



National  
Multiple Sclerosis  
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## Making Comfortable Treatment Decisions:

Tips for Thinking Clearly  
about Benefits and Risks

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## Schedule and Call Information

### Call One

- Wednesday, February 8, 2012
- 1-2:00 pm ET (12 pm CT, 11 am MT, 10 am PT)
- Participant Dial-In Number: 877-715-5282
- Conference ID: 49776024

*When asked after dialing in, please provide your First and Last Name, and City and State.  
This information is required for purposes of tracking attendance.*



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## Outline for Today

- From zero options to 8 and counting...
- Hot items outside the mainstream
- Factors that complicate medical decision-making
- Decision-making in the MS arena
- Lessons we are learning from Tysabri
- Interpreting benefits and risks
- Helpful tips for making comfortable decisions
- Introducing a valuable new resource
- Questions – comments – concerns



## Looking at the big picture

- **Prior to 1993** – “Diagnose and Adios” is the norm
  - For the fortunate few:
    - Relapse management
    - Symptom management
    - Rehabilitation
    - Emotional support
- **1993 to 2005** – five DMT options
  - interferon beta medications (Avonex, Betaseron, Rebif)
  - glatiramer acetate (Copaxone)
  - mitoxantrone (Novantrone)



## Still looking at the big picture

- **2006 to 2010** – three additional DMT options
  - natalizumab (Tysabri)
  - interferon beta-1b (Extavia)
  - fingolimod (Gilenya)
- **2010 to 2011** – three new sx management medications
  - dalfampridine (Ampyra) – walking
  - dextromethorphan/quinidine (Nuedexta) – PBA\*
  - onabotulinumtoxinA (Botox) – upper limb spasticity; urinary incontinence

\*pseudobulbar affect



## And the even bigger picture

- **2012 to 2013** – five more DMT options?
  - teriflunomide
  - alemtuzumab (Campath®)
  - ocrelizumab
  - PEGylated interferon beta-1a (extended release version of Avonex®)
  - BG00012 (dimethyl fumarate)



## Hot items from outside the mainstream

- Complementary therapies that are entering the mainstream through careful, controlled research:
  - Exercise
  - Cooling
  - Vitamin D



## Hot items from outside the mainstream, cont'd

- Interventions that are currently driven more by the media and wishful thinking than by science:
  - Overseas stem cell clinics – an example of charlatans making false/dangerous promises that capitalize on people's hopes and fears
  - CCSVI – an example of the cart before the horse
    - Internationally-funded studies underway



## Factors that complicate medical decision-making

- Human nature
- Financial/insurance issues
- Shift in the doctor-patient relationship
- Information overload
  - Scientific data
  - Pharmaceutical advertising
  - Personal anecdotes
  - Social media
- Complex benefit/risk trade-offs
- Statistics vs. individual experience
- Personal tolerance for risk



## Taking a closer look at the MS arena

- Impatience for the cure
- No “perfect” options
  - Injectable medications:
    - Extensive research and clinical experience
    - Excellent safety profile
    - Effectiveness ranging from excellent for some to moderate for others, and poor for the rest
  - New and emerging therapies:
    - Limited data; shorter history; potential for greater efficacy *and* risks



## Taking a closer look at the MS arena, cont'd

- Confusion about available options
  - Differences *among* disease-modifying medications
  - Differences *between* disease management and symptom management
- Variable levels of risk tolerance among patients, family members, clinicians, regulatory agencies
- Polarization within the MS community



## Natalizumab (Tysabri): A helpful model

- **2004** – FDA approved for relapsing forms of MS
- **2005** – voluntarily withdrawn from the market following 3 deaths from PML\*
  - Careful study to determine the cause of PML
- **2006** – FDA approved to return to the market as monotherapy with TOUCH safety-monitoring program
  - Prescribers, patients, pharmacies, infusion sites required to participate
  - Education, informed consent, repeat evaluations, prompt intervention for PML cases
- **2006 - present** – cases of PML carefully tracked and the data made public on a regular basis

\*progressive multifocal leukoencephalopathy



## Tysabri update as of January, 2012

- More than 95,000 people have used Tysabri
- 201 confirmed cases of PML
  - 20% have died
  - Disability among survivors ranges from mild (back to work) to very severe (requiring total care)
- FDA labeling updated in 2012 to identify risk factors:
  - Prior exposure to the JC virus (antibody-positive on the blood serum test)
  - Prior immunosuppressant therapy
  - On Tysabri for more than two years



## Efforts to reduce Tysabri-related risks

- For a person who tests antibody-positive but has no other risk factors, the risk of PML is <1/1000.
- For a person tests positive to the JC virus and has both of the other risk factors, the risk of PML is 11/1000.
- Per re-testing for JC virus antibodies is suggested.

Natalizumab exposure	Anti-JCV Antibody Positive*	
	No Prior Immunosuppressants	Prior Immunosuppressants
1-24 mos.	<1/1000	2/1000
25-48 mos.	4/1000	11/1000



## Efforts to reduce Tysabri-related risks, cont'd

- Strategy to manage PML when it occurs:
  - Clear Tysabri from the system ASAP (typically with plasma exchange)
  - Allow the immune system to rebuild itself
  - Aggressively treat IRIS\*, which often occurs as the immune system rebuilds itself following plasma exchange to remove the Tysabri

\*immune reconstitution inflammatory syndrome



## So what do the numbers mean to you ? And you? And you?

### Let's do some comparisons

- The risk of developing MS – 1 in 750
- The risk of developing PML – approaching 2 in 1000
- The risk of dying from PML – less than 1 in 5
- The lifetime risk for dying by:\*
  - Car crash – 1 in 83
  - Murder – 1 in 210
  - Crossing the street – 1 in 625
  - Plane crash – 1 in 5000
  - Fire – 1 in 1100
  - Asteroid – 1 in 200,000



\*National Safety Council, 2011

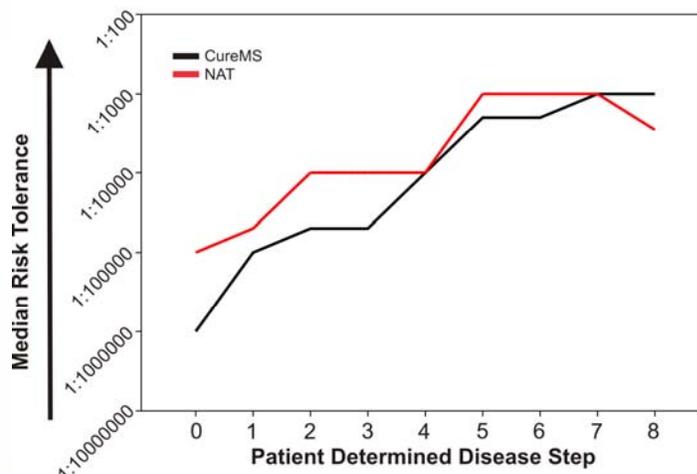


## The tricky part is...

- The numbers mean different things to different people:
  - Several different risks need to be considered at the same time:
    - Continuing disease progression without treatment
    - Impact of current medication on future treatment options
    - Dying from PML
    - Living with PML-related disability
  - Family members are likely to perceive the risks differently and differ in their tolerance for risk



## The worse off people *perceive themselves to be*, the greater the risks they will take



Fox et al, 2011



## Tricky part, cont'd

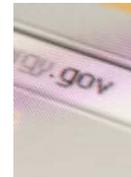


- Doctors and patients may also differ in their tolerance for risk:
  - **Doctor** is concerned about bad prognostic signs/  
**Patient** is feeling well and optimistic
  - **Doctor** sees good prognostic signs and thinks the current treatment is working /  
**Patient** fears the worst and wants more
  - **Doctor** wants to wait for more long-term data/  
**Patient** is impatient to try the newest medication
  - **Doctor** wants to try the newest medication/  
**Patient** wants to wait for more long-term data



## Tricky part, cont'd

- Government regulators may differ from doctors and patients in their tolerance for risk:
  - Cladribine:
    - Positive phase II and phase III trials completed
    - Additional phase III trials nearing completion
    - Cladribine approved to treat relapsing MS in Russia and Australia
    - Cladribine rejected by the FDA and European regulators for safety reasons
    - June 2011 – Merck Serono decides not to pursue approval



## What's a person to do?!?



## Some tips to help with treatment decisions

- Work with a physician you trust and respect
  - Discuss anticipated benefits and risks
  - Ask how current treatment choice will affect your future options
- Be an educated consumer
  - Pick sources carefully
  - Remember: some things are too good to be true
  - Listen with both ears – not just the one that hears what you want to hear
- Keep the statistics in perspective



## More tips to help you

- Allow yourself to think through the possible positive *and* negative outcomes
- Think about how you would feel about your decision in hindsight (which is always clearer than foresight)
- Remember: you're most likely to hear only the best- and worst-case scenarios
- Be open to differing opinions



## Emerging Therapies Collaborative – [www.ms-coalition.org/EmergingTherapies](http://www.ms-coalition.org/EmergingTherapies)

- Unique partnership “*to promote optimal, individualized treatment ...by facilitating effective communication and medical decision-making*”
  - Multiple Sclerosis Coalition\*
  - American Academy of Neurology
  - Multiple Sclerosis VA Centers of Excellence East/West
  - Americas Committee for Treatment & Research in MS
- Downloadable information for professional and lay readers:
  - Developed by members of the Collaborative
  - Approved by all participating organizations
  - Evidence-based



## \*Multiple Sclerosis Coalition

- Accelerated Cure Project for Multiple Sclerosis
- Can Do Multiple Sclerosis
- Consortium of Multiple Sclerosis Centers
- International Organization of Multiple Sclerosis Nurses
- Multiple Sclerosis Association of America
- Multiple Sclerosis Foundation
- National Multiple Sclerosis Society
- United Spinal Association



## S.E.A.R.C.H.™ Model from MSAA

- Developed by Multiple Sclerosis Association of America (MSAA) to help people evaluate treatment options:
  - S. = Safety
  - E. = Effectiveness
  - A. = Affordability
  - R. = Risks
  - C. = Convenience
  - H. = Health Outcomes (overall wellness/quality of life)
- Information and toolkit available at [www.MSAssociation.org/programs/Search](http://www.MSAssociation.org/programs/Search)



**QUESTIONS?**

**COMMENTS?**

**CONCERNS?**



**APPENDIX –  
Treatments in the Pipeline**



## Treatments in the Pipeline

- **teriflunomide** – oral daily
- **alemtuzumab (Campath®)** – IV infusion: 3-5 days once a year
- **ocrelizumab** – 2 IV infusions: 2 wks apart every 6 months
- **PEGylated interferon beta-1a** – possible subcutaneous or intramuscular injection: every 2-4 wks
- **BG00012 (dimethyl fumarate)** – oral 2x daily



## teriflunomide

- Decreases B-cells and T-cells to reduce inflammation
- Phase III trial in relapsing MS looked at two doses:
  - Reduced relapse rate by 37%
  - Reduced total lesion volume by 39-67%
  - Reduced risk of disability progression in high-dose group by 30%
  - Side effects: mild hair thinning, nausea, diarrhea [overall adverse event rates were same across all groups—tx and placebo]



## teriflunomide, cont'd

### Advantages

- Oral
- Once-daily dosing
- Effective
- Long-term experience
- Also being investigated in CIS and as add-on to other therapy

### Challenges

- Potential liver damage
- Long-term suppression of all types of blood cells means long washout period
- Potential harm to developing fetus



## alemtuzumab (Campath®)

- Monoclonal antibody: reduces or eliminates selective lymphocytes (T cells and/or B cells)
- In phase III trial compared to Rebif®
  - More likely to be relapse-free for two years
  - Greater improvement on MSFC
  - Greater reduction in lesion activity on MRI
  - Less brain atrophy
  - Effect continued for at least 24 months after last dose
- Infusion side effects: abnormal liver functions, slowed heart rate, hypertension
- Complications: immune thrombocytopenic purpura (ITP); hypo- and hyper-thyroidism; infections



## alemtuzumab, cont'd

### Advantages

- Infrequent dosing
- Highly effective
  - Relapse rate
  - Disability progression
  - MRI findings
- Long-lasting effect

### Challenges

- Infusion reactions
- Long-term depletion of lymphocytes
- Autoimmune diseases
  - ITP
  - Hyper- and hypothyroidism
- Infection risk
- Malignancies?
- One-year washout period for women



## ocrelizumab

- Monoclonal antibody: depletes B cells
- Phase II clinical trial of low and high dose rituximab compared to placebo and Avonex
  - 89-92% reduction in active lesions compared to placebo and Avonex
  - 73-80% reduction in annualized relapse rate vs. placebo
  - Overall, 67.3% - 76.4% had no relapses and no confirmed progression of disability over 96 weeks, and 78.2% - 80% had no relapses
- Side effects: fever, chills, arrhythmias, shortness of breath, headache, itchiness, rash
- Serious infection rates similar across both doses and didn't increase with time on treatment



## ocrelizumab, cont'd

### Advantages

- Infrequent dosing
- Highly effective – comparable to Tysabri
  - Relapse rate
  - MRI findings
- Long-term experience
- Phase III trials underway in RRMS and PPMS

### Challenges

- Infusion reactions can be severe (including one death)
- Long-term impact on immune system
  - Infection risk
  - PML has been reported in patients taking this medication for other diseases



## PEGylated interferon beta-1a

- Extended release formulation of interferon beta-1a (Avonex®)
  - Requires less frequent dosing (every 2-4 weeks)
  - Results in fewer side effects
  - Currently being evaluated in a Phase III trial
  - Fast-tracked by the FDA with expected availability in 2012
  - Likely to replace Avonex as a first-line option for people with relapsing forms of MS



## BG00012 – dimethyl fumarate

- Appears to be neuroprotective and anti-inflammatory
- Phase III trial: comparing low- and hi-dose to placebo
  - Compared to placebo:
    - Reduced risk of relapses by 49% and 50%
    - Reduced annualized relapse rate by 53% and 48%
    - Reduced risk of disability progression by 38% and 34%
    - Both doses significantly reduced lesion activity on MRI
  - Adverse events were similar across all three groups
    - No deaths related to study treatment; no increase in infections, serious infections, opportunistic infections or malignancies.



## BG00012 – dimethyl fumarate, cont'd

### Advantages

- Oral
- Very effective at both doses
- Allows for later treatment options

### Challenges

- Caused flushing
- No major challenges

