DMT UPDATE
Practical help to
DMT management in MS

Regional MS Summit 2018

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DISCLAIMER

Not a comprehensive review
Not equal weight to all drugs

Handout of 2017 talk is in your package:
Comprehensive practical guide to
DMT decision making reviewing all drugs

Research funding: Biogen, Alkermes
OBJECTIVES

• Review AAN DMT guidelines
• Learn about the 2017 /2018 DMT updates
• Case-based examples of DMT decision making

Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis

Rae-Grant et al. Neurology 2018:90:777-788
AAN DMT Practice Guidelines

Recommendations
• 17 on starting DMT
• 10 on switching DMT for breakthrough dz
• 3 on stopping DMT

A = “must”
B = “should”
C = “may”

4x “MUST”
Clinicians must...
1. Ascertain and incorporate patients’ preferences re safety, route of administration, lifestyle, cost, efficacy, common AE and tolerability in choice of DMT
2. Engage in an ongoing dialogue re treatment decisions throughout the disease course
3. Counsel patients on DMTs to notify providers of new or worsening symptoms
4. Counsel that there is an increased risk of relapse or MRI dz activity within 6 months of D/C natalizumab
Starting DMT

“SHOULD”
- Discuss & if interested prescribe DMT for CIS if ≥2 brain lesions
- Prescribe alemtuzumab, fingolimod or natalizumab if highly active
- Not prescribe mitoxantrone unless benefits greatly outweigh risks
- Offer ocrelizumab to PPMS “who are likely to benefit unless risks outweigh benefits”
- Monitor adherence, AE, tolerability, safety and effectiveness; should follow pt at least annually or per REMS

“MAY”
- Recommend serial MRI at least annually 1st 5 years and close follow up rather than DMT for CIS/RRMS not on DMT and stable x2y
- Initiate NTZ only if reasonable chance benefit if JCV ab pos >0.9
- Direct to financial support programs or recommend AZA/cladribine

Switching DMT

“SHOULD”
- Monitor MRI
- Discuss switch if 1 or more relapses or, 2 or more unequivocal new MRI lesions or increased disability over 1 year period - if long enough on and adherent to DMT
- Discuss oral or less frequent injectable DMT if intolerable AE or injection fatigue
- Discuss undefined malignancy and infection risk with newer DMTs without long-term safety data
- Switch to alternative DMT if on NTZ and JCV ab pos, esp if >0.9
- Check NTZ antibodies if infusion reactions or break through dz
Stopping DMT

“SHOULD”

• Advocate for MS patients who are stable on DMT to continue their current DMT unless D/C DMT trial warranted

• Counsel pts who are stable and want to stop DMT for need for ongoing FU and periodic re-evaluation D/C DMT

• Assess likelihood of future relapse in SPMS d/t age, dz duration, relapse hx and MRI activity

→ “MAY” advise D/C DMT SPMS w/o relapse or gd+ lesion and not ambulatory for at least 2 years

• Review risk of continuation vs D/C DMT in CIS who have not progressed to MS

“Real life case”

• 44yo male engineer with outside dx MS

• My assessment CIS rather than MS

• Partial TM 2011 sensory sx, Lhermitte → gd+ C2-3 lesion

• Brain MRI minimal WM changes

• CSF results?

• PMH: Low Vit D, HLP, BMI 34, MVA 2015

• No dz activity while on glatiramer acetate x 7 years
A. Treatment success, should stay on DMT
B. Counsel could consider DMT D/C trial
C. Stop DMT b/o did not progress to MS

AAN Patient DMT Guide

Find a copy of the AAN Patient Guide included in your materials
Glatiramer Acetate

- Now 2 generics available
  - Glatopa®
  - Mylan®

- Both available in daily 20 mg and 40 mg TIW formulations
Daclizumab/Zinbryta®

- Voluntarily withdrawn from market 3/2018 for safety concerns: 12x brain infections

Oral agents
Fingolimod / Gilenya®

- Once daily po 0.5 mg
- FDA approved in 2010
- 231,000+ patients to date (536K PY)

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

Fingolimod-related PML

- Exposure: 231,000
- PML cases: n=19 (excluding cases NTZ ≤6m PML dx)
- Risk factors: Treatment duration
  1:5,000 if rx >2 years (18/94K)
  <1:10,000 overall

- PI update:
  – Most cases in pts > 2 years rx
  – Some cases dx’ed by MRI while initially asymptomatic

Novartis Medical Information Service. PI update 12/2017
Report of 15 PML cases as of August 2017

- Mean age 53 (n=5 <50yo), MS duration 4-35 years
- 14/15 clinical sx whereas 1 identified d/t MRI findings
- 2/15 possible confounders: prior cancer, prior IS for UC
- 4/14 ALC ≤ 0.2
- 3 deaths, others deficits aphasia, mobility, cognition

Fingolimod-related PML

- No specific clinical features or guidelines at this point
- Lymphocyte counts and subsets appear not associated
- Challenge of weighing PML risk vs possibly inappropriate modification of effective MS treatment
- Patient, provider and staff education and vigilance
  - Importance of clinical and MRI surveillance
  - Stop drug immediately if concerns for PML
  - PML sx can resemble MS relapse but tend to be slowly and persistently progressive
  - Red flags clinically: subacute cognitive, language, seizures
26yo M engineer

- ON age 12 (his mom dx’ed with MS 1y earlier)
- ON age 18
- Overall thus far favorable clinical course, EDSS 1
- IFNb-1a sc (Rebif®) x 1.5 years, d/c “pill easier”
- FGL since 2015

53yo Female

- MS x 15 y
- Established care 2013 while on FGL x 1 year
- Prior DMT
  - IFNb-1a (Rebif®) x 2 y, D/C “relapses” q3m, stress high
  - NTZ (Tysabri®) x 36 inf, D/C after JCV ab conversion
- Main sx mood, pain, fatigue, some imbalance
Cryptococcal meningitis causing obstructive hydrocephalus in a patient on fingolimod

- 61yo on FGL x 3y, previously D/C NTZ d/t JCV ab +
- HA/neck pain (coughing\(^1\)), N, vertigo, 10 kg WL x 2wk
- R beat nystagmus, quickly became confused
- MRI extensive PF leptomeningeal nodular enhancement, edema w/ mass effect and early cerebellar tonsillar herniation
- CSF via external ventricle drain Cryptococcus +
- Antifungal iv/po, D/C FGL, VP shunt
- MRI improved at 6 wks but new UI and new MRI lesions bifrontal, ?fungal, ?IRIS, ?MS, iv/po steroids

Cryptococcus meningitis

- Overall risk 0.11/100 PY in post-marketing setting
- More cases than PML cases
- Unlike PML, any age group (27-68yo)
- Usually after longer FGL exposure (16 m – 5 years)
- 1/3 without meningeal sx
**PI Updates – Infections / Cancer**

Serious and life-threatening infections have occurred
- Varicella zoster, herpes simplex and cryptococcus infections incl fatal meningitis, encephalitis and disseminated infections
- Consider when atypical MS relapse and organ failure

Increased risk basal cell cancer and melanoma
- Vigilance skin lesions
- PI recommends advising pts to use sun protection

**PI Updates – Bradycardia 1st dose**

- Max decrease usually within 1st 6h, usually asymptomatic and recovers, though not baseline 8-10h
- D/t physiological diurnal rhythm 2nd period HR↓ w/i 24h
- Pre-existing ischemic heart dz, h/o MI, CHF, CVA, uncontrolled HTN, recurrent syncope, severe untreated OSA
  - Evaluate by cardiologist before FDO
  - Overnight continuous ECG monitoring
- Transient similar but to lesser reduction HR following dosing in 1st 2-4 weeks
Pediatric MS

PI Updates

• RRMS patients age 10 or older
• Recommended all vaccinations per guidelines before FGL
• If ≤40 kg: 0.25 mg once daily
• Pediatrics pts ≥10y + ≥40kg: 0.5 mg once daily

- 82% reduction AAR\(^1\)
- 53% reduction new T2 lesions\(^1\)
- 66% reduction gd+ lesions\(^1\)
- Ongoing open-label study

Chitnis et al. ECTRIMS 2017; manuscript under review. PI update 5/2018

Fingolimod: Clinical Pearls

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<tr>
<th>oral</th>
<th>0.5 once daily</th>
<th>Gilena®</th>
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- 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\(\uparrow\)
  - Co-meds \(\rightarrow\) HR\(\downarrow\)
- Lymphopenia not associated with infections
- Risk of opportunistic infections
- Increased PML rate after 2 years of treatment
Teriflunomide/Aubagio®

- Once daily po – 7 vs 14 mg
- FDA approved in 2012 for RRMS and CIS
- 84,000 patients to date (162K PY)
- Closely related to leflunomide (for RA)

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

1 PML Case on Teriflunomide

Due to teriflunomide vs carry-over from natalizumab?
Some PML cases reported on leflunomide¹

Stopped NTZ #33
JCV ab pos index 3.6
EDSS 1.0
MRI @ 6wk stable
↓
DMT hiatus x 5+m
Started TFL

R-sided weakness, aphasia @ 10 wk
EDSS 3.5
MRI suspicious PML
CSF JCV DNA+
11 copies/ml (false-positive?)

Chelation therapy
Clinical and MRI progression
PML-IRIS suspected; 3 day IVMP
Eventually improvement, EDSS 1.0
Started on GA

Lorefice et al. Neurology 2018;90:1-3. 1 FAERS: n=24, Sanofi n=7 PML in RA with prior IS
Lymphoma on Teriflunomide

Case report
A case of lymphoma in a patient on teriflunomide treatment for relapsing multiple sclerosis

- 54yo black woman dx’ed with follicular lymphoma
- Teriflunomide x 8 months
- No RF other than age
- Per Authors
  - 50-54yo: 7 FL /100,000
  - 10 cases on teriflunomide*
  - 82 cases on leflunomide*

Landais et al, Mult Scler Rel Dis 2017;17:92-94 (*VegiBase: WHO global database AE reports)

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\(^2\)
  - 84x skin exfoliation in post-market setting\(^2\)
  - 1 fatal TEN report in post-market setting\(^3\)

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

Teriflunomide
Day 19 transient FLS x 5 days
Day 28 fever, asthenia, D/C drug
Day 30 respiratory failure
Day 34 TEN suspected
Day 39 death

\(^1\) Leist et al. Pooled safety data 4 clinical studies (n=3044) AAN 2014, \(^2\) FAERS, \(^3\) Gerschenfeld. MS Journal 2015
Teriflunomide: Clinical Pearls

oral 7 or 14 mg once daily  
Aubagio®

- 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

Dimethyl fumarate / Tecfidera®

• Orally 240 mg twice daily

• FDA approved in 2013
• 311,000+ patients to date (544+K PY)

• Activates nuclear factor 2 (Nrf2) pathway; response to oxidative stress
• Th1 → Th2 shift
DMF-related PML

- Exposure: 311,000
- PML cases: n=5
- Risk factors: Prolonged lymphopenia, age
- PI updates:
  - Majority of PML cases ALC <0.5, some <0.8
  - In other MS drugs some cases of early PML dx based on MRI findings in asymptomatic pts, usually better outcome

DMF-related PML Cases

- 1 death, other survival but no specifics available
- Low CSF JCV viral copies: 2x 12 → ultrasensitive JCV PCR!
DMF-induced Lymphopenia

Mean ALC↓ by 30% in 1st y and stabilized above LLN

9.4% Mod (0.5 - <0.8)
2.1% Severe (<0.5)

ALC in 1st year predictive for severe, prolonged lymphopenia

- All ALC >0.8 in 1st year → 0.1%
- ALC <0.8 in 1st year → 12%
- ALC <0.5 in 1st year → 51%

Strong correlation of ALC with CD4 and CD8 subsets

Recovery Lymphopenia after D/C

6 months after D/C with severe, prolonged lymphopenia (n=34)

- At least 1x ALC >0.8: 41%
- At least 1x ALC >LLN: 24%
Dimethyl fumarate: Clinical Pearls

- Slower taper may help with side effects
- Montelukast (Singulair) for GI side effects
- Aspirin or anti-histamine for flushing
- Monitor lymphocyte counts and LFT
- Rare PML cases

Infusions
Natalizumab / Tysabri®

- Once monthly infusion
- FDA approved in 2006
- REMS program required (TOUCH)
- 181,300 patients to date

Monoclonal antibody to $\alpha_4$ integrin = VLA-4 → Prevents extravasation of T-cells and monocytes into CNS

“Real life case”

35 yo AA male professional
- Natalizumab since 2012
- Past glatiramer acetate x 3y, D/C for ISR, 1 relapse, MRI↑
- JCV ab 1x POS 0.45 in 2/2013, then 12x neg by 11/2015
- EDSS 2.0

4/2018 re-established care after 2.5 y hiatus d/t insurance
- Last MRI 5/2015
- JCV ab tested x3, remained negative

Safety monitoring up to date?
Natalizumab-related PML

- Exposure: 181,300 (638K PY)
- PML cases: n=763 in MS (Crohn’s n=3)

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

- PI update 4/2018 → JCV antibody index

Retrospective analyses of postmarketing data from various sources, including observational studies and spontaneous reports obtained worldwide, suggest that the risk of developing PML may be associated with relative levels of serum anti-JCV antibody compared to a calibrator as measured by ELISA (often described as an anti-JCV antibody index value).

PML risk algorithm

<table>
<thead>
<tr>
<th>Natalizumab exposure, months</th>
<th>Index value not available</th>
<th>Index ≤ 0.9</th>
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<td>1.6 (0.9-2.5)</td>
<td>0.2 (0.4)</td>
<td>0.8 (1.1-1.5)</td>
<td>2.6 (1.4-3.9)</td>
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<td>4.1 (2.8-5.7)</td>
<td>0.4 (0.1)</td>
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<td>10.0 (5.6-14.4)</td>
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Koendgen Biogen ECTRIMS 2016

Wait 2 weeks after PLEX to avoid false-neg result
Wait 6 months after IVIG to avoid false-pos result
PML risk algorithm

Wait 2 weeks after PLEX to avoid false-neg result
Wait 6 months after IVIG to avoid false-pos result

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

PML risk algorithm

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Natalizumab exposure, months

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Koendgen, Biogen ECTRIMS 2016

Koendgen, Biogen ECTRIMS 2016
**PML risk algorithm**

- Wait 2 weeks after PLEX to avoid false-neg result
- Wait 6 months after IVIG to avoid false-pos result

**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!

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<th>Natalizumab exposure, months</th>
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- TOUCH data as of 6/1/2017
- Included JCV ab positive patients only
- SID (standard interval): *average* dosing ≥3 and <5 wk
- EID (extended interval): *average* dosing >5 and ≤12 wk
- NO info available re JCV ab index or efficacy data!

*Keendeen Biogen ECTRIMS 2016*
Baseline demographics all groups:
- Age 43-44
- 5-6% prior IS
- EID: slightly higher total # and duration NTZ

Most EID pts switched from SID after >2 years treatment
- Relative small dosing interval; average EID 35-43 days vs SID 30-31 days
- No efficacy data available
Personalized NTZ dosing?

NTZ concentration varied 100-fold
Mean concentration lower in EID

NTZ concentration affected by cycle
length and body weight (BMI↓, conc ↑)

Retrospective chart review (6m):
self-reported relapse and MRI change
without difference EID vs SID

Single PML case in this cohort:
Particularly high concentration (low BMI)

JCV infection of granule cell neurons in the cerebellum

- AKA JC virus granule cell neuronopathy [JCV GCN]
- Cerebellar dfct: ataxia, incoordination, apraxia, visual sx
- MRI: cerebellar atrophy
- DX: MRI w/wo, CSF for JC viral DNA
- Distinct from PML but can occur with and without PML
- Should be managed similarly to PML
**Additional PI Updates Natalizumab**

**Acute retinal necrosis (ARN):**
- Fulminant viral infection of retina
- Decreased visual acuity, redness, or eye pain
- Refer PROMPTLY for retinal screening for ARN
- Some cases occurred with CNS herpes meningitis /encephalitis
- Serious cases of ARN led to blindness of one or both eyes
- Following ARN, consider discontinuation of TYSABRI

**Immunosuppression/infections:**
- <1% pt with opportunistic infections:
  - Pulmonary mycobacterium avium intracellulare, aspergilloma, cryptococcal fungemia and meningitis, candida pneumonia

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**Natalizumab: Clinical Pearls**

<table>
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<tr>
<th>iv once monthly</th>
<th>Tysabri®</th>
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- 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
Ocrelizumab / Ocrevus®

- Infusion q6 months
- FDA approved March 2017 for RRMS and PPMS
- Total exposure n= 40,000+ (15+K PY)

Monoclonal antibody to CD20 on B lymphocytes → B cell depletion
Open-label extension RRMS trials

Change EDSS from baseline

Double blind

Open label extension

Time to onset to Confirmed Disability Improvement

Double blind

Open label extension

Immature data

Hauser et al.
AAN 2018

Time to cognitive decline
Pooled RRMS phase III trials

Patients on OCR had significantly lower risk (HR 0.6) of sustained cognitive decline at 12 and 24 wks compared to pts on IFN

- mITT cohort; both 4% and 10% SDMT cut off
- Pts at risk of progression (EDSS 4.0)²
- similar trend in patients with baseline cognitive difficulties

Infection and PML risk

- Some increase URI, LRI, skin and herpes infections
- To date 1 opportunistic infections (systemic Pasteurella infection), none in trials
- Hepatitis B reactivation warning (anti-CD20 rx)
- Boxed warning PML
  - To date no PML cases d/t OCR
  - 3 carry-over PML cases (NTZ, fingolimod)
  - RTX approved 1997 for NHL, CLL, RA, PA, >4 million pt PML not only in hematological malignancies but also RA n=9, SLE n=12, MS n=1; est risk in RA 1:20,000+

Vaccinations

- Recommendation to complete vaccines 6 week BEFORE
- No live vaccines while on OCR
- Antibodies against common viral/bacterial antigens were maintained x 2 years in pivotal trials

Responses to vaccines while fully B-cell depleted by ocrelizumab

<table>
<thead>
<tr>
<th>Tetanus</th>
<th>23-PPV</th>
<th>Influenza</th>
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Bar-Or et al. AAN 2018
Malignancies

In phase III trials more malignancies in OCR compared to control groups (IFN, PLC), primarily breast CA

- Thus far incidence rates malignancies and breast cancer remain within range of epidemiologic background
- Appears that comparator groups lower than expected incidences

Hauser et al. Platform presentation AAN 2018

Deaths

- 40+K pts treated to date
- Incidence of fatalities 4/2017 – 3/2018: 0.28 per 100 PY
- No obvious pattern reported

<table>
<thead>
<tr>
<th></th>
<th>Phase 3 OPERA I/II trials*</th>
<th>Phase 3 ORATORIO trial*</th>
<th>All OCR MS clinical trials¹</th>
<th>Post-marketing setting²</th>
<th>French cohort study (n=27+K)</th>
<th>US retrospec study (n=30K)</th>
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<tbody>
<tr>
<td>Incidence rate</td>
<td>0.07</td>
<td>0.25</td>
<td>0.169</td>
<td>0.2806</td>
<td>0.37</td>
<td>0.9</td>
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<td>per 100-PY</td>
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Genentech Medical Information Services May 2018
Ocrelizumab: Clinical Pearls

iv once every 6 months Ocrevus®

- Infusion reactions: premedication, slow titration
- Hepatitis B testing required
- Consider more extensive baseline lab screening
- Consider pneumonia/Hep B vaccination

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