Multiple Sclerosis Treatment Updates
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**objectives**
- overview of MS treatment algorithm
  - 1st, 2nd and 3rd line plus agents
- hot news: MS pathophysiology
- review and safety updates
  - natalizumab and fingolimod
- new/emerging MS treatments
  - teriflunomide (Aubagio)
  - BG-12
  - alemtuzumab
- KPSC MS Research updates

**Hot News: MS Pathophysiology**
- Some MS patients have auto-antibodies against Potassium Channel KIR4.1
- Expression KIR4.1 restricted to oligodendrocyte cell bodies and astrocyte processes surrounding synapses and blood vessels
**Implications:**
- Raises the question whether NMO is a separate disease or a poor prognostic subset of MS
- Overlap with autoimmune encephalitides
  - Explain why sometimes scan looks fine but the patient has severe deficits?
  - Why plasmaphoresis often works for severe relapses?

**new and emerging MS treatments**

**Oral**
- Trafficking
  - Fingolimod
- Intracellular Chemotherapeutics
  - Cladribine
  - Laquinimod
- Teriflunomide
- Endogenous immunomodulator
  - BG12 (fumarate ester)

**Infusions (mAbs)**
- Trafficking
  - Natalizumab (alpha4-integrin)
- Cellular Targets/Lytics
  - Rituximab (B cells)
  - Ocrelizumab (B cells)
- Alemtuzumab (mature lymphocytes=T+B+Monocytes)
- Cell Surface Receptors
  - Daclizumab (ILR, on T cells)

**general schematic MS treatments**

**Infusions (mAbs)**
- Natalizumab Tysabri as Second Line Agent
- Add-on to Avonex

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**Natalizumab (Tysabri) as Second Line Agent**
- Superior to Avonex
  - 55% relative reduction relapses
- Mean age=40
- Median Disease Duration=7 yrs

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Figure 3. Approximate Incidence of PML Stratified by Natalizumab Treatment Duration, Prior Immunosuppressant Use, and Serum Anti-JCV Antibody Status*

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Status</th>
<th>Treatment Duration</th>
<th>Prior Immunosuppressant Use</th>
<th>Anti-JCV Antibody Positive with NO Prior Immunosuppressant Use</th>
<th>Anti-JCV Antibody Positive with Prior Immunosuppressant Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1-24 months</td>
<td>No</td>
<td>0.56/1000 (~1 in 1800)</td>
<td>11.1/1000 (~1 in 90)</td>
</tr>
<tr>
<td>Positive</td>
<td>1-24 months</td>
<td>Yes</td>
<td>0.56/1000 (~1 in 1800)</td>
<td>11.1/1000 (~1 in 90)</td>
</tr>
<tr>
<td>Negative</td>
<td>25-48 months</td>
<td>No</td>
<td>4.6/1000 (~1 in 220)</td>
<td>11.1/1000 (~1 in 90)</td>
</tr>
<tr>
<td>Positive</td>
<td>25-48 months</td>
<td>Yes</td>
<td>4.6/1000 (~1 in 220)</td>
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</tr>
</tbody>
</table>

*Based on natalizumab exposure data as of February 29, 2012; PML incidence 298 confirmed PML cases of ~104,300 patients treated with Tysabri as of Oct 3, 2012

Rebound disease activity after stopping natalizumab or fingolimod

- ~10% of patients coming off of natalizumab
- Emerging case reports in fingolimod as well
- Widespread inflammation
- Can be fatal/near fatal
- Switching from tysabri to fingolimod does not prevent this
  - Neither do pulse steroids, copaxone or betaIFNs
  - Rituximab may be helpful

Fingolimod safety: review

Toxicity profile is very broad - lots of patients with relative contraindications + relatively high incidence of adverse events

1. Macular Edema: 0.4% risk, dose-dependent; 20% risk in patients with hx of uveitis
2. Cardiac: 2-3mmHg increase BP; 1 limb vasospasm, 2 Strokes; bradycardia starts 2 hr after first dose started improving 6 hrs later mostly with first dose AV block 1st degree ~5%; 2nd degree 0.3%
3. Deaths: 5 Sudden Deaths ranging 1 day – 9 months on fingolimod, 4 with HTN, cardiac dz, 1 woman unk
4. Pulmonary: dose-related seen in non-MS studies; case reports post-marketing decreased DLCO; may not be reversible!!
5. Immunosuppression, Infections - disseminated varicella, severe leukopenia, pneumonias

Relative Contraindications?

HTN, DM2, Smokers, Asthma, hx of seizures or uveitis not varicella immune = 3 month delay in starting treatment

Check Varicella IgG early!!!

Fingolimod safety update

Hot News: Case reports of tumefactive MS developing on fingolimod

Complicated Zoster – shingles followed by polyneuritis cranialis and shingles followed by VZV encephalitis and vasculopathy

Updated Label

- Contraindicated in patients with certain heart conditions, stroke or on anti-arrhythymics
- Revised 1st dose monitoring
  - EKG is now required before and after 1st dose
  - Hourly BP (not just HR) monitoring required
  - Extend past 6 hours in high risk patients:
    - severe bradycardia during administration of the first dose of Gilenya
    - pre-existing conditions in whom bradycardia may be poorly tolerated
    - On other drugs that slow the heart rate or atroventricular conduction
    - QT interval prolongation prior to starting Gilenya, or at any time during the cardiovascular monitoring period
    - On other drugs that prolong the QT interval (check their antiarrhythmic/other) and that can cause a serious and life-threatening abnormal heart rhythm called Torsades de pointes

BG-12 dimethyl fumarate

- Fumarate ester similar to one approved in Germany to treat psoriasis since the early 1990s
- Mechanism of action is unclear: activation of nuclear factor-like 2 (Nrf2) antioxidant response pathway enhances defense against oxidative stress
- Initially tested in PPMS was not effective (due to putative neuroprotective effects based on MOA)
- Fumarate esters and acids are found naturally in mushrooms, used as food additives and until recently readily available as dietary supplement
- Serious adverse events only rare gastritis/gastroenteritis
- Tolerability is an issue: GI side effects, flushing
the placebo group matters: healthier populations make drugs look more effective

- Small difference in absolute reduction appears to have a greater relative effect
  - Copaxone ARR=0.59 vs placebo ARR=0.84
    - Absolute reduction=0.84 – 0.59 = 0.25
    - Relative reduction ~ 0.25/0.84 X100= 29.8%
  - Laquinimod ARR=0.30 vs placebo ARR=0.39
    - Absolute reduction=0.39 – 0.30 = 0.09
    - Relative reduction ~ 0.09/0.39 X100= 23.1%
  - Avonex ARR=0.67 vs placebo ARR=0.82
    - Absolute reduction=0.67 – 0.82 = 0.15
    - Relative reduction ~ 0.15/0.82 X100= 18.3%

- Don't accept the relative reductions at face value!!!!

BG-12 Clinical Outcomes at 2 Years

NO Better than GA!!

Does not slow disability !!!

teriflunomide

- Metabolite of leflunomide (Arava) a modestly effective DMARD for RA
- Once a day pill 7mg or 14 mg
- Cytostatic agent, inhibits de novo synthesis of purine and pyrimidine
- Major toxicities of leflunomide include hepatotoxicity (more so than methotrexate), GI upset, hypertension, headache, hair loss, peripheral neuropathy. Rare: interstitial lung disease
- Tetatogenic: women should not use 2 years prior to pregnancy; Men – at least 3 months prior to pregnancy
- Leflunomide: increased risk of lymphoma other malignancies with long term use??

teriflunomide

Annualized Relapse Rate and Sustained Disability Progression.

Similar in efficacy to beta-interferons

7mg dose not reach statistical significance for disability
**alemtuzumab (Campath-H)**

- Humanized monoclonal antibody CD52, depletes mature T and B cells and monocytes
- 12mg iv daily for 5 days, annually for days
- Initially tested in SPMS and PPMS without effect
- Major toxicities are:
  - Infusion reactions despite premed with solumedrol ~40%
  - Infec tions- particularly herpes infections (16% vs 2% on Rebif)
  - Mostly oral and genital herpes (13%), shingles (3%), rare meningitis, herpes pneumonia
  - UTI (17% vs 4%) and nasopharyngitis (20% vs 13%)
  - Thyroid disease (18% vs 6%) and
  - Immune thrombocytopenia (1% vs none)
  - Agranulocytosis (1% vs none)

**alemtuzumab (Campath-H) vs Rebif as 2nd line**

Proportion Relapse Free and Sustained Disability Progression over 6 months


Not as impressive as first line agent
because 6 month sustained disability progression is rare

**rituximab (Rituxan)**

- Antibody against CD20, depletes B cells, over 20 years on market to treat lymphoma including AIDS-related lymphomas but not a true chemo agent
- Typical MS protocol
  - 500-1000mg iv 2 weeks apart then 1000mg iv every 6 months
  - 375 mg/m2 weekly for 4 weeks, every 6 months is also used
- Tested as 2nd line agent in RRMS and 1st line in PPMS, both with impressive results
- Major toxicities are:
  - 5% risk reactivation hepatitis B and C this is a show stopper
  - Bladder, fungal and yeast infections (treatable)
  - 1:25,000 risk of PML (in RA patients, no reports in MS yet)
  - Shingles (prophylaxis with acyclovir in =>50 yrs old)

**Rituximab as 2nd line agent RRMS**

Phase 2 proof of concept, relapse rate over 1 year and mean gad+ MRI lesions

Showed 50% relative reduction ARR after only 6 months!!

Delay in effect on MRI max benefit 12-20 weeks

**Rituximab in PPMS**

Sustained Disability Progression

Overall trial negative but pre-planned subgroup analysis does show significant effect

Under 51 years old, a gad+ lesion at baseline, all were OCB+ as well
### Initial Therapy: Regular MS

- Full recovery from first attack
- Low lesion burden on MRI
- No gait impairment or motor/sphincter symptoms
- Risks outweigh benefits

### When to use which treatment varies by underlying disease severity

- Increasing Efficacy
  - cytoxan
  - alemtuzumab
  - natalizumab
  - rituximab
  - fingolimod
  - beta-interferons, glatiramer acetate, BG-12, teriflunomide

- Decreasing Toxicity
  - alemtuzumab
  - fingolimod
  - cytoxan
  - natalizumab
  - rituximab
  - beta-interferons, glatiramer acetate, BG-12

### When to use which treatment varies by underlying disease severity

#### Case 1
- 30 y/o woman with vertigo and diplopia; left 6th nerve palsy
- CSF >5 OCB, elevated IgG syn rate
- Treated with iv solumedrol and made complete recovery within 2 weeks
- No PMH, non-smoker
- Brain MRI shows small gad+ lesion in dorsal pons and small periventricular lesions, one is gad+

#### Case 2
- 36 y/o man at onset had vertigo, imbalance, left arm numbness and blurred vision
- CSF >5 OCB
- 90% recovery following 5 days of iv solumedrol, residual mild weakness of left upper and lower ext and minimal gait instability
- MRI showed several large lesions both hemispheres, multiple gad+

### MS treatments: in order of efficacy

- Increasing Efficacy
  - cytoxan
  - alemtuzumab
  - natalizumab
  - rituximab
  - fingolimod
  - beta-interferons, glatiramer acetate, BG-12, teriflunomide

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### Efficacy

- Increasing Efficacy
  - beta-interferons, glatiramer acetate, BG-12, teriflunomide

- Decreasing Toxicity
  - beta-interferons, glatiramer acetate, BG-12
Initial Therapy: Worrisome Scan at MS Onset

- Good but incomplete recovery from first attack
- Some gait impairment but no motor/sphincter symptoms
- Large active lesions on MRI
- JCV positive - rituximab
- JCV negative - tysabri

Initial Therapy: Fulminant MS Onset

- Iv methotrexate
- Alemtuzumab?
- Rapidity, relentless progression
- Necrosis on MRI

Case 3

13 y/o boy with sudden onset paraplegia and urinary retention 2 weeks: MRI showed Th spine lesion and multiple brain lesions; no change in mental status
- Improved dramatically with iv solumedrol, Dx ADEM
- 3 weeks later developed bilateral vision loss, 6th nerve palsy and significant progression on brain MRI including a large necrotic lesion, CSF >5OCB

KPSC Research

Preliminary findings newly diagnosed MS in 2008 (n=150)
- 18% cane or worse after ~4 years of f/u
- Only half had PPMS
- All were treated but
- Less than half were treated with a medication other than ABCR

Implications
1. Bad/not so good outcomes (scenarios 2 and 3) may be more common than we thought
2. We are using ABCRs in scenarios where they have been shown to be ineffective
3. Switch to second-line agent: room for improvement

Beta-IFNs, GA and long term disability

- Canadian study in JAMA showed no effect of beta-interferons on long-term disability in RRMS
- Glatiramer acetate has no effect on PPMS and yet to demonstrate slowing of even short-term disability in RRMS
- High quality randomized controlled trials of beta-interferons in SPMS and PPMS showed no effect on disability in non-relapsing patients

IMPLICATIONS
1. Treatment with bIFN and GA has not changed the face of the disease, impacts relapses and relapse-related disability at best
2. Treating non-relapsing forms of MS with bIFN and GA is wasteful and may be at the expense of treatments that do work,
Case 5 part 2
He declined treatment with tysabri and started avonex 2 months later neurological exam is normal except for end point tremor.
Repeat MRI brain with and without contrast showed increased number and size of gad + lesions with edema when compared to the previous study more consistent with tumefactive MS
Patient declined switching options

Case 5 part 3
3 months after sx onset had second relapse facial numbness, left sided numbness, bilateral blurred vision, worsened while on steroids
- MRI again showed lesion progression large new lesion, multiple gad + lesions and regression of some old lesion
Now on Tysabri, 80% improved after treatment with plasmaphoresis (3 wks post relapse onset)

Case 6 part 2
- 3 weeks later developed bilateral vision loss, 6th nerve palsy and significant progression on brain MRI including a large necrotic lesion, CSF >5OCB
- Brain biopsy showed demyelination, macrophages and mixed lymphocytic infiltration c/w MS
- Did not respond to steroids, ~70% improvement following plasmaphoresis

Case 6 part 3
- Within 2 weeks after discharge from 2nd hospitalization (now 3 months after sx onset) developed headaches and blurry vision,
- mother noticed that he was becoming increasingly forgetful and disinhibited
- Brain MRI scan shows new large frontal lobe lesion and no improvement in old lesions with significant edema and enhancement

What does he have?
Case 6 part 4

- Malignant MS
  - Highly aggressive disease course, virtually continuous disease activity
  - Large, necrotic lesions
- Treatment choices include Tysabri, fingolimod, cyclophosphamide, campath-h, rituximab
  - Chose not to try Tysabri or fingolimod because these drugs affect trafficking of lymphocytes into the brain and this boy already had huge numbers of lymphocytes inside his brain
  - Because of his age, risk of cumulative toxicity was a major consideration
- Started steroids without improvement, rituximab (375mg/m² weekly) followed 2 days later by plasmaphoresis 5 days with some clinical improvement but repeat brain MRI scan showed improvement in gad+ lesions but overall progression of lesions after second round of rituximab
- Cyclophosphamide 700mg/m² monthly, lesion progression stopped and gad+ improved. Discharged home.
  - Missed 2nd dose of cyclophosphamide and had relapse with left INO, subtle right hand weakness leg weakness
  - Brain MRI at that time with relatively small new lesions including pons and active midbrain lesion, other lesions unchanged with decreased overall enhancement
  - Now s/p 4th dose of cytoxan with no gad+ lesions on scan, no lesion progression, normal neurological exam, having difficulty in school, undergoing testing for cognitive deficits

Choosing among 1st line agents
Avonex, Betaseron/Extavia, Copaxone, Rebif

Not about efficacy, no clearly superior agent

This decision I make on an individual level based on lifestyle, history of depression and ability to give themselves injections

- Tolerability
  - Flu like symptoms (beta-interferons)
  - Injection site reactions (betaseron/extavia and copaxone)
  - Worsening of underlying spasticity (beta-interferons)
- Safety
  - Depression (beta-interferons)
- Convenience
  - Avonex is once a week

Why Switch Treatment?

Patients with more aggressive disease are more likely to require treatments with greater efficacy than beta-interferons and copaxone

Predictors of long-term disability in RRMS are:
- Incomplete recovery from 1st attack
- Sphincter and motor symptoms at onset or early in the disease course
- Disability at 5 yrs after onset
- Early relapse frequency
- Change in T2 lesion accumulation 1st five years (UK CIS study 25 yrs of folu)

Suggests that early intervention to prevent these outcomes may decrease risk of long term disability

When to Switch Treatments

Top Two Reasons:
1) Poorly tolerated
   - can try another 1st line agent
2) Lack of efficacy
   - continued relapses or progression on MRI scan after 6-12 months on a 1st line agent
3) Cost
   - If this is an issue consider Extavia, rituximab, azathioprine+prednisone

First-line agent head-to head trials
no clear evidence of superiority

<table>
<thead>
<tr>
<th>trial (n)</th>
<th>Tx group (n)</th>
<th>relapse-free 2yrs, %</th>
<th>ARR, 2yrs</th>
<th>disability progression, 2yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence (679)</td>
<td>Rebif 44mg (339)</td>
<td>62</td>
<td>0.54</td>
<td>16 (16months)</td>
</tr>
<tr>
<td>56 sites, 2002</td>
<td>Avonex 30mg (338)</td>
<td>52</td>
<td>0.65</td>
<td>17 (16months)</td>
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<tr>
<td>BEYOND (2447)</td>
<td>Betaseron 250mg (897), 500mg (899)</td>
<td>60, 58</td>
<td>0.36, 0.33</td>
<td>27, 22</td>
</tr>
<tr>
<td>198 sites, 2008</td>
<td>Copaxone (498)</td>
<td>59</td>
<td>0.34</td>
<td>21</td>
</tr>
<tr>
<td>REGARD (764)</td>
<td>Rebif 44mg (386)</td>
<td>62</td>
<td>0.30</td>
<td>12*</td>
</tr>
<tr>
<td>81 sites, 2009</td>
<td>Copaxone (378)</td>
<td>62</td>
<td>0.29</td>
<td>9*</td>
</tr>
</tbody>
</table>

*stained for 6 months, ns
Key outcomes other agents head to head trials

<table>
<thead>
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<th>ARR</th>
<th>disability progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimod (1292), 172 sites 1 yr outcomes</td>
<td>fingolimod (0.5, 1.25mg)</td>
<td>83, 80</td>
<td>0.16</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>avonex</td>
<td>69</td>
<td>0.33</td>
<td>8</td>
</tr>
<tr>
<td>Tysabri (1171), 124 sites, 2 yr outcomes</td>
<td>natalizumab</td>
<td>61</td>
<td>0.34</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>avonex</td>
<td>37</td>
<td>0.75</td>
<td>29</td>
</tr>
<tr>
<td>Alemtuzumab (334), 49 sites 3 yr outcomes</td>
<td>Campath (12mg/24mg)</td>
<td>77, 84</td>
<td>0.08</td>
<td>16, 11</td>
</tr>
<tr>
<td></td>
<td>Rebif 44µ</td>
<td>52</td>
<td>0.36</td>
<td>33</td>
</tr>
</tbody>
</table>

All 1:1(1:1) randomization, all sustained disability progression for 3 months

Key outcomes in pivotal trials for first-line agent RRMS trials

<table>
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<tr>
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<th>relapse-free 2yrs, %</th>
<th>ARR 2yrs</th>
<th>disability progression 2yrs, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betaseron (372) 11 sites</td>
<td>Betaseron (1.6, 8 miU)</td>
<td>23, 36</td>
<td>1.17, 0.84</td>
<td>28, 20 (3yrs)*</td>
</tr>
<tr>
<td>PRISMS (560) 22 sites</td>
<td>Placebo</td>
<td>18</td>
<td>1.22</td>
<td>28 (3yrs)</td>
</tr>
<tr>
<td>Avonex (301) 4 US sites</td>
<td>Avonex</td>
<td>38</td>
<td>0.67</td>
<td>22</td>
</tr>
<tr>
<td>Copolymer 1 (251) 11 US sites</td>
<td>Placebo</td>
<td>27</td>
<td>0.84</td>
<td>25</td>
</tr>
</tbody>
</table>

*did not reach statistical significance

Serious adverse events 2nd line agents in RCT

<table>
<thead>
<tr>
<th>Tx group</th>
<th>exposed / yr</th>
<th>Class</th>
<th>Types (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nat / placebo 627/2</td>
<td>infections</td>
<td>PML (2), HSV enceph (1), cytomegalovirus (1), muco-cutaneous (1), sarcoidosis (1), sepsis (1), volvulus (1)</td>
<td></td>
</tr>
<tr>
<td>Nat + avonex 539/2</td>
<td>infections</td>
<td>1st VZV, HSV enceph (1), lower respiratory and GI</td>
<td></td>
</tr>
<tr>
<td>Fingolimod / Avonex 849/1</td>
<td>infections</td>
<td>Craft (aco tdc), 70 vs 24 cases; met bilateral skin rash and nasal edema;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cancer, eye</td>
<td>HTN, bradycardia, AV block, macular edema; dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lab</td>
<td>lymphopenia, LFTs (8.5-12.5% vs 1.7%),</td>
<td></td>
</tr>
<tr>
<td>Cladribine 889/2</td>
<td>infections</td>
<td>RSV, 1st HZV, with pancreatitis, cholestasis, pancreatitis, Shingles (20 cases), 1st HZV,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cancer</td>
<td>10 vs 8, cutaneous hemangiomas, melanoma, pancreatic fistula, ovarian</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lab</td>
<td>pancreatitis, mostly neuts and lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab 216/3</td>
<td>infections</td>
<td>ITP (1), Thymol Dc,4 (21%) vs 1 (7%); dose</td>
<td></td>
</tr>
<tr>
<td>Rituximab 370/2</td>
<td>infections</td>
<td>Pancreatic, UTE (90%)</td>
<td></td>
</tr>
</tbody>
</table>

Evidence of non-responder subgroups

1. Pharmacogenetic non-responders to beta-interferons, unrelated to NABs
2. Evident clinically (continued relapses) and subclinically (gad+lesions, T2 accumulation) also unrelated to NABs
3. Different treatment effects of second-line agents in those with continued disease activity on first-line agents versus treatment-naïve patients

The proportion of non-responders is unknown

No high-quality studies comparing switching to another first-line agent versus second-line agent

What to do if you suspect PML

- Hold tysabri
- Admit to hospital for LP and brain MRI
  - Send CSF and serum for JCV PCR
  - If JCV PCR is positive or index of suspicion is extremely high, plasmaphoresis and supportive care
- Please note that JCV Antibody testing is different than JCV PCR
  - JC virus Antibody to assess PML risk is a non-formulary send out lab test to QUEST diagnostics
  - JCV PCR is in health connect; measures viral DNA in the sera

Evidence of non-responder subgroups

- Pharmacogenetic non-responders to beta-interferons, unrelated to NABs
- Evident clinically (continued relapses) and subclinically (gad+lesions, T2 accumulation) also unrelated to NABs
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Treating SPMS and PPMS

- If no evidence of ongoing inflammation, extremely unlikely to be beneficial
- Subgroup effect in Rituximab PPMS study (all were OCB+) if <51 yrs or gad+ helped, even better if <51 and gad+.
- Likely similar subgroup effects in mitoxantrone trials
- Note: T2 accumulation and relationship to disability plateaus with increasing dz duration

Fingolimod Safety

**Macular Edema:** 0.4% risk, dose-dependent; 20% risk in patients with hx of uveitis
- 13 tx vs 0 placebo/avonex; 10/13 within 4 months; 19/13 resolved 1-6 months later after tx stopped; 3/4 serious adverse events, at least 3 asymptomatic

**Cardiac:** 2-3mmHg increase BP; 1 limb vasospasm, 2 Strokes; bradycardia starts 2 hr after first dose started improving 6 hrs later majority with first dose
- AV block 1st degree ~5%; 2nd degree 0.3%
- Expected outcome of 6 hr first dose monitoring
  - 78-84% discharged at 6 hours
  - 10-12% extended monitoring
  - 0.4% symptomatic event
  - 0.2% will require hospitalization

**Cancer?** Not dose related: 8 tx vs 10 placebo: 12 tx vs 1 Avonex
- Lowest Effective Dose needs to be addressed