

Risk Tolerance in Multiple Sclerosis

“It’s a great drug . . . unless it kills you.”

Robert J. Fox, MD
Staff Neurologist and Medical Director
Mellen Center for Multiple Sclerosis
Assistant Professor, Lerner School of Medicine
Cleveland Clinic Foundation



Acknowledgements

- ◆ Sunny Kolatakuddy, CCLCM Medical Student
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- ◆ Jar-Chi Lee, Department of Quantitative Health Sciences, CCF



Objectives

- ◆ Background about MS
- ◆ Treatments for MS
- ◆ Risk tolerance in MS: pilot study
- ◆ Proposed future study



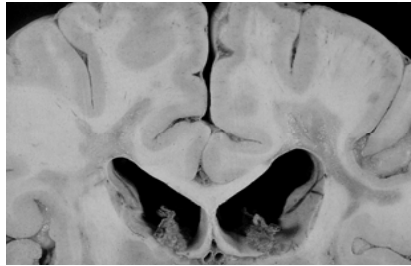
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What is MS?

- ◆ MS is a chronic, inflammatory demyelinating disease of the central nervous system
- ◆ Dissemination in time and space



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What is MS?

- ◆ The immune system causes the damage
- ◆ The myelin is damaged, which disrupts neural transmission
 - axons are also damaged
- ◆ The central nervous system includes the brain, optic nerves, and spinal cord



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Multiple Sclerosis

- ◆ US: 400,000 people with MS
 - Worldwide: 2 million
- ◆ Women more commonly than men (2:1)
- ◆ Typical age of onset: 20's - 30's
- ◆ Economic costs: \$20 billion
- ◆ Current annual marker for MS therapies: \$5 billion
 - Unmet treatment potential for MS therapies: \$5-8 billion

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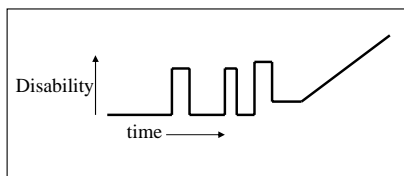
Typical Clinical Features

- ◆ Optic neuritis, diplopia
- ◆ Numbness: diffuse or focal
- ◆ Weakness: usually with numbness
- ◆ Coordination difficulties
- ◆ Bladder and bowel: frequency, urgency, constipation
- ◆ Walking: stiff, clumsy
- ◆ Mental: memory, concentration, mood

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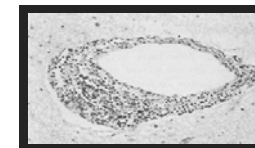
Variants of MS

- ◆ Relapsing-remitting (85%)
- ◆ Secondary Progressive (80% of RRMS)



Multiple Sclerosis: 3 Components

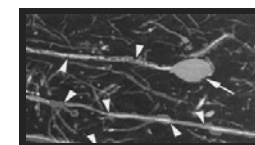
Inflammation



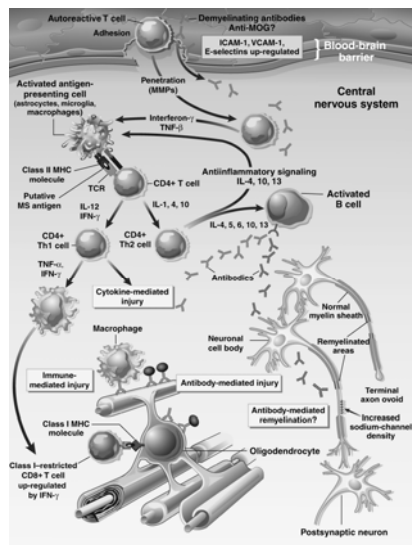
Demyelination and Axonal Transection



Neuron Loss

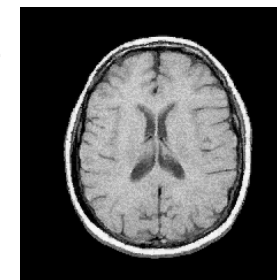


Theoretical pathophysiology of MS



Why disability in MS?

Lesion activity	Transected axons/mm ³
Normal brain	1 ± 1
MS patients:	
Normal regions	15 ± 3
Chronic active Core:	875 ± 246
Edge:	3,138 ± 688
Active inflammation	11,236 ± 2775



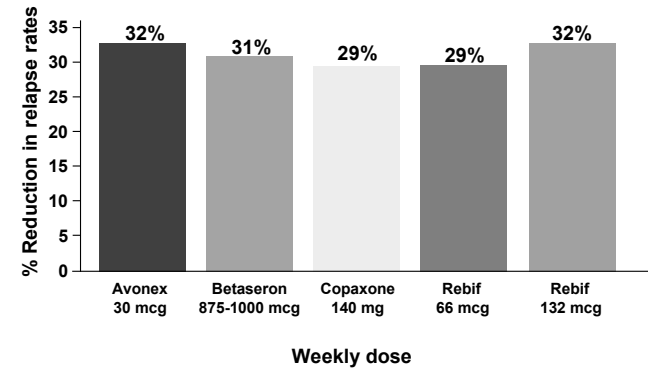
7 years of imaging in RRMS

Take-home message: there's lots of neurons being injured!

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Phase III Trials: Annual Relapse Rates



Jacobs et al. *Ann Neurol.* 1996;39:285; IFNB MS Study Group. *Neurology.* 1993;43:655; IFNB MS Study Group and University of British Columbia MS/MRI Analysis Group. *Neurology.* 1995;45:1277; Johnson et al. *Neurology.* 1995;45:1268; PRISMS Study Group. *Lancet.* 1998;352:1498.

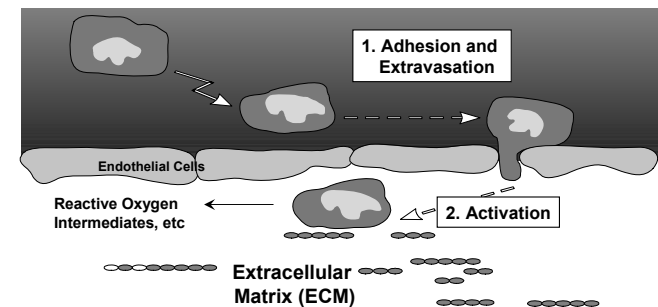
Annual Relapse Rates

- ◆ Despite our current therapies, there is a significant unmet need for MS therapies

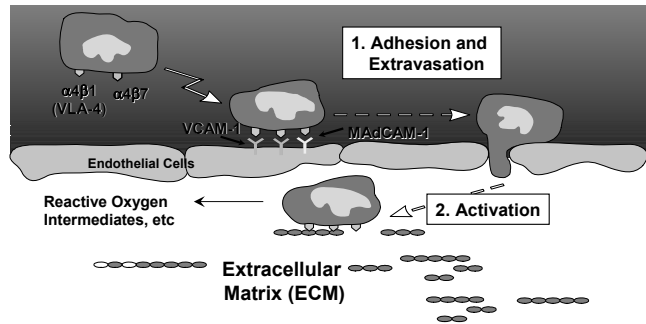


Jacobs et al. *Ann Neurol.* 1996;39:285; IFNB MS Study Group. *Neurology.* 1993;43:655; IFNB MS Study Group and University of British Columbia MS/MRI Analysis Group. *Neurology.* 1995;45:1277; Johnson et al. *Neurology.* 1995;45:1268; PRISMS Study Group. *Lancet.* 1998;352:1498.

Endothelial and Leukocyte Adhesion: $\alpha 4$ Integrins

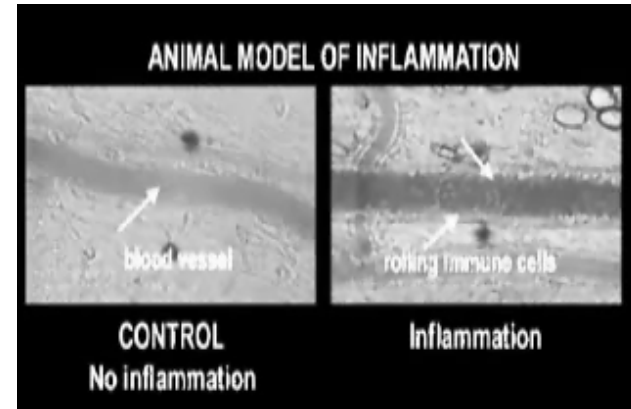


Endothelial and Leukocyte Adhesion: $\alpha 4$ Integrins



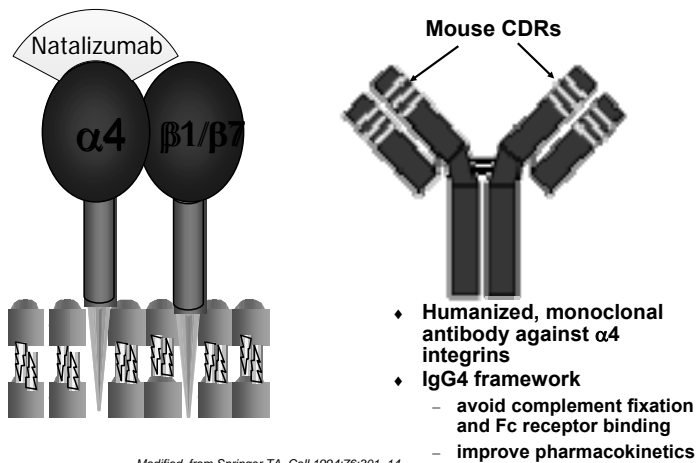
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Leukocyte Migration in Brain: Inflammation



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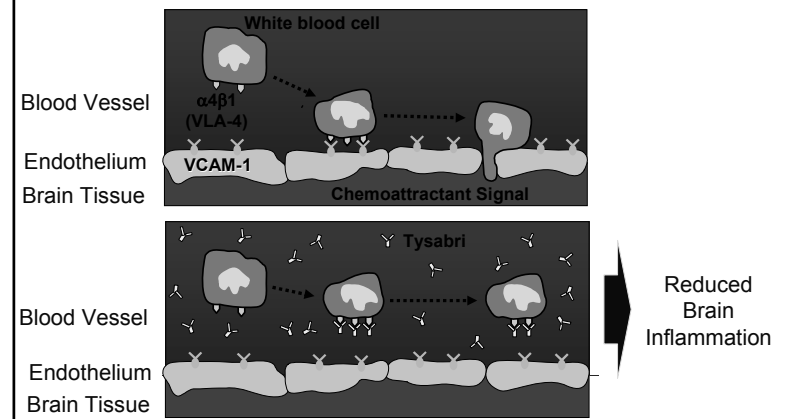
Natalizumab: A Humanized Monoclonal Antibody Against $\alpha 4$ Integrins



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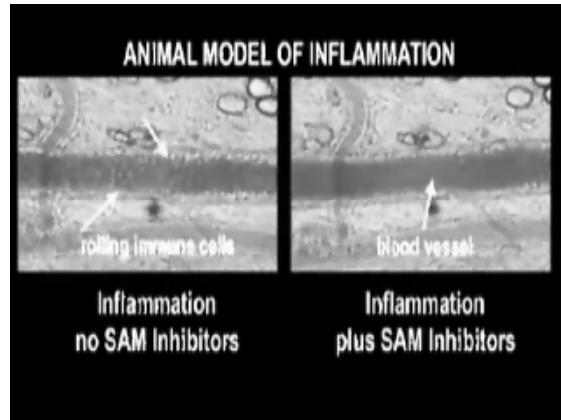
Modified from Springer TA, Cell 1994;76:301-14. And Butcher EC, et al. Science 1996;272:60-6.

Selective Adhesion Molecule Inhibition



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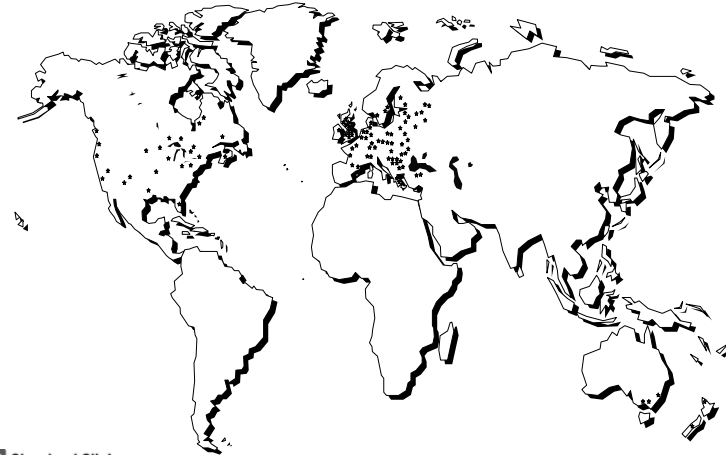
Leukocyte Migration in Brain: Surface Adhesion Molecule Inhibitor



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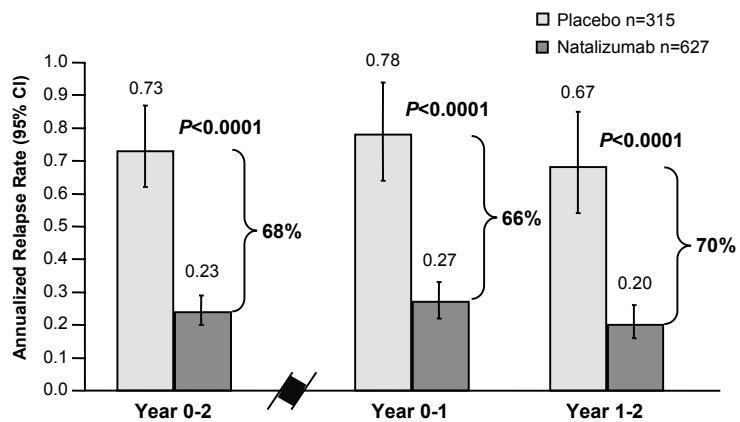
2 Phase III Trials

>125 Centers in Europe, North America, Australia, and New Zealand



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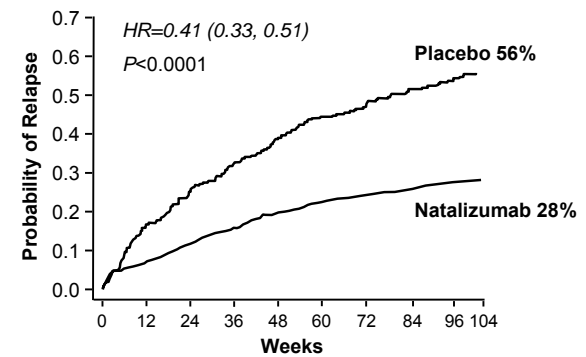
Annualized Relapse Rate



EUA per subject mean relapse rate at 2 years = 0.67 for placebo and 0.22 for natalizumab (67% reduction)

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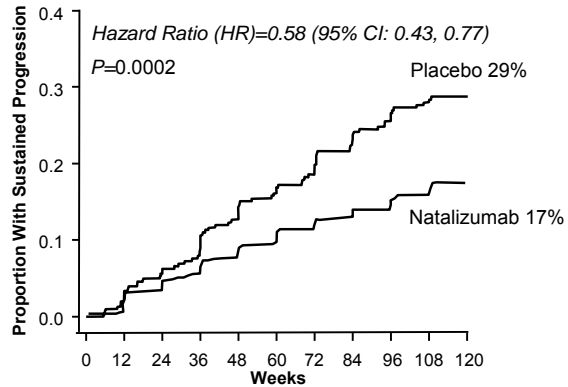
Risk of Relapse Over 2 Years Kaplan-Meier Plots of the Probability of Relapse



	0	12	24	36	48	60	72	84	96	104
Placebo	315	257	229	204	182	164	154	141	133	129
Natalizumab	627	577	542	515	487	464	447	436	424	418

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Sustained Disability Progression

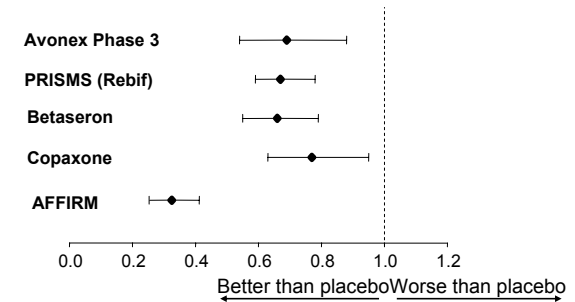


	0	12	24	36	48	60	72	84	96	108	120
Placebo	315	296	283	264	248	240	229	216	208	200	199
Natalizumab	627	601	582	567	546	525	517	503	490	478	473

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Natalizumab Vs. Available Therapies

Rate ratio (treated/placebo) and 95% CI for relapse rate



Data for Avonex are from subjects who completed ≥ 2 years on study. Data for Rebif and Betaseron are from the higher dose group. Except for Avonex and natalizumab, rates are based on aggregate data. Relapse rates are based on 2-year data except AFFIRM (data from 1-year analysis).

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Natalizumab (Tysabri)

- ◆ November 23, 2004:
 - FDA grants “accelerated” approval based on 1-year outcome
 - Required completion of 2-year placebo-controlled study and ongoing safety monitoring

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The New York Times
nytimes.com

March 1, 2005

Sales Halted in Biotech Drug Because of Link to a Death

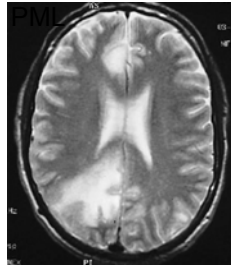
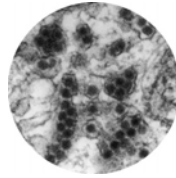
By Andrew Pollack

Sales of a new drug that had been hailed as a big advance in the treatment of multiple sclerosis were abruptly suspended yesterday after the product was linked to a rare but potentially fatal neurological disease.

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Progressive Multifocal Leukoencephalopathy (PML)

- Etiology: ubiquitous JC virus
- Usually remains dormant
- Can emerge as a demyelinating disorder in the brain:
 - AIDS, solid organ transplant, hematologic malignancies
- Clinically: impaired cognition, cortical blindness, hemiparesis
- MRI: Involves gray and white matter
- Usually fatal - 2 of 3 Tysabri-related PML patients died
- Estimated prevalence in Tysabri-treated patients - 1:1000 over 18 months



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Tysabri, Act II

- ◆ After a comprehensive safety assessment, no further cases of PML were identified
- ◆ June 2006: Tysabri is re-released by the FDA for clinical use
 - All patients, prescribers, pharmacists, and infusion centers must be registered
 - Only relapsing MS patients are allowed to receive Tysabri – no off-label use is allowed
 - All patients must agree to be followed in a registration/surveillance program (TOUCH)

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Alemtuzumab

- ◆ Anti-CD52 monoclonal antibody
 - Destroys B-cells and lymphocytes, leading to prolonged monocytic cell depletion
 - B-cell lymphoma: occasional reports of humoral autoimmunity: Grave's disease, Goodpasture's syndrome
 - Phase II MS trial halted due to 6 of 200 treated patients developing immune-mediated thrombocytopenic purpura (ITP); 1 was fatal.

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MS Treatments – Summary

- ◆ Standard injectible therapies: 1/3 reduction in relapses (compared to placebo), and are very safe
- ◆ Advanced biologic therapies: 2/3+ reduction in relapses, with rare, often-fatal side-effects

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Patient Care Questions

- ◆ Are MS patients tolerant of these risky therapies?
- ◆ How to we predict which patients are likely to be tolerant?
- ◆ What factors change their tolerance to risk over time?
- ◆ Does the utility of these therapies justify their use, despite the risks?

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Risk Tolerance Pilot Study

- ◆ Aim: Assess tolerance to risky therapies among a group of MS patients for whom treatment was recommended
- ◆ Population: 251 MS patients who planned to start Tysabri in 2004-2005 (pre-PML)
- ◆ Study: Telephone interview
 - Demographics and MS disease characteristics:
 - ◆ previous and current MS treatments, ambulatory status, and a self-assessment rating scale (from 1 to 10) regarding the harm MS has caused to the respondent's quality of life; knowledge of Tysabri complications
 - 3 standard gamble paradigms

Standard Gamble Paradigms

- ◆ “Miracle Drug” – pill that cures MS overnight – all relapses, disability, and all symptoms related to MS
 - But, risk of death overnight: 10%, or 1:10
 - Varied risk from 1:2 to 1:100,000
- ◆ “Miracle Drug, after progression”: You don’t take Miracle Drug, and over the next year you have 2 relapses of MS, one of which leaves you with persistent symptoms. Then you’re offered Miracle Drug
- ◆ “Tysabri”: Phase III trial results: 67% reduction in relapses, and 42% reduction in disability progression. But there’s a risk of a fatal brain infection of 1:1000.
 - Varied risk from 1:25 to 1:1,000,000

Statistical Analysis

- To evaluate the relationship between individual demographic and disease characteristics and risk tolerance, Wilcoxon test and Spearman rank correlation were used for the Miracle Drug and Miracle Drug After Progression scenarios,
- For natalizumab scenario, we divided patients into two risk tolerance groups: $\geq 1:1000$, and $< 1:1000$. Therefore, T-test and Chi-Square were used for the natalizumab scenario.
- Multiple regression (Miracle Drug scenario) and logistic regression (Natalizumab scenario) were used to analyze the association of each variable with risk tolerance and derive a predictive nomogram. The calibration of the model was assessed graphically.

Pilot Study - Results

Characteristics of study participants (N=128)

Mean Age (SD)	44 (9)	Mean Yrs since MS diagnosis (SD)	10 (7)
White	87%	Uses assistive device for walking or non-ambulatory	43%
Female	78%		
Married	73%	Currently receiving MS therapy	84%
Employed	63%	Received natalizumab 2004-2005	23%
Privately insured	81%	Received natalizumab in Ph III trial	9%

Pilot Study - Results

Median risk tolerance for potential death

<i>Scenario</i>	<i>Median Risk Tolerance</i>
Miracle Drug (cure of MS, including symptoms)	1:100
Miracle drug after progression (cure of MS, including symptoms, after 2 relapses in the next year, one of which left residual disability)	1:12
Natalizumab (2/3 reduction in relapses, 42% slowing of disability progression)	1:1000

Pilot Study - Results

Median risk tolerance for potential death

Scenario

Miracle Drug (cure of MS, including symptoms)	46% with 1:10 or greater
Miracle drug after progression (cure of MS, including symptoms, after 2 relapses in the next year, one of which left residual disability)	19% with 1:2
Natalizumab (2/3 reduction in relapses, 42% slowing of disability progression)	50% of patients tolerate risk of Tysabri

Problems: Ceiling: truncation at 1:2 risk - some patients would have gone higher
 Floor: some patients refused to accept any risk



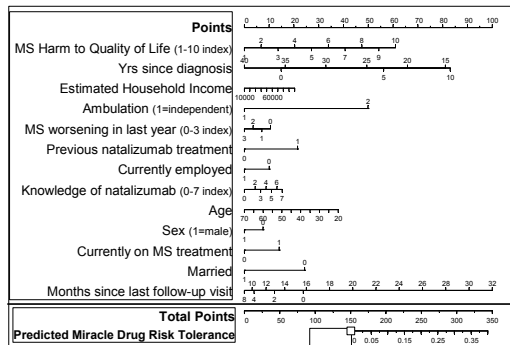
Pilot Study - Results

Factors related to risk tolerance

Clinical Factors	p-values		
	Miracle Drug	Miracle Drug After Progression	Natalizumab
Self-reported harm to quality of life	<0.001	<0.001	<0.001
Disease worsened in past 12 months	0.02	0.025	n.s.
Uses cane or device	0.01	<0.01	0.031
Younger age	n.s.	0.04	n.s.
Less than six months since last clinical visit	n.s.	n.s.	0.05
Unmarried	0.054	n.s.	n.s.
Unemployed	n.s.	n.s.	0.08
Longer time since diagnosis	0.07	n.s.	n.s.
Prior treatment with natalizumab	n.s.	n.s.	n.s.
Receiving MS treatment currently	n.s.	n.s.	n.s.
Male	n.s.	n.s.	n.s.
Greater patient knowledge re: natalizumab	n.s.	n.s.	n.s.
Lower estimated household income	n.s.	n.s.	n.s.

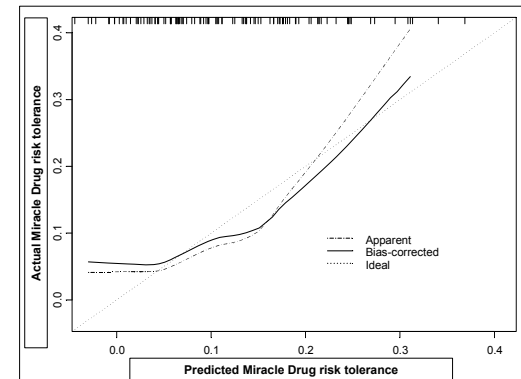


Nomogram for predicting patient risk tolerance to Miracle Drug



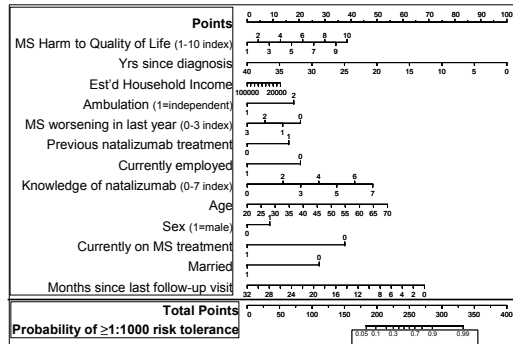
Calibration Curve

Predicting risk tolerance to Miracle Drug

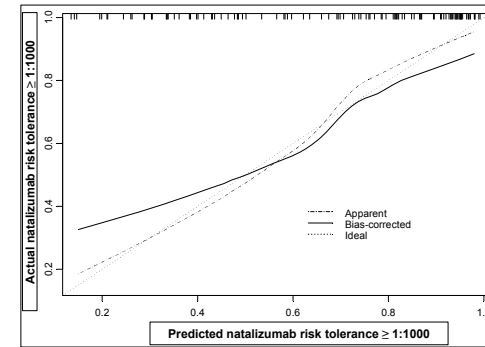


$r^2 = 0.10$

Nomogram for predicting risk tolerance $\geq 1:1000$ for Tysabri



Calibration Curve Predicting $\geq 1:1000$ risk tolerance to Tysabri



Concordance index = 0.75

Pilot Study Limitations

- ◆ Missing elements: dependents in the house, smoking
- ◆ Inappropriate scenarios: reversing all MS symptoms isn't realistic
- ◆ Truncation – 1:2 risk of death wasn't high enough for some scenarios; 1:100,000 wasn't low enough
- ◆ Plan: repeat survey this summer (n=128): fill in missing variables, expand scale; assess factors associated with shifts in risk tolerance
- ◆ Other thoughts or comments?

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Risk Tolerance – the Next Chapter

- ◆ Apply risk tolerance assessments to MS patients in NARCOMS project
- ◆ NARCOMS: North American Research Committee on Multiple Sclerosis Project
 - MS patient registry: 32,000 registrants, 18,000 of which are considered “active” (have responded to ≥ 1 survey in last 18 months)
 - Registrants fill out semi-annual surveys on disease characteristics, medications, and other items which vary from survey to survey
 - Ruth Ann Marrie has validated many aspects of the NARCOMS questionnaires. A May 2007 publication reported results of urologic survey from 9,688 subjects.



Risk Tolerance – the Next Chapter

- ◆ Invite all NARCOMS users to a web-based survey
 - Demographic and disease characteristics (many are already available within NARCOMS database)
 - Standard gamble paradigms: cure MS, cure MS after progression, and Tysabri scenarios
 - Repeat survey annually on original participants for 2 years and assess the impact of disease activity on shifts in risk tolerance
 - Assess predictive ability of risk tolerance regarding initiation of risky therapies (i.e. Tysabri)
 - Projected respondents: 6,000



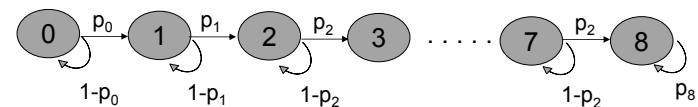
Risk Tolerance – the Next Chapter

- ◆ Utility assessment to reverse progression of disability
- ◆ Patient-determined disease steps (PDSS):
 - 0. Normal
 - 1. Mild disability: noticeable symptoms; small effect on lifestyle
 - 2. Moderate disability: problems that limit daily activities, but not walking
 - 3. Gait disability: limited walking, but usually don't need a cane
 - 4. Early cane: use a cane or other support part of the time
 - 5. Late Cane: Usually use a can or other support
 - 6. Bilateral Support: uses 2 canes or a walker to walk 25 feet
 - 7. Wheelchair/scooter: main form of mobility is a wheelchair
 - 8. Bedridden: unable to sit in a wheelchair for more than 1 hour



Markov Model

Patient-Determined Disease Steps - PDSS



NARCOMS survey:

1. Identify the patient's current step, then
 2. Have them imagine that they have progressed to the next step over 1 year (describe it to them), and
 3. Offer a pill to reverse back to the previous step, and use standard gamble of death to identify what risk they will tolerate to reverse back to previous step
 4. Translate this tolerance to Utility
- Over 2 years, NARCOMS can characterize the probabilities of progression through each step.
- Compare this summated utility to the utility of treatment



Risk Tolerance – the Next Chapter

◆ Outcomes:

- More accurate understanding of MS patient tolerance to risk across the spectrum of disabilities
- Nomogram tool to assist clinicians in guiding patients to therapies with risks that are most appropriate for them
- Guiding clinicians regarding how disease activity can shift patient tolerance to risk
- Assessment of utility of risky therapies.

Other thoughts or comments?

Summary

- ◆ We are developing very effective therapies for MS, but which involve significant risk
- ◆ A greater understanding of patient tolerance to these risks, and how this tolerance shifts over time, would help clinicians guide patients to the most appropriate therapies
- ◆ Utility assessments can help understand how these therapies should fit into the treatment of MS

Thank you for your attention