Fingolimod: Making the diagnosis of Multiple Sclerosis easier to swallow?

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Multiple Sclerosis

- Autoimmune disease believed to be mediated by B and T lymphocytes
- Stripping of the myelin sheath surrounding axons in the CNS
- Forms of MS
  - Relapsing-remitting
  - Primary-progressive
  - Secondary-progressive
  - Progressive-relapsing

Patient Case

- 15y F
- Track and field athlete
- Experiencing symptoms of generalized weakness and muscle fatigue
- MRI confirmed diagnosis of Multiple sclerosis
- Began therapy with Avonex

Patient Testimony

- One relapse cost me an entire track season
- Subcutaneous injections are more bothersome than previous IM
- Annoying to have to bring injections everywhere
- Could be worse

Current Therapeutic Options

- Disease Modifying Therapy
  - Interferon (Avonex, Rebif, Betaseron)
  - Glatiramir Acetate (Copaxone)
  - Natalizumab (Tysabri)

- Surgery
  - Venous Angioplasty
    - Chronic Cerebro-Spinal Venous Insufficiency

Current Therapeutic Options

**Baseline annualized relapse rate 0.5-1.3

Agent	Dosing Regimen	Efficacy (Annual Relapse Rate)	Other Efficacy Outcomes	Cost
Interferon alpha-1a (Avonex)	30mcg IM Once weekly	Decrease by ~ 30% vs. PBO	22% pts increase in EDSS by 1 pt vs. 35% in PBO Decrease in MRI lesion volume (74 v 122%)	$21000/yr
Interferon alpha-1a (Rebif)	44ug SC 3 x week	Decrease by ~ 30% vs. PBO NSS advantage over Avonex	Reduced MRI lesion burden vs. PBO and Avonex	$24000/yr
Interferon alpha-1b (Betaseron)	250 ug SC Every 2nd day	Decrease by ~ 30% vs. PBO Improved efficacy vs. Avonex	30% increase in MRI burden @ 5 years in PBO group 55% pts free of new lesions on MRI vs. Rebif	$21000/yr

Current Therapeutic Options

Agent	Dosing Regimen	Efficacy (Annual Relapse Rate)	Other Efficacy Outcomes	Cost
Glatiramer Acetate (Copaxone)	20mg SC Daily	Decrease by ~ 30% vs. PBO NSS over IFN	>1.5 pt increase in EDSS 22% vs. 41% in PBO	$16 000/yr
Natalizumab (Tysabri)	300mg IV infusion Over 1 hour once monthly	Decrease by ~ 60% vs. PBO	Risk of new lesion on MRI vs. PBO 0.11	$31 500/yr

Fingolimod (Gilenya)

- First oral agent approved for RRMS
- Approved by Health Canada in March 2011
- MOA
  - Pro-drug (CYP4E1)
  - Binds to sphingosine-1-phosphate receptors which down regulates lymphocytes and reduces amount in peripheral blood
- PK
  - Slow but extensive oral absorption
  - Elimination half life of 6-9 days

Gilenya: Product Monograph. Novartis. 2012

Clinical Question

Patients	Patients between the ages of 18 and 65 with relapsing remitting multiple sclerosis (RRMS)
Intervention	Fingolimod 0.5mg PO daily
Comparator	Available first line options for RRMD
Outcome	Mortality Annual relapse rate Disability Quality of life MRI changes Adverse Drug Reactions

Outcomes

- Expanded Disability Status Scale
  - A 20-step scale done by trained neurologist
  - Combines disability (ambulation) with functional status
  - Scored 0 (no impairment) – 10 (death due to MS)

- MRI Changes
  - Effectively able to detect atrophy and lesions characteristic of MS
  - Useful for diagnosis and initial prognosis but correlates poorly with progression of disability
  - Evidence of new lesions demonstrate progression of disease

Search Strategy

Databases	Pubmed, Medline, Embase, Cochrane, Google Scholar, IPA
Search Terms	Relapsing remitting multiple sclerosis, fingolimod, interferon, natalizumab, glatiramer acetate, relapse, disability, progression
Limits	Humans, English
Results	2 meta-analyses 2 RCTs
Analyzed	1 meta-analysis 2 RCTs

Results

- 2 RCTs
  - Fingolimod vs. Placebo
  - Fingolimod vs. Interferon beta-1a 30ug (Avonex)
- 2 meta-analysis
  - Both RCTs were included in the meta-analysis
  - Both MAs used mixed treatment comparison (indirect analysis)
  - 2nd MA only used trials that compared intervention vs. placebo

Fingolimod vs. Placebo

- FREEDOMS
- R, DB, PC, MC
- Patients: 37y, 70% Female, duration of disease ~ 8y, 1.5 relapses in previous year, EDSS score 2.4
- N=1033
- Fingolimod 0.5mg, 1.25mg or placebo
- Duration of 24 months
- Primary end point annualized relapse rate

Results

	Fingolimod 0.5mg	Placebo	p-value
Annualized relapse rate	0.18 (0.15 to 0.22)	0.4 (0.34 to 0.47)	<0.001
Absence of relapse during 24 month (%)	70.4 (66.0 to 74.8)	45.6 (40.7 to 50.6)	<0.001
Absence of disability progression (%)	87.5 (84.3 to 90.7)	81 (77.1 to 84.9)	0.01
Absence of new MRI lesions @ 24 months (%)	50.5	21.2	<0.001

Fingolimod vs Avonex

- TRANSFORMS
- R, DB, DD, MC
- 36y, 67% Female, duration of disease 7.5y, 1.5 relapses in previous year, EDSS score 2.2 N= 1153
- Fingolimod 0.5mg, 1.25mg or IFN-1a 30ug IM once weekly
- Duration of 12 months
- Primary end point: Annualized relapse rate

Results

	Fingolimod 0.5mg	IFN-1a 30ug IM	p-value
Annualized relapse rate	0.16 (0.12-0.21)	0.33 (0.26-0.42)	<0.001
New or enlarged MRI lesions (mean)	1.7±3.9	2.6±5.8	0.004
% Patients with no disability progression (EDSS)	94.1 (91.8 to 96.3)	92.1 (89.4 to 94.7)	0.25

Indirect Treatment Comparison

- Used when no direct comparisons have been done or the evidence is limited and insufficient
- Easiest comparison A vs. B and B vs. C allowing for a comparison between A and C
- Limitations: extrapolation of data to situations that have not been studies, heterogeneity in patient populations, study outcomes, and duration of studies

Mixed Treatment Comparison

- Combination of both direct and indirect evidence
- Direct comparisons are available between some but not all therapies
- Assumes that treatment effect is identical across trials and that event rates follow a normal distribution

Network Diagram

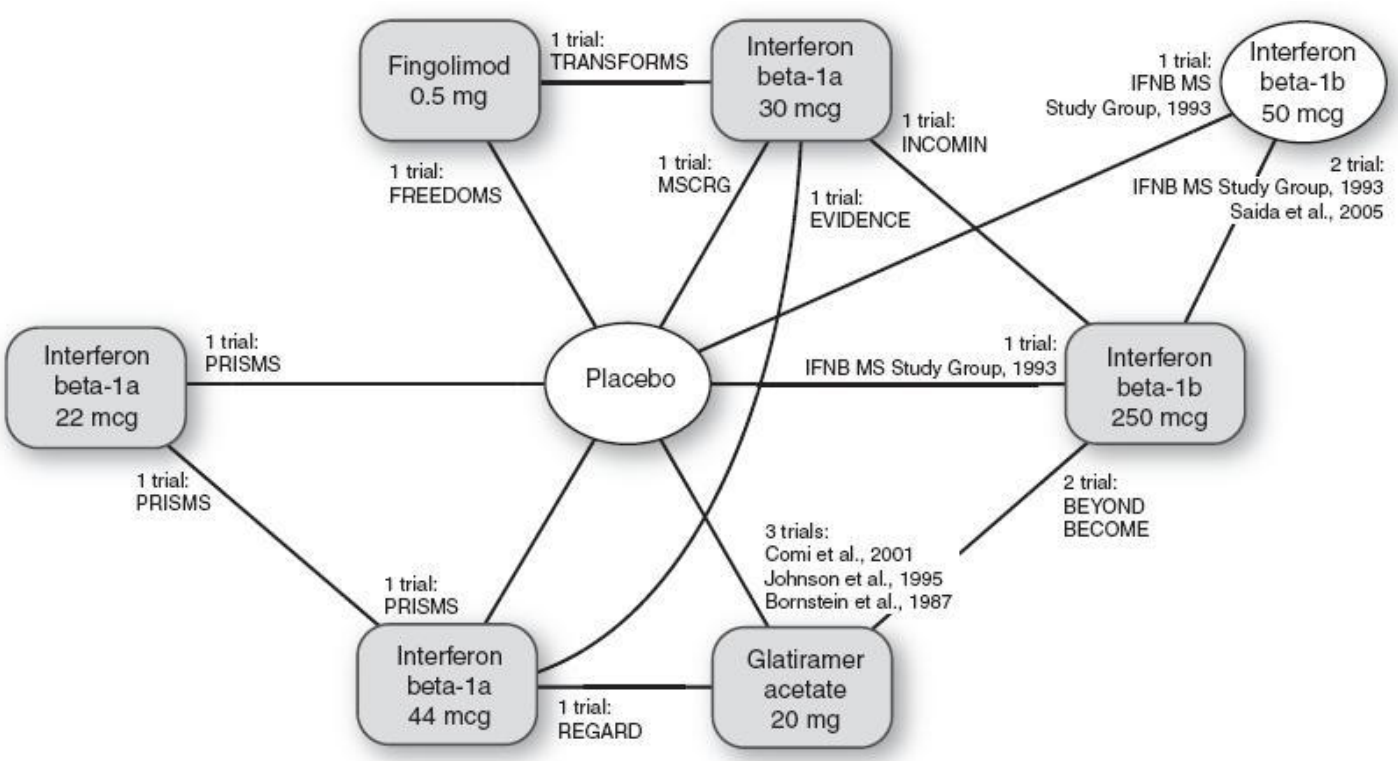

Figure 2. Network diagram for the annualized relapse rate mixed-treatment comparisons meta-analysis.
This figure displays the available network of evidence, specifically illustrating which trials link which treatments through common comparators. The included trials are TRANSFORMS[13], FREEDOMS[14], BEYOND[25], BECOME[26], REGARD[27], EVIDENCE[28], INCOMIN[29], PRISMS[30], MSCRG[31], Johnson (1995)[32], IFNB MS (1993)[33], Bornstein (1987)[34], Comi (2001)[35], and Saida (2005)[36].

Heterogeneity of Patients

- Fairly consistent across all studies analyzed
  - Age:
  - % Female:
  - Time since diagnosis:
  - EDSS Scores
  - Duration of study

Outcomes studied

- Annualized relapse rate
- Definition of relapse varied across studies but remained relatively consistent
- Defined as new or worsening symptoms accompanied by:
  - Changes in EDSS or functional scores
  - Duration of 24–48 hours
  - Separated from previous event by 30 days
  - Not combined with fever or infection

Forrest Plot

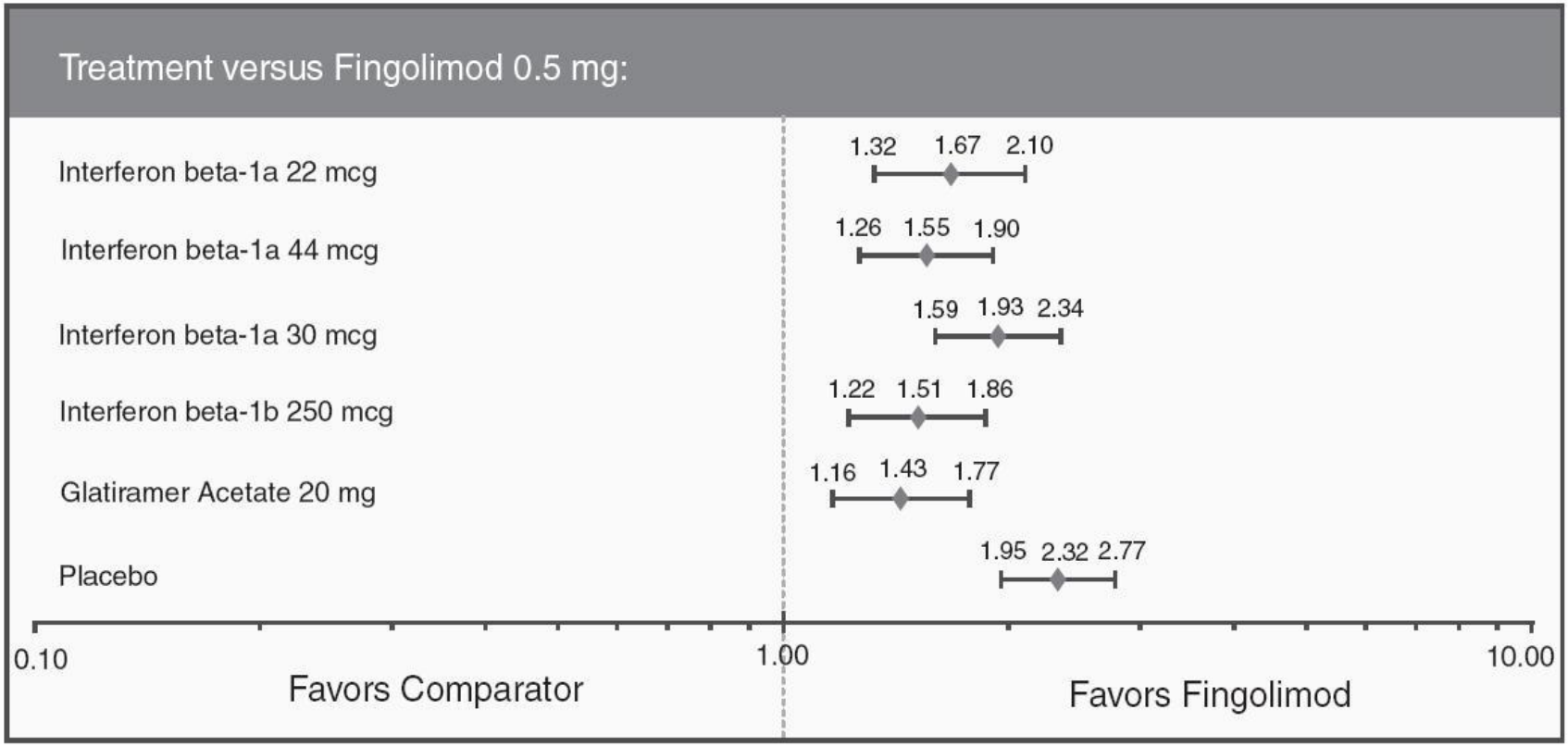

Figure 3. Mixed-treatment comparison derived relative rates of selected treatments versus fingolimod.
This figure presents a forest plot for the results from the mixed treatment comparison meta-analysis, specifically showing the relative treatment effect (relative annualized relapse rate and 95% confidence interval) of each treatment separately versus fingolimod.

Adverse Effects

- Serious infection
  - Decrease in lymphocyte counts (up to 70%)
  - 2 fatal herpes virus infections (TRANSFORMS)
- Cancer
  - Skin cancer identified in phase II studies
- Cardiac
  - First dose, transient bradycardia
  - 10-15bpm that persisted in some patients
  - AV block
- Macular Edema
  - Occurred in fewer than 1% of patients in RCT

Health Advisories

- FDA and Health Canada
  - 1 report of a patient dying within 24 hours of first dose (cause unidentified)
  - Eleven deaths have been linked to the use of fingolimod internationally as of late February 2012, including four patients who had cardiac events and seven with unexplained death
  - Recommend monitoring in specific patients

Current Recommendations

- No available national or international guidelines that describe the use of fingolimod in RRMS
- UpToDate – ".. we suggest **NOT** starting fingolimod for patients with MS until the cause of death in these cases has been clarified"
- ".. should be considered only for patients who have had recent inflammatory disease activity and those who do not benefit from or cannot tolerate alternative disease-modifying therapies" – N Engl J Med 2012; 366:339-47

Clinical Question – Outcomes

	vs. Placebo	vs. IFN
Mortality	No data	
Annual Relapse Rate	0.18	0.40
Disability (Δ in EDSS score from baseline	0.13 point increase in PBO	No difference
Quality of Life	Not studied	
MRI Changes (new or enhanced lesions)	Mean 7.3 fewer	Mean 0.9 fewer
Adverse Drug Reactions	Bradycardia Increase in ALT Macular Edema	Herpesvirus infection Bradycardia Increase ALT Macular edema

Conclusions

- An effective oral agent for patients with RRMS
- Superior efficacy to placebo and Avonex
  - Possibly the most effective option
- Clinically important?
  - How many relapses/year is the patient experiencing?
  - How debilitating are they?
- Benefit seen after switching from IFN
  - Extension of TRANSFORMS
  - Extensions of FREEDOMS currently awaiting publication

Conclusions

- Lack of long term data
  - Safety concerns remain
- Cost
  - Yearly cost is >$31 000 CDN per year
  - Cost effect analysis have shown it to not be cost effective compared to IFN
  - ICER of $74 000 per QALY compared to IFN beta-1a
  - ICER $19 000 per relapse avoided

Recommendations

- Would not recommend for all patients initially
- Beneficial for patients who are unwilling to inject or intolerant
  - More data is becoming available following switch to fingolimod
- Cost can be prohibitive for some patients

- What would I recommend to my cousin?
  - Continue her current therapy

Questions