 cases of listeriosis and listeria meningitis, including fatal cases
- In 2016, altered labeling:
  "Listeriosis/Listeria meningitis has been reported in LEMTRADA treated patients, generally within one month of infusion. To reduce this risk, patients receiving LEMTRADA should avoid ingestion of uncooked or undercooked meats, soft cheeses and unpasteurized dairy products for at least one month after LEMTRADA treatment."
- Risk of Listeria meningitis/septicemia estimated at 0.25% in the first month after each cycle of alemtuzumab

- Co-trimoxazole 960 mg 3 times weekly for 1 month has been recommended +/- dietary practices above
- If complying with Listeria-free diet post infusion, an alternative is 8 days of amoxicillin 1 g tid or co-trimoxazole 960 mg bid to eliminate Listeria colonization before treatment
Fingolimod and Infections
Mechanism of Action

Massberg and von Andrian. NEJM 2006
Fingolimod and Infections - Lymphocyte Counts

- Fingolimod reduces lymphocyte counts by 70%
- Within 6 weeks of discontinuation, most counts to normal range

Table 2. Lymphocyte counts and serious infections (All Studies group).

<table>
<thead>
<tr>
<th>Lymphocyte count (× 10^9/l)</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Range</th>
<th>Nadir (SD)</th>
<th>Last measurement (mean) before SAE (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious infections (n = 54)</td>
<td>0.49 (0.24)</td>
<td>0.41</td>
<td>0.10–1.40</td>
<td>0.31 (0.20)</td>
<td>0.50 (0.39)</td>
</tr>
<tr>
<td>All patients with serious infection (n = 48)</td>
<td>0.52 (0.24)</td>
<td>0.47</td>
<td>0.10–1.40</td>
<td>0.31 (0.20)</td>
<td>0.52 (0.40)</td>
</tr>
<tr>
<td>Patients with serious herpes infections (n = 12)</td>
<td>0.34 (0.11)</td>
<td>0.46</td>
<td>0.12–0.70</td>
<td>0.29 (0.16)</td>
<td>0.36 (0.14)</td>
</tr>
</tbody>
</table>
Infections and Fingolimod

Pivotal studies (FREEDOMS, TRANSFORMS, Extensions)
- Lower respiratory tract infections 9.6% FTY 0.5 mg v 6.0% placebo
- Any herpes infections 8.7% on FTY 0.5 mg v 7.9% on placebo
- VZV infection 1.6% FTY 0.5 mg v 1.0% on placebo
  - Two fatal infections – HSVE and Disseminated primary varicella infection
- Among other infections observed:
  - Pulmonary TB
  - Asymptomatic pulmonary Cryptococcus
  - Culture negative fungal infection
  - Ocular toxoplasmosis

- No difference in the rate of serious infection FTY 0.5 and placebo
- BUT, Proportion of patients with infection (74%) greater in those with nadir LC>0.2x10^9/l compared to LC>0.4x10^9/l

*In trials, patients with LC < 0.2 were stopped on drug
• Cryptococcus cases
  • Meningitis – 30 cases as of February 2017
    • Incidence rate is 0.08-0.11/1000 patient year:
  • Pulmonary
  • Disseminated
  • Cutaneous

Figure 1. A cutaneous lesion of the left mandible. A: Three months prior to admission. There was an erythematous nodule beneath the lower lip. B: On admission, there was an erythematous multilocular lesion with ulcer that measured 5×3 cm in size on his left mandible.
Infections and Fingolimod
Toxoplasmosis, Leishmaniasis, Kaposi’s, Merkel cell

- Toxoplasmosis
  - Both ocular and cerebral
  - Cerebral toxoplasmosis case had leukopenia and lymphocyte count of 200 cells/mm³
- Visceral Leishmaniasis
- Kaposi’s sarcoma (HHV-8) at least 2 cases
- Merkel cell carcinoma (MCPyV) at least 3 cases

Visceral leishmaniasis infection in a fingolimod-treated multiple sclerosis patient

AK Artemiadis, G Nikolopoulo, D Kolokythopoulos, N Tegos, A Terentiou, N Triantafyllou and I Papamastiou

Multiple Sclerosis Journal
2016, Vol 22(6):765-776
DOI: 10.1177/1352458516663708
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Natalizumab and Immunosurveillance

- Natalizumab monoclonal Ab directed against both α4β1 and α4β7 integrin inhibitor
- α4β1 inhibits interaction with VCAM and CNS immunosurveillance
- α4β7 inhibits interaction with MadCAM and GI immunosurveillance
- α4 integrins and VCAM-1 are essential for mast cell progenitor recruitment to lung

In patients with IBD, O.I.s more common with anti-integrin inhibitors

Reported infections with UC and Crohns treated with natalizumab

- CMV
- Varicella zoster
- TB peritonitis
- Candida
- Pulmonary aspergillosis
- Pneumocystis carinii pneumonia
Population based study from British Columbia, first demyelinating event 1996-2013: 6793 MS cases followed for mean of 8.5 years

- 1716 (25.3%) DMT exposed
- 5077 (74.7%) never exposed to DMT

IFN exposure NOT associated with infection-related claims

Natalizumab associated with 59% increased risk of infection

Oral DMTs and/or natalizumab increased the hazard of infection-related claim (adjusted HR: 1.47; 95% CI 1.16-1.85)

- Natalizumab aHR 1.59 (95% CI 1.19-2.11)
- Oral DMTs aHR 1.17 (95% CI 0.88-1.56)

URIs most common; no statistical association with UTI, bronchitis or skin infection
Case reports with natalizumab for MS

- HSV encephalitis\(^6,7\)
- Reactivation of HHV-6\(^8\)
- Acute necrotizing retinitis due to VZV\(^10\)
- Varicella zoster-associated retinal and CNS vasculitis\(^5\)
- Cavitary pulmonary tuberculosis\(^1\)
- Pulmonary *Mycobacterium kansasii*\(^2\)
- Skin *Mycobacterium marinum*\(^3\)
- Severe cutaneous Candidiasis\(^4\) and Candida pneumonia\(^10\)
- Ocular toxoplasmosis\(^9\)
- Cryptococcal fungemia\(^10\)
- Aspergilloma\(^10\)
- Cryptosporidiosis\(^10\)

https://doi.org/10.1371/journal.pone.0002028
5.3. Herpes Infections

Herpes Encephalitis and Meningitis

TYSABRI increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. Serious, life-threatening, and sometimes fatal cases have been reported in the postmarketing setting in multiple sclerosis patients receiving TYSABRI. Laboratory confirmation in those cases was based on positive PCR for viral DNA in the cerebrospinal fluid. The duration of treatment with TYSABRI prior to onset ranged from a few months to several years. Monitor patients receiving TYSABRI for signs and symptoms of meningitis and encephalitis. If herpes encephalitis or meningitis occurs, TYSABRI should be discontinued, and appropriate treatment for herpes encephalitis/meningitis should be administered.

Acute Retinal Necrosis

Acute retinal necrosis (ARN) is a fulminating viral infection of the retina caused by the family of herpes viruses (e.g., varicella zoster, herpes simplex virus). A higher risk of ARN has been observed in patients being administered TYSABRI. Patients presenting with eye symptoms, including decreased visual acuity, redness, or eye pain, should be referred for retinal screening for ARN. Some ARN cases occurred in patients with central nervous system (CNS) herpes infections (e.g., herpes meningitis or encephalitis). Serious cases of ARN led to blindness of one or both eyes in some patients. Following clinical diagnosis of ARN, consider discontinuation of TYSABRI. The treatment reported in ARN cases included anti-viral therapy and, in some cases, surgery.
Ocrelizumab and Infection Risks

Figure 3: B cells in the pathophysiology of MS [8-11].
In OPERA, infection rate was 58.4% in OCR and 52.4% IFNβ-1a groups.

- URI and nasopharyngitis (≥10% in either group) more frequent with OCR.
- Most infections were mild to moderate.
- 2 OCR-treated patients (< 1%; both non-serious) withdrew due to infections.
- Serious infection was 1.3% in OCR and 2.9% in IFNβ-1a group.

In ORATORIO, infection rate was 69.8% in OCR and 67.8% in PBO groups.

- URI and influenza reported more frequently in the OCR group.
- Most infections were mild to moderate.
- Withdrawal due to infections was low (OCR, 0.8%; PBO, 1.3%).
- Serious infections rates were 6.2% in OCR and 5.9% in PBO groups.

No opportunistic infections were reported in any study group.
Hepatitis B reactivation may lead to fulminant liver failure and death

- A negative HBsAg does not rule out active HBV
- +anti-HBc may be only evidence of HBV (risk of activation 19-33%)

In RTX-treated CTD: 10% have ↓γ-globulin after 1st course of RTX and 30% by 4th course

Other immunosuppressive agents, e.g., MMF and cyclophosphamide frequently used concomitantly and substantially increase infection risk

Prolonged B cell depletion → ↓T cell immunity

Appears to ↑risk of O.I.s (CMV, PML, fungal infection, Pneumocystis)
# Infectious Complications of Rituximab

<table>
<thead>
<tr>
<th>Established increased infectious complications</th>
<th>Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall infections</td>
<td>Meta-analyses in hematologic malignancies(^{11,12})</td>
<td>Increased severe infections (grade 3 or 4) when used as maintenance therapy in follicular lymphoma</td>
</tr>
<tr>
<td></td>
<td>Randomized trials in RA(^1)</td>
<td>Mild infections in RA</td>
</tr>
<tr>
<td></td>
<td>Case series(^{13-15})</td>
<td>Reports only in hematologic malignancies</td>
</tr>
<tr>
<td></td>
<td>Case reports(^{16-18})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case series(^{19}) case reports(^{20-22})</td>
<td>Most cases in hematologic malignancies, but a few in RA, SLE, and immune cytopenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possibly increased infectious complications</th>
<th>Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis jirovecii</em> pneumonia</td>
<td>Retrospective series compared to historical controls(^{23,24}) Case series(^{25-27}) Case reports(^{28-31}) Case reports(^{32-35})</td>
<td>Cases in hematological malignancies, RA, autoimmune diseases, solid organ transplant</td>
</tr>
<tr>
<td>Enterovirus encephalitis</td>
<td></td>
<td>Known complication of other B-cell immunodeficiencies</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Case reports(^{36-39}) Case reports(^{20,28,40})</td>
<td>Good response to IVIG</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td></td>
<td>CMV disease is very uncommon except in HIV or following allogeneic transplant; there are several reports in hematologic malignancies treated with combination chemotherapy</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>Case reports(^{41,42})</td>
<td>Increased severity and negative serology may be anticipated because of effect of rituximab on B cells</td>
</tr>
<tr>
<td>Babesiosis</td>
<td>Case-control study(^{43})</td>
<td>Most patients with persistent babesiosis had received rituximab</td>
</tr>
<tr>
<td>Mycobacterial disease</td>
<td>Case reports(^{44})</td>
<td>Severe <em>Mycobacterium avium</em> and <em>M. kansasii</em>, no other reports</td>
</tr>
</tbody>
</table>

Abbreviations: PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; IVIG, intravenous immunoglobulin; CMV, cytomegalovirus; HIV, human immunodeficiency virus.
During the first year in clinical trials, mean lymphocyte counts decreased by approximately 30%.

Four weeks after stopping TECFIDERA, mean lymphocyte counts increase but do not return to baseline.

Six percent (6%) of TECFIDERA patients and <1% of placebo patients experienced lymphocyte counts <0.5x10^9/L (lower limit of normal 0.91x10^9/L).

In controlled and uncontrolled clinical trials, 2% of patients experienced lymphocyte counts <0.5x10^9/L for at least six months, and in this group, the majority of lymphocyte counts remained <0.5x10^9/L with continued therapy.

It has been recommended to consider interruption of TECFIDERA in patients with lymphocyte counts persistently <0.5x10^9/L.

Infections other than PML appear to be rare with DMF.
Teriflunomide and Infections

- No imbalance of infectious complications in pivotal/comparison trials
- But, given leflunomide experience with reactivation of latent Tuberculosis, TB screening recommended prior to treatment

Risk of Malignancy

Unclear if any true increased risk of Cancer in MS patients, especially in absence of newer treatments

From 1% to a quarter of immunosuppressed patients develop malignancies

- Rates are 3x to several hundred-fold higher in this population

↑ risk for second malignancy in treated cancer patients

↑ risk of malignancy in transplant patients

- Lymphoproliferative tumors (ex: EBV-related)
- Cutaneous, KS, renal, hepatobiliary, anogenital
<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence on drug</th>
<th>Incidence control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platform Therapies</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Natalizumab SENTINEL</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Natalizumab AFFIRM</td>
<td>5/627</td>
<td>1/315</td>
</tr>
<tr>
<td>Cladribine</td>
<td>6/430 (low), 4/454 10/884 (high)</td>
<td>0</td>
</tr>
<tr>
<td>Fingolimod TRANSFORMS</td>
<td>4/420 (1.25mg) 8/429 (0.5mg)</td>
<td>1/431</td>
</tr>
<tr>
<td>Fingolimod FREEDOMS</td>
<td>4/429 (1.25mg) 4/ 425 (0.5mg)</td>
<td>10/418</td>
</tr>
<tr>
<td>Teriflunomide (TEMSO)</td>
<td>1/358 (14mg) 0/360 (7mg)</td>
<td>3/360</td>
</tr>
<tr>
<td>Alemtuzumab CAREMS1</td>
<td>2/376</td>
<td>0/187</td>
</tr>
<tr>
<td>Alemtuzumab (CARE MS2)</td>
<td>3/161 (24mg) 2/435 (12mg)</td>
<td>2/202</td>
</tr>
<tr>
<td>Dimethyl fumarate CONFIRM</td>
<td>0 / 704 (both doses)</td>
<td>1/363</td>
</tr>
<tr>
<td>Dimethyl fumarate DEFINE</td>
<td>2/410 (BD) 2/396 (TDS)</td>
<td>2/408</td>
</tr>
<tr>
<td>Daclizumab DECIDE</td>
<td>7/919</td>
<td>1/922</td>
</tr>
<tr>
<td>Daclizumab SELECT</td>
<td>3/ 417</td>
<td>1/204</td>
</tr>
<tr>
<td>Ocrelizumab OPERA1 and 2</td>
<td>4/ 825</td>
<td>2/ 826</td>
</tr>
</tbody>
</table>
Crohns study (1688 patients)
- 0.6% v. 0.2% in those on placebo
- Lung, bladder, breast, colon, malignant melanoma

AFFIRM study (932 patients)¹
- 1 patient died from malignant melanoma
  - Hx of melanoma; noted new lesion after 1st NZ dose; received 5 doses prior to dx
- 6 cases of cancer: 5/627 (0.79%) Natalizumab : 1/315 (0.32%) Placebo
  - Breast cancer (3); cervical cancer (1); new malignant melanoma (1)

Suggestion of ↑ risk of melanoma in MS recipients²
- Post marketing surveillance hasn’t identified further signal

¹ Polman CH et al.. N Engl J Med 2006;899-910
Malignancy with Ocrelizumab

- Up to 6 cases breast CA across trials (Pbo:0)
- Some have advocated mammography in certain populations, or caution if personal history of breast CA
- Time will tell
Some concern over skin CA

- Basal cell carcinoma
- Melanoma

Unclear if these should be contraindication to use

*Some advocate dermatologic screening = reasonable practice for general health
Thyroid CA, but autoimmune issues primary
1/3 to up to 40% with Graves’ disease
ITP in 2%, potentially life-threatening
0.1% Anti-GMB nephropathy~goodpasture’s
Case reports of autoimmune hemolytic
anemia, hepatitis, +
A chemotherapy used to treat specific forms of leukemia, approved to treat MS outside US

One of original trials had 1+% CA incidence, vs. unusually low rate in placebo group

In part, concerns delayed approval

Unclear if malignancy a contraindication and not one type of CA in particular
Vaccines

Goal is to mimic 1° immune response, leading to protective long term immunity

Classification

- live attenuated vaccine
- noninfectious vaccines

Complications of vaccination are rare but if perceived risk outweighs benefit, don’t

That said, benefit from vaccinating is proven and specifically encouraged in some instances
Vaccination Rationale*

- Infectious diseases are common cause of death
- In the US, childhood vaccinations have prevented hundreds of millions of illnesses, millions of hospitalizations, and hundreds of thousands of deaths in the last decade alone
  - net savings of $300 billion in direct costs, >$1 trillion total societal costs
- Vaccinations are considered one of the most important and lifesaving medical interventions in human history

*Phil Trans R Soc 2015; 370:20140340
Types of Vaccines

- Live attenuated vaccines
- Inactivated vaccines
  - Subunit vaccines
  - Toxoid vaccines
  - Conjugate vaccines
  - Recombinant vector vaccines
Live Attenuated Vaccines

- Derived from disease-causing virus or bacteria
- Closest to natural infection
- Attenuated/weakened in lab; remote possibility of reversion to virulent form
- Relatively small dose and generally given once
- Pathogen must grow/replicate in immunized
- Goal/often possible to develop/demonstrate antibodies
Live Attenuated Vaccines

- Not used in immunocompromised
  - may have uncontrolled pathogen growth
- Most are for viruses > bacteria
- Viral vaccines: measles, mumps, rubella; varicella; yellow fever; influenza (intranasal); polio (oral)
- Bacterial vaccines: BCG, oral typhoid
Inactivated Vaccines

- Microbes killed with chemicals, heat, or radiation
- Safer
- More stable (no refrigeration)
- Weaker immune response (extra doses/boosters)
  - mostly humoral immunity
- Inactivated whole virus vaccines (polio, rabies, hepatitis A)
Toxoid Vaccines

- Used for diseases caused by bacterial toxins
- Toxins inactivated by formalin (toxoids)
- Diphtheria, tetanus vaccines
Subunit Vaccines

- Involve microbe antigens/epitopes that stimulate immune system
- Low adverse reactions
- Hepatitis B, influenza, HPV, zoster recombinant vaccines
- Also have conjugate vaccines (polysaccharides oft attached to antigen or toxoids to boost potency)
- *H. influenza* type B, pneumococcal, meningococcal are conjugate polysaccharide vaccines
- Have pneumococcal, meningococcal, *Salmonella typhi* (Vi) pure polysaccharide vaccines
Experimental vaccines

DNA Vaccines

- Inject microbe genes - Naked DNA, or mixed with molecules
- Cannot produce the infection
- Relatively easy, inexpensive
- Host cells express microbe antigen

Recombinant Vector Vaccines

- Use attenuated carrier virus/bacteria to introduce target microbial DNA
Current Recommendations

- Influenza
  - inactivated recombinant, live attenuated
  - annual vaccination for all aged 6 months or older
- Tetanus, diphtheria, acellular pertussis (Td/Tdap)
  - one time dose of Td/Tdap, Td booster every 10 years
  - one dose to pregnant women (27-36 weeks)
- Measles mumps rubella (MMR)
  - all born in or after 1957 should have had 1-2 doses
Varicella
- Now given to pediatrics
- All non-immune adults should receive 2 doses of single antigen vaccine

Zoster
- single dose for elderly, immunity wanes

Human papillomavirus (HPV)
- females receive bivalent or quadrivalent HPV vaccines and males may get HPV4 in 3 dose series
- Pediatrics and special populations
- recommended in unvaccinated immunocompromised pts
Current Recommendations

Pneumococcal vaccines (PCV13, PCV23)
  - inactivated
  - recommended when there is risk factor

Meningococcal quadrivalent conjugate and meningococcal polysaccharide vaccines
  - inactivated
  - 1 or more doses recommended when risk factor
**Current Recommendations**

- Hepatitis A and hepatitis B
  - recommended when there is risk factor
  - 2 to 3 doses

- *H. influenza* type B
  - recommended when there is risk factor
Can vaccines cause MS or MS disease activity?

Can MS patients get live vaccines?

Are there DMTs where vaccines are an issue?
Vaccines and Risk of CNS Demyelinating Disease*

- Kaiser Permanente Southern California EHR 2008-2011; nested case control study
- 780 incidence cases of CNS acute demyelinating disease, 3,885 controls
  - MS (54.7%), ON (22.7%), TM (15.6%), other CIS (4.2%), ADEM (2.7%)
- No association between hepatitis B, HPV, or any other vaccine and risk for CNS disease over subsequent 3 years

*JAMA Neurol 2014; 71:1566
Several studies find ↑ relapse rate during infection “at risk” period (2 weeks prior, 5 weeks post infection)

- Adenoviruses, rhinoviruses especially implicated
- Bacterial infections also implicated

MS pt: “should I get my flu shot?”

- MS at higher risk for influenza related hospitalization in Swedish cohort (↑ relative risk 3.57); risk of mortality 5.19
- US MS deaths peak coincident with MS pneumonia
- influenza ↑ relapse risk (33% of infected MS in one study)

*Vaccine 2014; 32(37):4730-4735*
Infection-related relapses may be more severe.

Viral and bacterial infections portend worsening, even if they don’t induce/trigger relapses.

Vaccinations can avoid infection

Avoiding infection should lower mortality if not relapse risk

MS patients may be on treatments that increase risk for infection

Thus vaccinations can be beneficial (so long as they are relatively safe)

aside from safety, we’ll discuss efficacy concerns
Case crossover study evaluated MS patients with relapse between 1993-1997

N=643

2.3% vaccinated in 8 week risk period vs. 2.8-4% vaccinated during control periods

Conclusion: vaccinations did not ↑ short term risk of relapse

*NEJM 2001; 344:319
Evidence supports strategies to minimize infectious diseases that can trigger MS relapses

Influenza, hepatitis B, varicella, and tetanus vaccines safe

Inactivated vaccines generally safe, despite DMT

Live attenuated vaccines generally not recommended

Patients with serious relapse should defer vaccination for 4-6 weeks

Unclear risks when close family member receives live virus vaccines

*NMSS; Living Well with MS
Injectable seasonal flu vaccine

- studied extensively, safe regardless of DMT
- for cell depleting DMTs should be given 6 weeks before cycle
- IFNβ: 3 studies with >200 pts, 500 untreated/healthy controls = comparable efficacy
- GA: single study; lower titers vs. healthy controls
- mitoxantrone: single study documented marked interference
- natalizumab: 2 studies vs. HC, conflicting results (lower protection vs. no difference)
- fingolimod: initial study said not impaired (recent study noted ↓ response rates)
- teriflunomide: TERIVA study mounted effective response (slightly ↓ 14 mg dose)

*live attenuated (nasal spray) not recommended
Hepatitis B vaccine

- recommended for those at risk, involves 2-3 vaccinations
- Despite reports of association, 2002 study by IOM found no associated with MS onset

Varicella and zoster vaccines

- Not only recs, but method depends on history
- If IgG negative, encouraged prior to starting fingolimod, alemtuzumab +
Two vaccines used: Gardasil (HPV-16, 18, 6, 11) and Cervarix (HPV-16, 18)

Given to females and males, to prevent cervical and anal cancer, genital warts

Initial reports of immune-mediated neurologic complications appear not to be true link

In Denmark/Sweden population-based cohort study, quadrivalent vaccine not associated with MS/demyelinating risk

SS RNA virus endemic in South America/Africa transmitted by blood-sucking insects

- mortality 5-40%, but only 1 in 7 develop symptoms

Vaccination involves live attenuated virus

- Immunosuppressive/immunomodulatory therapies are contraindication

Encephalitis, meningitis may occur

Associated with ↑ relapses, MRI activity in one small case series (N=7)*

Generally avoided in MS unless risk felt to be great

*Arch Neurol 2011; 68:1267
**Varivax**
- for those never infected with VZV
- live attenuated
- given in two doses one month apart
- 98-99% protection against varicella

**Zostavax**
- for those previously infected with VZV
- single vaccine to prevent zoster (↓ 51%; ↓ severity by 61%)
- approved for ≥50 years of age
- contraindicated in pregnancy, 1°/acquired immunodeficiency, h/o anaphylaxis to gelatin/neomycin/vaccine component
Novel [and not live] Zoster Vaccine*

- Recombinant vaccine subunit
- Given in 2 doses
- 97.2% efficacy in preventing zoster
  - ≥age 50, not immunocompromised
MS DMTs and Vaccinations

- INFβ: normal humoral and cellular immune responses to influenza vaccine
- GA: no known issues
- Natalizumab: lower to normal humoral response to influenza vaccine; response to tetanus, KLH adequate
- Teriflunomide: TERIVA study: immune response mounted to influenza; response to rabies vaccine, DTH skin result unaffected (vs healthy controls)

*PlosONE 2013; 8:e78532; Neurol Res 2012; 34:730; Neurology 2013; 81:552, 872*
Dimethyl fumarate: tetanus evaluated; live vaccines not recommended

Fingolimod: decreased response to influenza, tetanus toxoid, pneumococcal vaccine, KLH; DTH skin reaction ↓ to candida, tetanus toxoid;

- prescreening for VZV serology; vaccinate prior to drug initiation if Ab is low or negative, then wait one month
- avoid live vaccines on therapy, and for 2 months post

*PlosONE 2013; 8:e78532; Neurol Res 2012; 34:730; Neurology 2013; 81:552, 872
Alemtuzumab: pilot study indicated normal vaccine responses to DTP, meningococcus, pneumococcus in majority

- patients within a few months of therapy did not respond
- recommended to vaccinate pre-therapy, or wait at least 6 months post therapy and measure antibody levels at 4 weeks if possible

Ocrelizumab: immunity may be impaired

- live vaccines not recommended
- Recommended to vaccinate at least 6 weeks prior, wait 3 months before introducing vaccinations given suspected impaired immunity
- In the VELOCE study, humoral responses were attenuated at all time points in patients who were B-cell depleted having received ocrelizumab, compared with those who did not
  - Patients were nonetheless able to mount humoral responses to the vaccines and neoantigen studied
  - Cellular immune responses were not assessed
- Patients should still receive seasonal influenza vaccinations since a potentially protective humoral response, even if attenuated, can be expected

*PlosONE 2013; 8:e78532; Neurol Res 2012; 34:730; Neurology 2013; 81:552, 872*
Killed vaccines are safe for MS

Live vaccines (such as for VZV) can be used in MS but limited data and some safety concerns specific to therapies

Fingolimod and cell depleting therapies like Alemtuzumab, Ocrelizumab have issues

Analyze risk-benefit ratio case-by-case
Recommendations for Surveillance with Newer MS Therapies

Maintain a high level of vigilance for the following:
- Opportunistic infections
- Alteration in expression of infections
  1. CNS infection may be masked by neurologic disease and thus not recognized
  2. Nonspecific signs such as altered mental status or abnormal results of tests may be the sole basis on which to investigate potential infections
- Or Emerging infections, e.g., West Nile virus
- Altered response to vaccination
- Malignancies or Lymphoproliferative disorders
- Autoimmune disorders
- Other unusual adverse events