Drug Class Review

Disease-modifying Drugs for Multiple Sclerosis

Final Update 1 Evidence Tables

August 2010

The Agency for Healthcare Research and Quality has not yet seen or approved this report

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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Abbreviations used in evidence tables

Abbreviation	Meaning
ACTH	Adrenocorticotropic hormone
Abs dif	Absolute difference
ACT	Active-control trial
AE	Adverse event
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AI	Ambulation index
AL	Alemtuzumab
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APAP	Acetaminophen
ARR	Annualized relapse rates
AUC	Area under the curve
AZA	Azathioprine
BAB	Binding antibodies
BECOME	Betaseron vs Copaxone in MS with Triple-Dose Gadolinium and 3-T MRI Endpoints
BENEFIT	Betaseron in Newly Emerging Multiple Sclerosis For Initial Treatment
BEYOND	Betaferon/Betaseron Efficacy Yielding Outcomes of a New Dose
BHS	Beck Hopelessness Scale
bid	Twice daily
BL	Baseline
BMI	Body mass index
CCT	Controlled clinical trial
CES-D	Center for Epidemiologic Studies Depression Scale
CHAMPS	Controlled High-Risk Subjects Avonex MS Prevention Study
CI	Confidence interval
CIS	Clinically isolated syndrome
CNS	Central nervous system
Cop 1	Co-polymer-1
CPA	cyclophosphamide
CPMS	Chronic Progressive Multiple Sclerosis
CR	Controlled release
CU	Continuous use
CV	Cardiovascular
CVS	Cardiovascular system
d	Day
DB	Double-blind
dL	Deciliter
DMT	Disease-modifying therapy
DTPA	Diethylenetriaminepentaacetic Acid
ECG	Electrocardiogram

Abbreviation	Meaning
EDSS	Expanded Status Disability Scale
EEG	Electroencephalogram
EF	Ejection fraction
EP +/-	Estroprogenic status
ER	Extended release
ETOMS	Early treatment of multiple sclerosis
EVIDENCE	Evidence of Interferon Dose-Response: European North American Comparative Efficacy
FDA	US Food and Drug Administration
FSS	Functional System Score
FU	Follow-up
g	Gram
GA	Glatiramer acetate
GI	Gastrointestinal
GP	General practitioner
h	Hour
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HMO	Health maintenance organization
HR	Hazard ratio
HRQOL	Health related quality-of-life
HTLV-1	Human T-lymphotropic virus Type I
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
IFN	Interferon
IFN β	interferon beta
IFN β-1a	interferon beta-1a
IFN β-1b	interferon beta-1b
IM	Intramuscular
IMPACT	International Multiple Sclerosis Secondary Progressive Avonex Controlled Trial
INCOMIN	Independent Comparison of Interferon
IR	Immediate release
ISP	Injection site pain
ISR	Injection site reaction
ITT	Intention-to-treat
IV	Independent variable
IVIG	Intravenous immunoglobulin
L	Liter
LA	Long acting
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
LOCF	Last Observation Carried Forward

Abbreviation	Meaning
LS means	Least squares means
LVEF	Left ventricular ejection fraction
MANCOVA	Multivariate analysis of covariance
mcg	Microgram
mcL	Microliter
mg	Milligram
min	Minute
MITO	Mitoxantrone
MIU	Million international units
mL	Milliliter
mo	Month
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSCRG	Multiple Sclerosis Collaborative Research Group
MSFC	Multiple Sclerosis Functional Composite
MSQLI	Multiple Sclerosis Quality of Life Inventory
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NAb	Neutralizing antibody
Nat	Natalizumab
NHPT	Nine-hole peg test
NR	Not reported
NS	Not significant
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSD	No significant difference
OR	Odds ratio
OWIMS	Once Weekly Interferon for Multiple Sclerosis
P	*P* value
P	Placebo
PCT	Placebo-controlled trial
PPMS	Primary Progressive Multiple Sclerosis
PPY	Per person year
PR	Partial response
PreCISe	Study to Evaluate Early Glatiramer Acetate Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis of Subjects Presenting With Clinically Isolated Syndrome
PRISMS	Prevention of Relapses and Disability by Interferon-ß-1a Subcutaneously in Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
PROMise	Study to evaluate the safety and efficacy of glatiramer acetate in Primary Progressive Multiple Sclerosis
PROOF	Prospective and Retrospective Observational Study of Avonex and Rebif

Abbreviation	Meaning
qd	Once daily
qod	Every other day
QOL	Quality-of-life
RCT	Randomized controlled trial
REGARD	Rebif vs Glatiramer Acetate in Relapsing Multiple Sclerosis Disease
RFSS	Regional Functional System Score
RR	Relative risk
RRMS	Relapsing-Remitting Multiple Sclerosis
SB	Single-blind
SD	Standard deviation
SE	Standard error
SENTINEL	Safety and Efficacy of Natalizumab in Combination with Interferon β-1a in Patients with Relapsing Remitting Multiple Sclerosis
SPECTRIMS	Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon β-1a in Multiple Sclerosis
SPMS	Secondary-progressive multiple sclerosis
SQ	Subcutaneous
SR	Sustained release
SS	Statistically significant
T1	T1-hypointensity
T2	T2-hypointensity
tid	Three times daily
TTMW	Timed ten-meter walk
ug or µg	Microgram
UTI	Urinary tract infection
VAS	Visual analog scale
vs.	Compared with (versus)
WBC	White blood cell
WD	Withdrawal
WMD	Weighted mean difference
XR	Extended release
y	Year

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of β interferons

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Namaka et al 2006 Fair-Good Limited data provided on types of trials included	To determine the incidence and clinical importance of NAbs in patients with RRMS	1983-2005	NR, however included studies had to meet American Academy of Neurology standard on reliability of trial data	NR	10 trials: 3 head-to-head trials; 5 PCTs; 2 dose comparison trials
Rice 2001 (Cochrane) Good	To assess the effects of recombinant IFNs in adults with RRMS	1966-2000	DB, placebo-controlled RCTs of SQ or IM IFNs	919	7 trials: all placebo-controlled, DB RCTs

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of β interferons

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups
Namaka et al 2006 Fair-Good Limited data provided on types of trials included	RRMS patients only	IFN β-1a IM 30 µg/wk IFN β-1a IM 60 µg/wk IFN β-1a SQ 22 µg/wk IFN β-1a SQ 22 µg 3x/wk IFN β-1a SQ 44 µg 3x/wk IFN β-1b SQ 1.6 MIU qd IFN β-1b SQ 8.0 MIU qd Placebo	Presence of NAbs varies from 2-45% in IFN β treated patients Odds of relapse during NAb-positive period between 1.51 and 1.58 (*P*<0.03) Time to relapse also shortened with NAb-positive status to 244 days IFN β-1a IM appeared to have lowest rates of antibody presence compared to other IFN products	NR
Rice 2001 (Cochrane) Good	RRMS patients only	IFN β-1a IM 6.0 MIU/wk IFN β-1b SQ 1.6 MIU and 8.0 MIU qd Placebo This systematic review also included IFN α-2a studies, however these are outside the scope of this review	Exacerbation free: Pooled risk difference for IFNs (including IFN α-2a): RR -23% (95% CI, -8% to -39%) with no differences among IFNs Exacerbations: Pooled RR of exacerbations with IFN use: 1.11 (95% CI, 0.73 to 1.68; *P*=0.6) Disease progression: WMD in EDSS change: -0.25 (95% CI, -0.05 to -0.46; *P*=0.001)	NR

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of β interferons

Author Year	Adverse events	Comments
Namaka et al 2006 Fair-Good Limited data provided on types of trials included	NR	
Rice 2001 (Cochrane) Good	Pooled rates: IFNs vs placebo Flu-like symptoms (P=0.001) Fever (P<0.0001) Myalgias/arthralgias (P<0.0001) Fatigue (P<0.05) Nausea/vomiting (P<0.2) Headache (P<0.02) ISRs (P=0.0001)	

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of β interferons

Author	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Goodin et al 2007 Fair-Good Methods of article selection not reported, very limited data on included studies	To assess the clinical impact of NAbs to IFN β; Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology	1966-2005	Studies reporting clinical or radiographic outcomes in both antibody positive and antibody negative patients - design criteria not stated	923	List of 13 studies includes trials and non-RCT designs
Rojas 2009 (Cochrane) Good	To determine the effectiveness of recombinant IFNs in patients with PPMS	1966 - April 2008	Placebo-controlled RCT's, double or single-blinded in PPMS	123 (2 trials)	2 placebo-controlled RCT's, DB of IFN; Leary 2003 was a trial of IFN β-1a at 30 µg and 60 µg x 24 mos; Montalban 2004 was a trial of IFN β-1b at 8 MIU qd x 24 mos

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of β interferons

Author	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups
Goodin et al 2007 Fair-Good Methods of article selection not reported, very limited data on included studies	Any MS patient	IFN β-1a IM 30 µg/wk IFN β-1a IM 60 µg/wk IFN β-1a SQ 22 µg/wk IFN β-1a SQ 22 µg 3x/wk IFN β-1a SQ 44 µg 3x/wk IFN β-1b SQ 1.6 MIU qd IFN β-1b SQ 8.0 MIU qd Placebo	Class II and III evidence indicates all 3 IFNs are associated with the production of NAbs (Level A). NAbs in the serum are probably associated with a reduction in the clinical effectiveness of IFN β treatment (Level B). The rate of NAb production is probably less with IFN β-1a treatment than with IFN β-1b treatment, although the magnitude and persistence of this difference is difficult to determine (Level B). It is probable that there is a difference in seroprevalence due to variability in the dose of IFN β or in the frequency or route of its administration (Level B). IFN β-1a IM is less immunogenic than IFN β-1a or IFN β-1b given >1 times per week SQ (Level A). Because NAbs disappear in some patients even with continued IFN β treatment (especially with low titers), the persistence of this difference is difficult to determine (Level B). Sustained high-titer NAbs (>100 to 200 NU/mL) is associated with a reduction in the therapeutic effects of IFN β on clinical measures of MS disease activity.	NR
Rojas 2009 (Cochrane) Good	Adults (18-60 in one trial and 18-65 in another) with PPMS; EDSS 2.0-7.0 or 3.0-7.0	IFN β-1a IM at 30 µg or 60 µg dose vs placebo in one trial; IFN β-1b SQ at 8 MIU vs placebo in the other	1°- Progression of disability by EDSS score: IFN 1β - RR 0.89 (0.55,1.43), *P*=0.32 Trend in favor of IFN β-1b but overall NS change EDSS Mixed result - NS at 1 yr: mean difference -0.10 (-0.47 to 0.27) *P*=0.60; no difference at 2 yrs with mean difference -0.10 (-0.51 to 0.31) *P*=0.64	NR

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of β interferons

	Comments
Author	**Adverse events**
Goodin et al 2007 Fair-Good Methods of article selection not reported, very limited data on included studies	NR
Rojas 2009 (Cochrane)	2°- Severe AEs: no difference - IFN β-1a RR 0.80 (0.33,1.92) Any AE: RR 1.90 (1.45,2.48) Flu-like: RR 2.48 (1.60,3.83) ISR: RR 10.80 (3.34,35.03) Fatigue: NS RR 1.62 (0.68,3.85) Anemia: NS RR 2.51 (0.27,23.20) Leukopenia: RR 4.10 (1.34,12.57) Spasticity: no difference

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of glatiramer acetate

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Martinelli Boneschi 2003 Fair No systematic search for included studies; no quality assessment or data validation methods reported	To assess the efficacy of GA in treating the following outcomes in RRMS patients: annualized relapse rate, on-trial number of relapses, time to first relapse and accumulated disability and to explore the role of individual clinical variables as predictors of relapse rate and treatment efficacy	NR	DB, placebo-controlled RCTs assessing efficacy of GA	540	3 RCTs, described in 4 papers
Munari 2003 (Cochrane) Good	To determine efficacy and safety of GA in MS patients	1966-2004	RCTs, either single or double blind, of GA vs placebo in MS patients	646	4 RCTs, described in 17 papers (including 5 abstracts and 1 letter)

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of glatiramer acetate

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups
Martinelli Boneschi 2003 Fair No systematic search for included studies; no quality assessment or data validation methods reported	Adults (18-50 yrs) with RRMS with at least one (one study) or two (two studies) documented relapses within the previous 2 yrs with no clinical relapses in 30 days preceding study entry. EDSS between 0.0 and 5.0 (two studies) or 6.0 (one study)	GA: 20 mg/day self-administered SQ Placebo	Annualized relapse rate GA vs placebo: 0.82 vs 1.14 (*P*=0.004) Number of relapses: RR 0.64 (95 % CI, 0.52 to 0.78; *P*<0.0001) Time to first relapse GA vs placebo: 322 days vs 219 days (ratio 1.59; 95% CI, 1.16 to 2.19; *P*=0.005)	NR
Munari 2003 (Cochrane) Good	Adults (18-60 yrs) with RRMS (3 trials) and "chronic progressive" MS (Note: "Chronic progressive" refers to a combo of PPMS and SPMS) Concomitant meds included methylprednisolone and/or unspecified "standard steroids" as rescue therapy in all trials; "symptomatic" medication in 1 trial; "conventional" medication in 1 trial	GA: 20 mg/day self-administered SQ (RRMS) 30 mg bid self-administered SQ (CPMS) Placebo	Disease progression: 2 yrs - pooled RR of progression 0.77 (95% CI, 0.51 to 1.14; *P*=0.19) in RRMS patients and 0.69 (95% CI, 0.33 to 1.46; *P*=0.19) in CPMS. For all patients, regardless of MS type, RRMS 0.75 (95% CI, 0.53 to 1.07; *P*=0.11) Mean change in EDSS: 2 yr mean difference: -0.33 (95% CI, -0.58 to -0.08; *P*=0.01) in favor of GA in RRMS patients 35 mo mean difference: -0.45 (95% CI, -0.74 to -0.16; *P*=0.002) in favor of GA in RRMS patients Exacerbations: RRs of at least 1 exacerbation: 0.77 (0.61-0.99, *P*=0.04) within 1 yr of treatment 0.87 (0.74-1.02, *P*=0.08) at 2 yrs, and 0.89 (0.74-1.06; *P*=0.19) at 35 mos. Conclusion: No beneficial effect of GA use for main outcomes (disease progression and risk of relapse/exacerbations)	Relapse rate was higher for patients with higher BL EDSS regardless of treatment (GA or placebo). GA vs placebo Interpolated figures: EDSS 0-2: Relapse rate 0.7 vs 0.875 EDSS >2-4: Relapse rate 0.8 vs 1.15 EDSS >4: Relapse rate 0.9 vs 1.3

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of glatiramer acetate

Author Year	Adverse events	Comments
Martinelli Boneschi 2003 Fair No systematic search for included studies; no quality assessment or data validation methods reported	NR	
Munari 2003 (Cochrane) Good	WDs due to AEs: 10/269 (3.7%) for GA; 3/269 (1.1%) for placebo Serious AEs: none were described in any of the 4 trials. Non-serious AEs: Patterned reactions consisting of flushing, chest tightness, sweating, palpitations and anxiety in GA patients (RR 3.40; 2.22-5.21, *P*≤0.00001) Dizziness in GA patients (RR 1.96, 1.38-2.78, *P*=0.0002) Palpitations in GA patients (RR 2.23, 1.16-4.28, *P*=0.02) No difference between GA and placebo for other non-serious AEs	

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of mitoxantrone

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Martinelli Boneschi 2005 (Cochrane) Good	To assess efficacy and safety of MITO for RRMS, PRMS and SPMS	1966-2005	DB, placebo-controlled RCTs	270	4 studies: all DB, placebo-controlled RCTs; one study, identified as placebo-controlled, was of MITO + steroid vs steroid alone

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of mitoxantrone

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups
Martinelli Boneschi 2005 (Cochrane) Good	Adults (18-65 yrs) with diagnosis or RRMS or SPMS and clear disease progression based on EDSS scores. Disease duration was <10 yrs in two studies and unspecified in two studies. One study included patients identified as PRMS, however the description of disability described more closely matches the definition of worsening RRMS.	MITO Placebo	MITO vs placebo Disease progression: 1 yr results (data available from 51 patients, 1 study): 8 patients had disease progression (2/27 (7.4%) vs 6/24 (25%). Fixed effect model OR 0.24 (95% CI, 0.04 to 1.33; *P*=0.1) 2 yr results (data available from 179 patients in 2 studies): 27 patients had disease progression (6/90 (6.6%) vs 21/89 (23.6%)). Fixed effects OR 0.23 (95% CI, 0.09 to 0.59; *P*=0.0002) Mean change in EDSS: 1 yr results (data available from small (n=25) subgroup): NSD between treatments (mean difference -0.35; 95% CI, -0.86 to 0.16; *P*=0.18) 2 yr results (data from 175 patients): SS difference between treatments (mean difference -0.36; 95% CI, -0.7 to -0.02; *P*=0.04) Relapse rate: 6mo/1yr results: 45/93 (48.3%) of patients in 2 studies experienced no relapse (68.7% vs 28.8%) OR 5.4 (95% CI, 2.2 to 13.1; *P*=0.0002) 2 yr results: 79/179 (44.1%) of patients in 2 studies experienced no relapse (56.6% vs 31.4%) OR 3.11 (1.68-5.72, *P*=0.0003)	NR

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of mitoxantrone

Author Year	Adverse events	Comments
Martinelli Boneschi 2005 (Cochrane) Good	MITO vs placebo All WDs (include lost to FU): 33/139 (23.7%) vs 30/131 (22.9%) AE WDs: 13/139 (9.4%) vs 3/131 (2.3%) Specific AEs: Nausea/vomiting: 86/138 (62.3%) vs 20/130 (15.4%) Alopecia: 65/138 (47.1%) vs 25/130 (19.2%) UTI: 35/138 (25.4%) vs 14/130 (10.8%) Amenorrhea: OR 22.3 (4.0-123.0, *P*=0.0004) for MITO vs placebo-treated female patients; OR 8.3 (1.0-67.2, *P*=0.05) for persistent amenorrhea following end of therapy for MITO vs placebo-treated patients. Cardiac: decrease of LVEF below 50% in 5/138 patients (3.6%) of MITO patients OR 5.7 (95% CI, 0.7 to 48.4, *P*=0.11). No serious cardiac AEs reported in any MITO or placebo patients.	Some heterogeneity among studies regarding types of patients (diagnosis) and intervention schedules

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of immunomodulatory drugs for MS

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Clegg et al 2000, 2001 Fair-Good Summary of total number of included patients with detailed summary of their BL characteristics not included	To compare the clinical and cost effectiveness of various immunomodulatory treatments for MS	1980-2000	Previously conducted systematic reviews; comparative RCTs, including PCTs; cost utility studies	NR	7 PCTs of relevant interventions - IFN βs, GA and MITO (numerous other trials included relating to interventions outside the scope of this review)

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of immunomodulatory drugs for MS

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups
Clegg et al 2000, 2001 Fair-Good Summary of total number of included patients with detailed summary of their BL characteristics not included	Not prespecified although patients from included studies were a mix of RRMS and SPMS	IFN β-1a IFN β-1b GA MITO	No comparative analysis of effectiveness; summary of trial results presented and discussed within this review	NR

Evidence Table 1. Systematic reviews of disease-modifying drugs

Systematic reviews of immunomodulatory drugs for MS

Author Year	Adverse events	Comments
Clegg et al 2000, 2001 Fair-Good Summary of total number of included patients with detailed summary of their BL characteristics not included	No comparative analysis of AEs; summary of trial results presented and discussed within this review	

Evidence Table 2. Quality assessment of systematic reviews

Author, Year	Clear review question and inclusion/exclusion criteria?	Substantial effort to final all relevant research?	Validity of included studies adequately assessed?	Sufficient detail of individual studies?	Appropriate summary of primary studies?	Overall rating
Systematic reviews: PPMS and IFN						
Rojas, 2009	yes	yes	yes	yes	yes	Good

Evidence Table 3. Head-to-head trials of disease-modifying drugs

Study	Population type	Design	Recruitment	Eligibility
Cadavid 2009	RRMS or CIS	Randomized single-blind (assessor) head-to-head trial; 2 yrs	Screened: 168 Eligible: 98 Enrolled: 75 Withdrawn: 8 Lost to FU: 11 Analyzed: 75	Adults 18-55 yrs, RRMS or CIS, EDSS 0-5.5
Durelli 2002 Italy INCOMIN	RRMS	Open Parallel Multicenter Setting: NR	Screened: 205 Eligible: 188 Enrolled: 188 Withdrawn: 24 Lost to FU: 6 Analyzed: 188	Adults 18-50 yrs with clinically definite RRMS, baseline EDSS 1-3.5, two documented relapse in preceding 2 yrs with no relapse in 30 days prior to study
Etemadifar 2006 Iran	RRMS	Single-blind Parallel Multicenter Specialty clinic	Screened: NR Eligible: 90 Enrolled: 90 Withdrawn: 0 Lost to FU: 0 Analyzed: 90	Men and women of 15-50 yrs with a clinical or laboratory supported diagnosis of relapsing MS and with ≥2 relapses within the 2 yr period to treatment initiation documented by a neurologist and should have an EDSS score of ≤5

Evidence Table 3. Head-to-head trials of disease-modifying drugs

Study	Exclusion	Sample size, Age, Gender, Ethnicity
Cadavid 2009	Relapse before start of trial, inability to obtain MRI, pregnancy, allergy to study drug, heart disease, medically unstable, contraindicated to Tylenol or NSAIDs or steroids, inability to understand or be compliant, peptic ulcer disease, prior use of specified drugs, steroids within 21 days	N=75 (IFN β-1b: 36; GA: 36) Mean age: 36 (range 18-55) 69% female 31% male
Durelli 2002 Italy INCOMIN	Previous systemic IFN β treatment, immunosuppressive or immunomodulatory drugs except corticosteroids; pregnant or lactating women and/or unwillingness to practice birth control; major depression or suicide attempt; clinically significant heart, liver, renal or bone marrow disease	N=188 Mean age: 36 (range 18-50) 34.57% male 65.43% female
Etemadifar 2006 Iran	History of severe allergic or anaphylactic reaction to any IFN, or to other components of drug formulation; no evidence of neurologic, psychiatric, cardiac, endocrinologic, hematologic, hepatic, renal, active malignancy, auto immune diseases or other chronic diseases; history of an uncontrolled seizure or suicidal ideation or an episode of severe depression within 3 mos before enrollment; lactation and pregnancy as determined by history, physical examination and screening blood tests	N=90 Mean age (SD): 28.5 (7.0) (range 18-49) 24.44% male 75.56% female

Evidence Table 3. Head-to-head trials of disease-modifying drugs

Study	Population type	Design	Recruitment	Eligibility
Etemadifar 2007	RRMS	Single-blind (outcome assessor) x 52 weeks; computer randomization; IFN β - Betaferon, Avonex, Rebif vs AZA	Screened: 100 Eligible: 94 Enrolled: 94 Withdrawn: 6 (AE) Lost to FU: 0 Analyzed: 94	Men and women 13-50 yrs with RRMS, ≥2 relapses within 2 yr period, EDSS ≤5 with at least 2 yrs of disease
Koch-Henriksen 2006 Denmark Danish Multiple Sclerosis Study Group	RRMS	Single-blind Parallel Multicenter Research Center	Screened: NR Eligible: 421 Enrolled: 301 Withdrawn: 77 Lost to FU: NR	RRMS by Poser criteria or laboratory supportive of definitive MS, at least 2 relapses within 2 yrs prior to enrollment, stable symptoms for 30 days, 18-55 yrs, EDSS 0-5.5
Mikol 2008 REGARD TRIAL	RRMS	Randomized (computer generated stratified by center), open-label, multicenter; ITT, 96 weeks	Screened: 803 Eligible: 766 Enrolled: 766 Randomized: 764	RRMS, 18-60 yrs, treatment drug naïve, 81 centers in 14 countries, EDSS 0-5.5, ≥1 relapse in prior 1 yr, clinically stable x 4 weeks

Evidence Table 3. Head-to-head trials of disease-modifying drugs

Study	Exclusion	Sample size, Age, Gender, Ethnicity
Etemadifar 2007	Evidence of neurological, psychiatric, cardiac, endocrinological, hematological, hepatic, renal, pulmonary disease, active malignancy, auto-immune diseases, or other chronic diseases; history of uncontrolled seizure or suicidal ideation or an episode of severe depression within the 3 mos before enrollment; lactation and pregnancy as determined by history, physical exam, and screening blood tests	Betaferon n=15; Avonex n=19; Rebif n=13; AZA n=47 Iranian ethnicity Age: IFN 28.3; AZA 27.1 EDSS: IFN 1.6; AZA 1.4 IFN 25.5% male, AZA 17% male
Koch-Henriksen 2006 **Denmark** **Danish Multiple Sclerosis Study Group**	Pregnancy or risk of pregnancy, breast feeding, serious epilepsy, liver disease, prior treatment with IFN β-1b, hypersensitivity to IFN β, gentamicin or paracetamol	N=301 Mean age: 37 (range 18-55)
Mikol 2008 **REGARD TRIAL**	Pregnant or breast feeding, progressive MS, treatment with steroid or ACTH within 4 weeks, prior treatment with IFN β, GA or cladribine; total lymphoid irradiation, plasma exchange within prior 3 mos, IV gamma globulin in prior 6 mos, cytokine or anticytokine therapy within prior 3 mos, or immunosuppressant use in prior 12 mos	N=764 Median age 36.75 yrs 70.5% female 93.5% white

Evidence Table 3. Head-to-head trials of disease-modifying drugs

Study	Population type	Design	Recruitment	Eligibility
O'Connor 2009 BEYOND Trial	RRMS	RCT 2:2:1 - central SAS-based block randomization with regional stratification; evaluating physicians masked, patients and treating physicians unmasked to drug but masked to dose, multicenter - 198 centers in 26 countries; baseline EDSS 0-5; 2-3.5 yrs	Screened: 2447 Eligible: 2244 Enrolled: 2244 Withdrawn: 109 Lost to FU: 44 Analyzed: 2220 (24 did not receive treatment)	RRMS, 18-55, ≥1 relapse in 1 yr, EDSS 0-5.5, negative pregnancy and took contraception
Panitch 2002 USA, Canada, Europe EVIDENCE	RRMS	Single-blind Parallel Multicenter Research Center	Screened: 767 Eligible: 688 Enrolled: 677 Withdrawn: 46 Lost to FU: 1 Analyzed: 677	IFN-naïve, definite RRMS, EDSS 0-5.5, ≥2 exacerbations in past 2 yrs

Evidence Table 3. Head-to-head trials of disease-modifying drugs

Study	Exclusion	Sample size, Age, Gender, Ethnicity
O'Connor 2009 BEYOND Trial	Progressive MS, heart disease, treatment-experienced, severe depression, alcohol or drug misuse, prior suicide attempt or current ideation, liver or renal or bone marrow dysfunction, monoclonal gammaglobulinopathy, uncontrolled epilepsy, intolerance to any of drugs in the study, unable to have MRI, unable to administer drug	N=2220 Median age: 35 (range 27-43) 70% female 92% white Median EDSS: 2.3
Panitch 2002 USA, Canada, Europe EVIDENCE	Prior IFN use, cladribine or lymphoid irradiation, GA or cytokine therapy in past 3 mos, IVIG in past 6 mos, other immunomodulatory agents in past 12 mos	N=677 Mean age: 38 (range 18-55) 25.26% male 74.74% female 91% white

Evidence Table 3. Head-to-head trials of disease-modifying drugs

Study	Population type	Design	Recruitment	Eligibility
Schwid 2007 EVIDENCE trial	RRMS	Single-blind (outcome assessor) x 48-94 weeks (median 62 weeks) + median 34 weeks in crossover; randomized by computer with block design	Screened: 100 Eligible: 94 Enrolled: 94 Withdrawn: 6 (AE) Lost to FU: 0 Analyzed: 94	Men and women 13-50 yrs with RRMS, ≥2 relapses within 2 yr period, EDSS ≤5 with at least 2 yrs of disease

Evidence Table 3. Head-to-head trials of disease-modifying drugs

Study	Exclusion	Sample size, Age, Gender, Ethnicity
Schwid 2007 EVIDENCE trial	Evidence of neurological, psychiatric, cardiac, endocrinological, hematological, hepatic, renal, pulmonary disease, active malignancy, auto-immune diseases, or other chronic diseases; history of uncontrolled seizure or suicidal ideation or an episode of severe depression within the 3 mos before enrollment; lactation and pregnancy as determined by history, physical exam, and screening blood tests	Rebif vs Avonex Randomized: 339 vs 338 Completed comparative phase: 299 vs 306 Entered crossover phase: 272 vs 223 Completed crossover phase: 249 vs 190 Mean age: 38.3 vs 37.4 Percent female: 74.9% vs 74.6% Percent white: 92.3% vs 89.6%

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Dosage, Population	Outcomes	Withdrawals
Cadavid 2009	IFN β-1b 250 µg qod (Betaseron) vs GA 20 mg qd RRMS or CIS, Rx naïve n=75 (IFN β-1b n=36 and GA n=39) ITT IFN β-1b vs GA Median ARR: 1.8 vs 1.9 EDSS: 2.0 vs GA 2.7	1° - MRI lesions; 2° - clinical exacerbations IFN β-1b vs GA Annualized RR: 0.37 vs 0.33, *P*=0.68 Relapse Free N (%): 19 (53%) vs 28 (72%)	Total WDs: 8 AE WDs: 1 Lost to FU: 11
Durelli 2002 Italy INCOMIN Efficacy Quality: Fair AE quality: Poor	IFN β-1a (Avonex) 30 µg (6MIU) once a week for 24 mos N=92 Male: 35 (38%) Female: 57 (62%) Mean age (SD): 35 (7.9)	EDSS increase of at least 1.0 or more or 0.5 or more: 28 (20%) Mean change in EDSS: -0.54 Mean EDSS scores (SD): 2.5 (1.1) Annualized relapse rate (SD): 0.7 (0.9), *P*=0.3 Mean rate of steroid use per relapse (SD): 0.5 (0.8) Relapse-free patients: 33 (36%), *P*=0.03	Total WDs: 19 (20.6%) AE WDs: 1 (1%)
Durelli 2002 Italy INCOMIN Efficacy Quality: Fair AE quality: Poor	IFN β-1b (Betaseron) 250 µg (8MIU) qod for 24 mos N=96 Male: 30 (31%) Female: 66 (69%) Mean age (SD): 39 (7.1)	EDSS increase of at least 1.0 or more or 0.5 or more: 13 (13%) Mean change in EDSS: -0.13 Mean EDSS scores (SD): 2.1 (1.0) Annualized relapse rate (SD): 0.5 (0.7), *P*=0.03 Mean rate of steroid use per relapse (SD): 0.38 (0.62) Relapse-free patients: 49 (51%), *P*=0.03	Total WDs: 11 (11.5%) AE WDs: 5 (5.2%)

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Adverse events	Comments
Cadavid 2009	NR	
Durelli 2002 Italy INCOMIN Efficacy Quality: Fair AE quality: Poor	Abnormal LFT: 23/88 (26.1%) Depression: 18/88 (20.5%) Fatigue/Tiredness: 52/88 (59.1%) Fever: 63/88 (71.6%) Flu-like illness: 68/88 (77.3%) Headache: 6/88 (6.8%) Injection site reactions (e.g. bleeding): 7/88 (8%)	On outcome: Time to sustained progression 1b > 1a, *P*<0.01 On AE: AE analysis is based only on patients completing FU
Durelli 2002 Italy INCOMIN Efficacy Quality: Fair AE quality: Poor	Abnormal LFT: 22/94 (23%) Depression: 18/94 (19.1%) Fatigue/Tiredness: 45/94 (47.9%) Fever: 69/94 (73.4%) Flu-like illness: 72/94 (76.6%) Headache: 15/94 (16%) Injection site reactions (e.g. pain): 35/94 (37.2%)	

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Dosage, Population	Outcomes	Withdrawals
Etemadifar 2006 Iran Efficacy quality: Fair AE quality: Poor	IFN β-1a (Avonex) Injection 30 µg once a week for 24 mos N=30 Male: 6 (27%) Female: 24 (35%) Mean age (SD): 28 (1.2)	Mean change in EDSS: 0.1; 95% CI, -0.2 to 0.5 Mean EDSS scores (SD): 1.8 (1.4) Mean change in relapses per person-yr: 0.8, *P*≤0.001; 95% CI, 0.5 to 1.2 Relapse-free patients: 6 (20%)	Total WDs: NR AE WDs: NR
Etemadifar 2006 Iran Efficacy quality: Fair AE quality: Poor	IFN β-1a (Rebif) Injection 44 µg three times a week for 24 mos N=30 Male: 7 (32%) Female: 23 (34%) Mean age (SD): 27 (1.4)	Mean change in EDSS: 0.3 at 24 mos, *P*≤0.05; 95% CI, 0.03 to 0.5 Mean EDSS scores (SD): 1.8 (1.2) Mean change in relapses per person-yr: 1.8, *P*≤0.001; 95% CI, 1.3 to 2.2 Relapse-free patients: 17 (57%)	Total WDs: NR AE WDs: NR
Etemadifar 2006 Iran Efficacy quality: Fair AE quality: Poor	IFN β-1b (Betaseron) Injection 250 µg qod for 24 mos N=30 Male: 9 (41%) Female: 21 (31%) Mean age (SD): 30 (1.4)	Mean change in EDSS: 0.7, *P*≤0.001; 95% CI, 0.5 to 0.9 Mean EDSS scores (SD): 1.2 (0.6) Mean change in relapses per person-yr: 1.5, *P*≤0.001; 95% CI, 1.2 to 1.8 Relapse-free patients: 13 (43%)	Total WDs: NR AE WDs: NR

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Adverse events	Comments
Etemadifar 2006 Iran Efficacy quality: Fair AE quality: Poor	NR. See comments.	On population: Mean age is for onset of MS, not at the time of study. Age at time of study NR. On outcome: ANOVA analysis of EDSS at end of trial indicated all groups improved significantly (*P*<0.001), but significant differences were found between the drugs, favoring IFN β-1b, but p-value not reported. On AE: IFN products were well tolerated and most of the AEs reported were mild in severity.
Etemadifar 2006 Iran Efficacy quality: Fair AE quality: Poor	NR	
Etemadifar 2006 Iran Efficacy quality: Fair AE quality: Poor	NR	

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Dosage, Population	Outcomes	Withdrawals
Etemadifar 2007	IFN β: n=44 (Betaferon n=15, Avonex n=19, Rebif n=13) AZA: n=44 RRMS	RR: IFN β 0.64, AZA 0.28, *P*<0.05 EDSS: IFN β -0.30 units, *P*<0.05; AZA -0.46 units, *P*<0.001; Betaferon -0.1 units, NS; Avonex -0.2 units, NS; Rebif -0.4 units, *P*=0.05; AZA -0.4 units, *P*<0.001	WD due to AE: AZA 6.4% vs IFN β 6.4%

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Adverse events	Comments
Etemadifar 2007	AZA vs IFN β Severe nausea: 4.3% vs 0.0% Severe headaches: 2.1% vs 0.0% GI side effects: 2.1% vs 4.3% Severe depression: 0.0% vs 2.1% Flu-like side effects: 0.0% vs 4.3%	

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Dosage, Population	Outcomes	Withdrawals
Koch-Henriksen 2006 **Denmark Danish Multiple Sclerosis Study Group** Efficacy quality: Fair AE quality: Poor	IFN β-1a (Rebif) 22 µg weekly N=143 Mean age: 37 Ratio of female to male=1.83:1 Relapses in previous 2 yrs mean: 3.2 (range 2-15) EDSS at BL mean: 2.98	EDSS increase of at least 1.0 or more or 0.5 or more: 36 (25.1%) at 2 yrs Time to confirmed progression: 651 days Annual exacerbation rates (per patient-year): 0.66 at 2 yrs; 95% CI, 0.52 to 0.83 Annual exacerbation rates (per patient-year): 0.71 at yrs 1 and 2; 95% CI, 0.61 to 0.82 Annual exacerbation rates (per patient-year): 0.74 at 1 yrs; 95% CI, 0.60 to 0.90 Exacerbation requiring hospitalization: 0.17 at 2 yrs; 95% CI, 0.12 to 0.23 Mean rate of steroid use per relapse: 0.21 at 2 yrs; 95% CI, 0.16 to 0.28 Median Time to first relapse (days): 450	Total WDs: 33 (23%) AE WDs: 18 (12.5%)
Koch-Henriksen 2006 **Denmark Danish Multiple Sclerosis Study Group** Efficacy quality: Fair AE quality: Poor	IFN β-1b (Betaseron) 250 µg qod N=158 Mean age: 38 Ratio of female to male=1.83:1 Relapses in previous 2 yrs mean: 3.04 (range 2-8) EDSS at BL mean: 2.82 (range 0-5.5)	EDSS increase of at least 1.0 or more or 0.5 or more: 33 (20.9%) at 2 yrs Time to confirmed progression: 645.6 days Annual exacerbation rates (per patient-year): 0.70 at 1+2 yr; 95% CI, 0.60 to 0.81 Annual exacerbation rates (per patient-year): 0.76 at 1 yr; 95% CI, 0.63 to 0.92 Annual exacerbation rates (per patient-year): 0.66 at 2 yrs; 95% CI, 0.52 to 0.82 Exacerbation requiring hospitalization: 0.19 at 2 yrs; 95% CI, 0.14 to 0.25 Mean rate of steroid use per relapse: 0.20 at 2yrs; 95% CI, 0.15 to 0.27 Median Time to first relapse (days): 431	Total WDs: 44 (28%) AE WDs: 24 (15.2%)

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Adverse events	Comments
Koch-Henriksen 2006 Denmark Danish Multiple Sclerosis Study Group Efficacy quality: Fair AE quality: Poor	Depression: 12/301 (4%) Fever: 14/301 (4.7%) Flu-like illness: 29/301 (9.6%) AE data reported only for combined groups, stated to be NS between groups	On design: Those who qualified but refused randomization were given IFN β and followed as well. On population: Ratio of female to male=1.83:1; Mean relapses in previous 2 yrs (range): IFN β-1a 3.2 (2-15), IFN β-1B: 3.04 (2-8); Mean EDSS at BL (range): IFN β-1a 2.98 (0-5.5), IFN β-1b 2.82 (0-5.5) On outcome: Annualized relapse rate IFN β-1b vs 1a: 1 yr P=0.86, 2 yr P=0.97; Time to first relapse IFN β-1a vs 1b: HR 0.98 (0.72-1.32); Time to sustained progression IFN β-1a vs 1b: HR 0.905 (0.56-1.45). Multivariate regression: age, gender, center not found SS.
Koch-Henriksen 2006 Denmark Danish Multiple Sclerosis Study Group Efficacy quality: Fair AE quality: Poor	Depression: 12/301 (4%) Fever: 14/301 (4.7%) Flu-like illness: 29/301 (9.6%) AE data reported only for combined groups, stated to be NS between groups	

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Dosage, Population	Outcomes	Withdrawals
Mikol 2008 REGARD TRIAL	Rebif vs GA RRMS, ≥1 relapse prior 1 yr	NSD on all measures Time to first relapse: No difference HR 0.94 (0.74,1.21), *P*=0.64 IFN vs GA Percent free of relapse: 62% vs 62%, NS ARR: 0.30 vs 0.29, NS Percent EDSS progression: 11.7% vs 8.7%, NS Annualized steroid use: 0.19 vs 0.17, NS	WDs including due to AE: 139 WDs due to AE: Rebif 23, GA 19 Lost to FU: 19
O'Connor 2009 BEYOND Trial	IFN β-1b 250 µg or 500 µg qod vs GA 20 mg qd 1° Relapse risk (new or recurrent symptoms lasting >24 hours and separated by 30 days) 2° EDSS and MRI lesions RRMS, Rx naïve N=2244 (IFN β-1b 250 µg n=897; IFN β-1b 500 µg n=899; and GA n=448) ITT for AE but uncertain for outcomes IFN β-1b 250 µg vs IFN β-1b 500 µg vs GA Median ARR: 1.6 vs 1.6 vs 1.6 EDSS: 2.35 vs 2.33 vs 2.28	HR: IFN β-1b 500 µg vs 250 µg: 0.93 (0.81-1.07), P=0.16; IFN β-1b 500µg vs GA 0.98 (0.82-1.18), P=0.43; IFN β-1b 250µg vs GA 1.06 (0.89-1.26), P=0.73 ARR: IFN β-1b 500 µg vs 250 µg: P=0.1.0; IFN β-1b 500 µg vs GA: P=0.42; IFN β-1b 250 µg vs GA: P=0.79, NS	WDs including due to AE: 336 Lost to FU: 44

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Adverse events	Comments
Mikol 2008 REGARD TRIAL	Rebif vs GA Abnormal LFT: 21/381 (6%) vs 5/375 (1%), P=0.002 Depression: 30/381 (8%) vs 22/375 (6%), NS Fatigue/Tiredness: NR Fever: 23/381 (6%) vs 15/375 (4%), NS Flu-like illness: 119/381 (31%) vs 5/375 (1%), P<0.0001 Headache: 74/381 (19%) vs 35/375 (9%), P<0.0001 Injection site reaction: Pruritus- 8/381 (2%) vs 75/375 (20%), P<0.0001; Swelling- 4/381 (1%) vs 42/375 (11%), P<0.0001 Total patients reporting any AE: 632 of 1880 events (34%) vs 618 of 1917 events (32%), NS	
O'Connor 2009 BEYOND Trial	IFN β-1b: higher flu-like symptoms (*P*<0.0001), elevated LFT's (*P*<0.0001), pyrexia (*P*=0.003), insomnia (*P*=0.005) GA: ISR higher (*P*=0.0005)	

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Dosage, Population	Outcomes	Withdrawals
Panitch 2002 **USA, Canada, Europe** **EVIDENCE** Efficacy quality: Fair AE quality: Poor/Fair	IFN β-1a (Avonex) 30 µg once weekly N=338 Mean age: 37 Mean EDSS: 2.0 Median (mean) duration of MS: 4 yrs (6.6) Median (mean) number of relapses in 2 yrs: 2.0 (2.6)	Proportion of patients with EDSS deterioration: 49% at 48 weeks Proportion of patients with EDSS deterioration: 17% at 60 weeks NAb: 7/330 (2%) at 48 weeks Annual rate of 1-point EDSS progressions: 0.28 at 60 weeks Annualized relapse rate: 0.65 at 60 weeks Mean rate of steroid use per relapse: 0.19 at 24 weeks Mean relapse rate: 0.40 at 24 weeks Mean relapse rate: 0.64 at 48 weeks Median Time to first relapse (days): 6.7 at 60 weeks Proportion of relapse-free patients: 63% (214/338) at 24 weeks Proportion of relapse-free patients: 52% (177/338) at 48 weeks Proportion of relapse-free patients: 48% at 60 weeks	Total WDs: 21 (6.2%) AE WDs: 14 (4.1%)

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Adverse events	Comments
Panitch 2002	Abnormal LFT: 10/337 (3%)	On outcome: Relapse free at 24 weeks: OR adjusted for Center = 1.9 (1.3-2.6)
USA, Canada, Europe	Depression: 18/337 (5.3%)	
EVIDENCE	Fatigue/Tiredness: 20/337 (5.9%)	
	Fever: 8/337 (2.4%)	Time to first relapse: HR 0.70 (0.55-0.98) 44 µg/30 µg
	Flu-like illness: 53/337 (15.7%)	
	Injection site inflammation: 9/337 (2.7%)	
Efficacy quality: Fair	Injection site pain: 10/337 (3%)	
	Injection site reactions (e.g.bleeding): 33/337 (9.8%)	
AE quality: Poor/Fair	Lymphopenia: 5/337 (1.5%)	

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Dosage, Population	Outcomes	Withdrawals
Panitch 2002 **USA, Canada, Europe** **EVIDENCE** Efficacy quality: Fair AE quality: Poor/Fair	IFN β-1a (Rebif) 44 µg three times weekly N=339 Mean age: 38	Proportion of patients with EDSS deterioration: 43% at 48 weeks Proportion of patients with EDSS deterioration: 16% at 60 weeks NAb: 84/335 (25%) at 48 weeks Annualized relapse rate: 0.54 at 60 weeks Mean annual rate of steriod courses: 0.19 at 60 weeks Mean rate of steroid use per relapse: 0.12 at 48 weeks Mean relapse rate: 0.29 at 24 weeks Mean relapse rate: 0.54 at 48 weeks Median Time to first relapse (days): 13.4 at 60 weeks Median Time to first relapse (days): HR 0.70 at 60 weeks, *P*=0.002; 95% CI, 0.50 to 0.88 Proportion of relapse-free patients: 75% (254/339) at 24 weeks Proportion of relapse-free patients: 62% (209/339) at 48 weeks Proportion of relapse-free patients: 56% at 60 weeks Proportion of relapse-free patients: OR 1.5 at 60 weeks, *P*=0.023; 95% CI, 1.1 to 2.0	Total WDs: 25 (7.4%) AE WDs: 16 (4.7%)

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Adverse events	Comments
Panitch 2002	Abnormal LFT: 18/339 (5.3%)	
USA, Canada, Europe	Depression: 17/339 (5%)	
EVIDENCE	Fatigue/Tiredness: 18/339 (5.3%)	
	Fever: 6/339 (1.8%)	
Efficacy quality: Fair	Flu-like illness: 45/339 (13.3%)	
	injection site inflammation: 35/339 (10.3%)	
AE quality: Poor/Fair	ISP: 19/339 (5.6%)	
	ISR (e.g.bleeding): 85/339 (25.1%)	
	Lymphopenia: 14/339 (4.1%)	

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Dosage, Population	Outcomes	Withdrawals
Schwid 2007 EVIDENCE trial	IFN β-1a: Rebif 44 µg SQ three times weekly vs Avonex 30 µg IM per week with a subsequent crossover from Avonex to Rebif x 8 mos RRMS: 18-55 yrs, ≥2 relapses in 2 years EDSS: 0-5.5 N=677 in 56 sites in 10 countries Rebif vs Avonex Randomized=339 vs 338 Patients who continued treatment throughout the comparative phase: 299 (88.2%) vs 306 (90.5%) Patients entering crossover phase: 272 (80.2%) vs 223 (66%) ITT performed	1° - proportion relapse free: Rebif adjusted OR 1.5 (1.1-2.0), *P*=0.023 2° - ARR: Rebif -17%, *P*=0.033 Time to first relapse: Rebif HR 0.70, *P*=0.002 EDSS change: No difference Crossover: 50% decrease in mean relapse rate, *P*<0.001 Those continuing on Rebif had a 26% reduction, *P*=0.028 Steroid course per patient per year: Rebif 0.19, Avonex 0.28, *P*=0.009	72 during comparative phase, 45 during crossover phase

Evidence Table 4. Effectiveness and adverse events in head-to-head trials

Study	Adverse events	Comments
Schwid 2007 **EVIDENCE trial**	Injection site reactions more common with Rebif 85% vs 33%, *P*<0.001 NAb higher with Rebif 26% vs 3%, *P*<0.001, and occurred earlier Discontinued due to AE: Rebif 5.6% vs Avonex 5.3%	Not a true crossover as all took Rebif.

Evidence Table 5. Active-control and placebo-controlled trials for interferon beta 1a

Study	Population type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Andersen 2004 **Multiple European Countries**	SPMS	DB Parallel Multicenter Setting: NR	Screened: NR Eligible: NR Enrolled: 371 Withdrawn: 63 Lost to FU: NR Analyzed: 301	18-65 yrs of age, diagnosis of clinically definite MS for at least 1 yr, classified as SPMS with an EDSS score <7.0, prior history of RRMS and had experienced progressive deterioration of disability for at least 6 mos, with an increase of at least 1.0 point on the EDSS in the previous 4 yrs (or 0.5 point if the entry EDSS score was 6.0 or 6.5), with or without superimposed exacerbations, stable neurological condition for the 4 weeks preceding study day 1	Similar to those used in previous IFN β trials (no further criteria specified by authors)	N=371 Mean age: 45.7 (range 18-65) 60% female 40% male
Cohen 2002 **US, Canada, Europe** **IMPACT**	SPMS	DB Parallel Multicenter Setting: Research Center	Screened: NR Eligible: NR Enrolled: 436 Withdrawn: 115 Lost to FU: 5 Analyzed: 321	Clinically definite SPMS with or without recent relapses, disease progression over the previous yr, cranial MRI demonstrating lesions consistent with MS, EDSS 3.5-6.5, age 18-60 yrs	Primary progressive course, inability to perform the component tests of the MSFC at BL, prior treatment with IFN β	N=436 Mean age: NR Gender NR
Comi; Fillipi 2001; 2004 **Multiple European Countries**	CIS	DB Parallel Multicenter Setting: Specialty Clinic	Screened: 375 Eligible: NR Enrolled: 309 Withdrawn: 31 Lost to FU: NR Analyzed: 308	Clinical syndromes indicating unifocal or multifocal involvement of the CNS, age 18-40 yrs, first neurological episode suggestive of MS in 3 mos prior to study entry, one or more abnormalities in neurological exam, positive MRI brain scan	Previous immunosuppressive or immunomodulatory treatment, participation in an experimental procedure during yr before study, other serious intercurrent systemic illness or psychiatric disorders, pregnancy, unwillingness to use reliable contraception	N=309

Evidence Table 5. Active-control and placebo-controlled trials for interferon beta 1a

Study	Population type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Investigators, 2008 CAMMS223 trial	RRMS	RCT 1:1:1 (algorithm), open-label with blinded assessors	Screened: NR Eligible: NR Enrolled: 334 Randomized: 334 Withdrawn:6 Lost to FU: 6 Analyzed: 333	RRMS with symptom onset ≤36 mo before screening, ≥2 episodes in 2 yrs, EDSS 0-3.0, ≥1 MRI lesions	Prior DMD treatments, history of significant autoimmunity, precense of antithyrotropin-receptor antibodies	N=334 (IFN 111, AL 12 mg 113, AL 24 mg 110) Mean age: 32.1 (range 18-54) 64% female 90.1% white EDSS 2.0 +/- 0.74
Jacobs 2000	RRMS	DB Multicenter Setting: Specialty Clinic	Screened: NR Eligible: NR Enrolled: 301 Withdrawn: NR Lost to FU: NR Analyzed: 301	Definite MS for at least 1 yr, BL EDSS of 1.0-3.5 inclusive, at least two documented exacerbations in the prior 3 yrs, no exacerbations for at least 2 mos at study entry, age 18-55 yrs	NR	N=301 Mean age: NR Gender NR
Jacobs et al 1996 USA	RRMS	DB Parallel Multicenter Setting: Research Center	Enrolled: 301	Definite MS for at least 1 yr, BL EDSS of 1.0-3.5 inclusive, at least two documented exacerbations in the prior 3 yrs, no exacerbations for at least 2 mos at study entry, age 18-55 yrs	Prior immunosuppressant or IFN therapy, ACTH or corticosteroid treatment within 2 mos of study entry, pregnancy or nursing, an unwillingness to practice contraception, the presence of CPMS, or any disease other than MS compromising organ function	N=301 Mean age (SD): 36.8 (7.4) (range 16-55) 73.42% female 26.58% male 92% white 7% black 0% Asian 0% Hispanic 2% other
Leary 2003 UK	PPMS	DB Parallel Single Center Setting: Research Center	Screened: 57 Eligible: NR Enrolled: 50 Withdrawn: 7 Lost to FU: 0 Analyzed: 49	PPMS of at least 2 yrs' duration, age 18-60 yrs, EPSS score 2-7 inclusive	IFN, immunosuppressant, or chronic steroid therapy within the previous 3 mos; pregnancy or lactation; seizure within the previous 3 mos; history of severe depression	N=50 Mean age: 45 (range 25-59) 64% male 36% female

Evidence Table 5. Active-control and placebo-controlled trials for interferon beta 1a

Study	Population type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Liu 1999 PRISMS	RRMS	DB Parallel Multicenter Setting: Research Center	Enrolled: 560 Analyzed: 533	See PRISMS(1), 1998	See PRISMS(1), 1998	See PRISMS(1), 1998
Liu (2) 2002 PRISMS (Re-analysis of PRISMS)	See PRISMS(1), 1998	See PRISMS (1), 1998	See PRISMS(1), 1998	See PRISMS(1), 1998	See PRISMS(1), 1998	N=560
Miller 2006 USA, Canada IMPACT	SPMS	DB Parallel Multicenter Setting: Research Center	See Cohen, 2002	See Cohen, 2002	See Cohen, 2002	N=324
MS Collaborative Research Group (2) 1995 USA MSCRG	RRMS	DB Parallel Multicenter Setting: Research Center	See Jacobs, 1996	Males and females between the ages of 18-55, definite diagnosis of MS of at least 1 yr duration, exacerbating-remitting MS, at least 2 exacerbations in the 3 yrs before study entry, patients with disease duration <3 yrs must have had at least 1 exacerbation per yr prior to study entry, free of exacerbations for at least 2 mos before study entry, Kurtzke EDSS ≥1.0 but ≤3.5, capable of understanding and complying with protocol, pre-study exacerbation rates of at least 0.67 per yr	Prior therapy with immunosuppressant drugs (e.g. CPA, AZA), prior treatment with IFN, treatment with ACTH or corticosteroids within 2 mos before study entry, concurrent infection, the presence of any serious disease other than MS requiring specific treatment or compromising organ system function, CPMS, pregnant women or nursing mothers, unwilling to practice a form of contraception during the study that is acceptable to the investigator	N=301 Mean age (SD): 36.8 (7.4) (range 16-55) 73.09% female 26.91% male 92% white

Evidence Table 5. Active-control and placebo-controlled trials for interferon beta 1a

Study	Population type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
MS Collaborative Research Group (3) 1997 USA MSCRG **(Post-hoc analysis)**	RRMS	DB Parallel Multicenter Setting: Research Center	Enrolled: 301	See Jacobs, 1996	See Jacobs, 1996	See Jacobs et al, 1995 & 1996
Oger 2005 PRISMS **(Analysis of PRISMS data)**	RRMS	DB Crossover Multicenter Setting: Research Center	Screened: 187 Eligible: 177 Enrolled: 172 Withdrawn: 36 Lost to FU: 1 Analyzed: 172	See PRISMS, 1998	See PRISMS, 1998	N=187
OWIMS Study Group 1999 OWIMS Study	RRMS	DB Multicenter Setting: Research Center	Screened: NR Eligible: NR Enrolled: 293 Withdrawn: 22 Lost to FU: 1 Analyzed: 293	Clinically definite or laboratory supported definite RRMS of at least 1 yr's duration and Kuirtzke EDSS scores of 0-5.0, one relapse in the prior 24 mos but not in the 8 weeks before entry, at least 3 lesions consistent with MS on a screening MRI, no corticosteroids within 8 weeks of study start	Prior IFN, CPA, or lymphoid irradiation treatment; any immunosuppressive or experimental therapies in the preceding 12 mos; pregnancy or lactation; severe medical or psychiatric illness	N=293 Mean age (SD): 35.2 (7.6) (range 18-50) 72.7% female 27.3% male
Patten 2002 SPECTRIMS Trial	SPMS	DB Parallel Multicenter Setting: NR	See SPECTRIMS, 2001	See SPECTRIMS, 2001	See SPECTRIMS, 2001	N=365 Mean age (SD): 42.6 (range 19-55) 63.56% female 36.44% male

Evidence Table 5. Active-control and placebo-controlled trials for interferon beta 1a

Study	Population type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
PRISMS (1) 1998 Multiple (Europe, North American & Australia)	RRMS	DB Parallel Multicenter Setting: Research Center	Screened: NR Eligible: NR Enrolled: 560 Withdrawn: 31 Lost to FU: 27 Analyzed: 502	Adults with relapsing/remitting MS that had had at least 2 relapses in the preceding 2 yrs, EDSS scores of 0-5.0, had clinically definite or laboratory-supported definite MS of at least 1 yr's duration	Any previous systemic treatment with IFNs, lymphoid irradiation, or CPA, or with other immunomodulatory or immunosuppressive treatments in the preceding 12 mos	N=560 Mean age (SD): 34.9 (range 29.1-40.4) 68.93% female 31.07% male
SPECTRIMS 2001	SPMS	DB Parallel Multicenter Setting: NR	Screened: NR Eligible: NR Enrolled: 618 Withdrawn: 112 Lost to FU: 47 Analyzed: 506	Clinically definite SPMS defined as progressive deterioration of disability for at least 6 mos with an increase of at least 1 EDSS point over the last 2 yrs (or 0.5 point between EDSS score)	Immunosuppressive or immunomodulatory treatments during the previous 3 to 12 mos depending on the drug, prior treatment with IFN or total lymphoid irradiation, corticosteroid use or a disease exacerbation in the previous 8 weeks	N=506 Mean age (SD): 42.8 (7.1) (range 18-55) 63% female 37% male

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Andersen 2004 Multiple European Countries Efficacy quality: Good AE quality: Fair	IFN β-1a (Rebif) Injection 22 µg weekly, over 3 yrs N=186 Male: 74 (40%) Female: 112 (60%) Mean age: 45 µ	Total WDs: 38 (20.4%) AE WDs: NR	Annualized relapse rate: 0.25 (RR 0.90) at 3 yrs, *P*= 0.55; 95% CI, 0.64 to 1.27 Proportion of relapse-free patients: 61% (OR=1.03) at 3 yrs, *P*=0.89; 95% CI, 0.67 to 1.58 Proportion of relapse-free patients (men): 60%, (OR=0.68) at 3 yrs, *P*=0.27; 95% CI, 0.34 to 1.36 Proportion of relapse-free patients (women): 62% (OR=1.14) at 3 yrs, *P*= 0.65; 95% CI, 0.65 to 1.98

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Andersen 2004 **Multiple European Countries** Efficacy quality: Good AE quality: Fair	Abnormal LFT: 6/186 (3.2%) Depression: 37/186 (19.9%) Fatigue/Tiredness: 35/186 (18.8%) Fever: 19/186 (10.2%) Flu-like illness: 69/186 (37.1%) Headache: 67/186 (36%) Injection site inflammation: 58/186 (31.2%) ISRs (e.g. bleeding): 50/186 (26.9%) Lymphopenia: 2/186 (1.1%) Weakness/muscle weakness: 28/186 (15.1%)	On outcome: Time to progression based on change in EDSS, INF-1a vs placebo: HR=1.13, 0.82-1.57; P=0.45 Increase in RFSS INF-1a vs placebo: 80/146 (43%) vs 79/178 (44%) Time to progression based on change in RFSS: HR=0.93, 0.68-1.28; P=0.67 Subgroup analysis of previous relapsers vs non-relapsers in 4 yrs preceding study found NSD in treatment effect between groups regardless of intervention On population: Demographic characteristic were similar between the 2 groups. Placebo patients had a longer duration of SPMS, and a larger BL EDSS and AI. The difference for duration of SPMS was significant (P=0.03). However author reports that the duration of SPMS did not significantly affect the primary outcome, nor the treatment impact on primary outcome. On intervention: Mean BL values, INF-1a vs placebo EDSS: 4.7 vs 5.0 Relapses 4 yrs preceding study: 1.7 vs 1.6 In case of toxicity, the dose could be reduced or treatment interrupted according to protocol. Steroids were to be given only for disabling acute exacerbations.

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Andersen 2004 **Multiple European Countries** Efficacy quality: Good AE quality: Fair	Placebo Injection weekly, over 3 yrs N=178 Male: 71 (40%) Female: 107 (60%) Mean age: 46	Total WDs: 25 (14%) AE WDs: NR	Annualized relapse rate: 0.27 at 3 yrs Proportion of relapse-free patients: 62% at 3 yrs Proportion of relapse-free patients (men): 67% at 3 yrs Proportion of relapse-free patients (women): 58% at 3 yrs
Cohen 2002 **US, Canada, Europe** **IMPACT** Efficacy quality: Good AE quality: Fair	IFN β-1a (Avonex) Injection 60 µg weekly, over 24 mos N=217 Male: 76 (36%) Female: 138 (64%) Mean age (SD): 47 (8.2)	Total WDs: 29 (13%) AE WDs: 5 (2.3%)	Mean change in EDSS: 0.258 at 24 mos Mean change in MSFC: -0.362 at 24 mos, *P*=0.333 Annualized relapse rate: 0.20 at 24 mos, *P*=0.008 Mean annual rate of steroid courses: 0.19 at 1 yr, *P*=0.030

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Andersen 2004 **Multiple European Countries** Efficacy quality: Good AE quality: Fair	Abnormal LFT: 0/178 (0%) Depression: 25/178 (14%) Fatigue/Tiredness: 23/178 (12.9%) Fever: 7/178 (3.9%) Flu-like illness: 39/178 (21.9%) Headache: 36/178 (20.2%) Injection site inflammation: 3/178 (1.7%) ISRs (e.g. bleeding): 14/178 (7.9%) Lymphopenia: 4/178 (2.2%) Weakness/muscle weakness: 14/178 (7.9%)	
Cohen 2002 **US, Canada, Europe** **IMPACT** Efficacy quality: Good AE quality: Fair	Total patients reporting any AE: 215/217 (99%) Flu-like illness: 151/217 (70%) Headache: 106/217 (49%) Myalgia: 65/217 (30%) Depression: 56/217 (26%) UTI: 54/217 (25%) Arthralgia (joint pain): 52/217 (24%) Fever: 38/217 (18%)	On population: The authors state that the subjects in this trial were similar to those of the North American IFN β-1b study and SPECTRIMS On intervention: Mean BL values, INF-1a vs placebo EDSS: 5.2 vs 5.2 Relapses 3 yrs preceding study: 1.5 vs 1.3 Disease duration: 16.2 vs 16.7

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Cohen 2002 **US, Canada, Europe** **IMPACT** Efficacy quality: Good AE quality: Fair	Placebo Weekly, over 24 mos N=219 Male: 78 (36%) Female: 141 (64%) Mean age (SD): 48 (7.7)	Total WDs: 23 (10.5%) AE WDs: 4 (1.8%)	Mean change in EDSS: 0.272 at 24 mos Mean change in MSFC: -0.495 at 24 mos Annualized relapse rate: 0.30 at 24 mos Mean annual rate of steroid courses: 0.26 at 1 yr
Comi; Fillipi 2001; 2004 **Multiple European Countries** Efficacy quality: Good AE quality: Fair	IFN β-1a (Rebif) N=154 Male: 60 (39%) Female: 94 (61%) Mean age (SD): 29 (6.0)	Total WDs: 13 (8%) AE WDs: NR	Number of patients converting to MS: 52 (34%) at 2 yrs, *P*=0.047 Time to conversion for CIS to MS: 569 days, *P*=0.034 Annualized relapse rate: 0.33 at 2 yrs, *P*=0.045

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Cohen 2002 **US, Canada, Europe** **IMPACT** Efficacy quality: Good AE quality: Fair	Total patients reporting any AE: 215/218 (99%) Flu-like illness: 72/218 (33%) Headache: 107/218 (49%) Myalgia: 67/218 (31%) Depression: 49/218 (22%) UTI: 45/218 (21%) Arthralgia (joint pain): 43/218 (20%) Fever: 16/218 (7%)	
Comi; Fillipi 2001; 2004 **Multiple European Countries** Efficacy quality: Good AE quality: Fair	Chills: 17/154 (11%) Fever: 43/154 (27.9%) ISRs (e.g. bleeding): 92/154 (59.7%) Myalgia: 26/154 (16.9%)	Subgroup analysis based on brain-volume change on MRI scan: 41/131 (31%) INF-1a vs 62/132 (47%) placebo patients converted to MS at 24 mos

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Comi; Fillipi 2001; 2004 **Multiple European Countries** Efficacy quality: Good AE quality: Fair	Placebo SQ injection once a week, over 2 yrs N=155 Male: 52 (34%) Female: 103 (66%) Mean age (SD): 28 (6.1)	Total WDs: 18 (11.6%) AE WDs: NR	Number of patients converting to MS: 69 (45%) at 2 yrs Time to conversion for CIS to MS: 252 days Annualized relapse rate: 0.43 at 2 yrs
Investigators, 2008	IFN β (Rebif vs AL) RRMS	5 WDs 6 lost to FU	EDSS: AL showed improvement while IFN showed worsening; worsening by IFN: 0.77 (95% CI, 0.48 to 1.06), *P*=0.001 Sustained disability: AL reduced risk of sustained disability by 71% (HR 0.29; 95% CI, 0.16 to 0.54), *P*=0.001; NNT with AL 5.8 Risk of sustained disability at 3 mos: 64% for AL (HR 0.36; 95% CI, 0.21 to 0.60), *P*<0.001 RR: AL reduced rate of relapse by 74% (HR 0.26, 95% CI, 0.16 to 0.41), *P*<0.001 ARR at 36 mos: IFN 0.36 vs AL 0.10 Percent relapse free at 36 mos: IFN 52% vs AL 80%; NNT to prevent 1 relapse at 36 mos = 3.5 for AL

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Comi; Fillipi 2001; 2004 **Multiple European Countries** Efficacy quality: Good AE quality: Fair	Chills: 17/154 (11%) Fever: 18/154 (11.7%) ISRs (e.g. bleeding): 18/154 (11.7%) Myalgia: 14/154 (9.1%)	
Investigators, 2008	IFN β vs AL Immune thrombocytopenic purpura: 1 (0.9%) vs 6 (2.8%) Cancer: 1 (0.9%) vs 3 (1.4% but 2.8% of those in higher dose group) - 1 case Burkitt's lymphoma Death: 0 (0%) vs 2 (0.9%) Abnormal LFT: 16 (15%) vs 5 (2.3%) Depression: 19 (17.8%) vs 31 (14.4%)	Although high attrition rate of all groups due to WD of AL from market, continued ITT x 36 mos per protocol

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Jacobs 2000 Efficacy quality: Fair AE quality: Poor/Fair	IFN β-1a (Avonex) Injection 30 µg weekly, up to 104 weeks N=301	Total WDs: NR AE WDs: NR	Time to confirmed progression: 21.9% at week 104, *P*= NR Mean change in EDSS: mean 0.02 at week 104, *P*= 0.02; SE 0.14 Annualized relapse rate: 0.67, *P*= 0.04
Jacobs 2000 Efficacy quality: Fair AE quality: Poor/Fair	Placebo Injection weekly, up to 104 weeks	Total WDs: NR AE WDs: NR	Time to confirmed progression: 34.9% at week 104 Mean change in EDSS: 0.61 at week 104; SE 0.18 Annualized relapse rate: 0.82

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Jacobs 2000 Efficacy quality: Fair AE quality: Poor/Fair	No data reported. See comments on AE.	On population: "There were no significant group differences in BL demographic, clinical disease, or MRI characteristics." (Jacob et al, 1995, 1996) On intervention: BL EDSS and previous relapses NR On AE: No data reported except narrative: "93% of patients completed treatment as scheduled. Symptoms reported more frequently (P<0.1) by IFN β-1a recipients were restricted to flu-like symptoms, muscle aches, asthenia, chills and fever. ISRs occurred rarely and with equal frequency in IFN β-1a and placebo patients." Flu-like symptoms were reported more frequently in IFN β-1a recipients.
Jacobs 2000 Efficacy quality: Fair AE quality: Poor/Fair	NR	

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Jacobs et al 1996 USA Efficacy quality: Good AE quality: Poor/Fair	IFN β-1a (Avonex) 30 µg (6 million IU) weekly, up to 104 weeks N=158 Male: 40 (25%) Female: 118 (75%) Mean age: 37	Total WDs: 14 (8.8%) AE WDs: 7 (4.4%)	Probability of Onset of Sustained Progression: 21.9% at 104 weeks, *P*=0.02 Probability of Onset of Sustained Progression: 12.5% at first 52 weeks Probability of Onset of Sustained Progression: 10.8% at second 52 weeks Proportion of patients with confirmed progression: 21.2% at week 104 Mean change in EDSS (sustained changed): 0.02 at week 104 Mean change in EDSS (unsustained change): 0.25 at week 104 Annual exacerbation rates (per patient-yr): 0.67 at week 104, *P*=0.04

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Jacobs et al 1996 **USA** Efficacy quality: Good AE quality: Poor/Fair	Chills: 33/158 (20.9%) Fever: 37/158 (23.4%) Flu-like illness: 96/158 (60.8%) Headache: 106/158 (67.1%) Nausea/vomiting: 49/158 (31%) Weakness/muscle weakness: 53/158 (33.5%)	On population: mean BL values: EDSS: 2.3 Disease duration: 6.5 yrs (SD 5.8) Pre-study relapse rate: 1.2 (SD 0.6) On intervention: mean BL values, IFN-1a vs placebo EDSS: 2.3 vs 2.4 Pre-study relapse rate: 1.2 vs 1.2 Disease duration: 6.4 vs 6.6

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Jacobs et al 1996 **USA** Efficacy quality: Good AE quality: Poor/Fair	Placebo N=143 Male: 40 (28%) Female: 103 (72%) Mean age: 37	Total WDs: 9 (6.2%) AE WDs: 2 (1.4%)	Probability of Onset of Sustained Progression: 16.5% at second 52 weeks Probability of Onset of Sustained Progression: 34.9% at week 104 Probability of Onset of Sustained Progression: 22.0% at first 52 weeks Proportion of patients with confirmed progression: 33.3% at week 104 Mean change in EDSS (sustained change): 0.61 at week 104 Mean change in EDSS (unsustained change): 0.74 at week 104 Annual exacerbation rates (per patient-yr): 0.82 at week 104
Leary 2003 **UK** Efficacy quality: Good AE quality: Good	IFN β-1a (Avonex) 30 µg weekly, over 24 mos N=15 Male: 10 (67%) Female: 5 (33%) Mean age: 46	Total WDs: 1 (6.6%) AE WDs: 1 (6.6%)	Probability of Onset of Sustained Progression: 0.8 at 12 mos Probability of Onset of Sustained Progression: 0.45 at 24 mos NHPT - left: 27.2 secs at 24 mos NHPT - left: 27.1 secs at 12 mos NHPT - right: 23.8 secs at 24 mos NHPT - right: 23.6 secs at 12 mos TTMW: 19 secs at 24 mos TTMW: 12 secs at 12 mos

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Jacobs et al 1996 **USA** Efficacy quality: Good AE quality: Poor/Fair	Chills: 10/143 (7%) Fever: 18/143 (12.6%) Flu-like illness: 57/143 (39.9%) Headache: 82/143 (57.3%) Nausea/vomiting: 32/143 (22.4%) Weakness/muscle weakness: 21/143 (14.7%)	
Leary 2003 **UK** Efficacy quality: Good AE quality: Good	Abnormal LFT: 0/15 (0%) Anemia: 1/15 (6.7%) Depression: 7/15 (46.7%) Flu-like illness: 13/15 (86.7%) ISRs (e.g. bleeding): 1/15 (6.7%)	On outcome: Outcomes were read off figure that had "survival distribution function" on y-axis although the legend states "survival cures for time to sustained disease progression -- see Figure 2-page 47." The primary clinical endpoint was reached in 48% of subjects. There was no significant difference in disease progression between the individual or combined treatment arms and placebo. On intervention: mean BL values: EDSS: 5.25 Disease duration: 8 yrs TTMW: 11 secs NHPT - left: 28.7 secs NHPT - right: 28.9 secs In the event of study drug intolerance there was an option to half the dose.

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Leary 2003 UK Efficacy quality: Good AE quality: Good	IFN β-1a (Avonex) 60 µg weekly, over 24 mos N=15 Male: 7 (47%) Female: 8 (53%) Mean age: 47	Total WDs: 4 (26.6%) AE WDs: 4 (26.6%)	Probability of Onset of Sustained Progression: 0.66 at 12 mos Probability of Onset of Sustained Progression: 0.55 at 24 mos NHPT - left: 27.9 secs at 12 mos NHPT - left: 30.9 secs at 24 mos NHPT - right: 28.6 secs at 12 mos NHPT - right: 29.0 secs at 24 mos TTMW: 13 secs at 12 mos TTMW: 13 secs at 24 mos
Leary 2003 UK Efficacy quality: Good AE quality: Good	Placebo Weekly, over 24 mos N=20 Male: 15 (75%) Female: 5 (25%) Mean age: 43	Total WDs: 2 (10%) AE WDs: 0 (0%)	Probability of Onset of Sustained Progression: 0.5 at 24 mos Probability of Onset of Sustained Progression: 0.6 at 12 mos NHPT - left: 29.9 secs at 12 mos NHPT - left: 31.2 secs at 24 mos NHPT - right: 31.1 secs at 24 mos NHPT - right: 30.3 secs at 12 mos TTMW: 11 secs at 12 mos TTMW: 14 secs at 24 mos

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Leary 2003 **UK** Efficacy quality: Good AE quality: Good	Abnormal LFT: 5/15 (33%) Depression: 6/15 (40%) Fatigue/Tiredness: 3/15 (20%) Flu-like illness: 15/15 (100%) ISRs (e.g. bleeding): 2/15 (13.3%) Lymphopenia: 3/15 (20%)	
Leary 2003 **UK** Efficacy quality: Good AE quality: Good	Abnormal LFT: 0/20 (0%) Depression: 2/20 (10%) Fatigue/Tiredness: 5/20 (25%) Flu-like illness: 11/20 (55%) ISRs (e.g. bleeding): 1/20 (5%)	

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Liu 1999 PRISMS (Re-analysis of PRISMS)	IFN β-1a (Rebif) Injection 22 µg (6 MIU) 3x/week, over 2 yrs (66 µg/wk)	NR	Mean change in EDSS: 0.23 (SD 1.29) at 2 yrs, *P*=0.026 Mean change in AI: 0.46 (SD 1.25) at 2 yrs
Liu 1999 PRISMS (Re-analysis of PRISMS)	IFN β-1a (Rebif) Injection 44 µg (12 MIU) 3x/week, over 2 yrs (132 µg/wk) N=533	NR	Mean change in EDSS: 0.24 (SD 1.13) at 2 yrs, *P*=0.052 Mean change in AI: 0.24 (SD 0.96) at 2 yrs
Liu 1999 PRISMS (Re-analysis of PRISMS)	Placebo Injection 3x/week	NR	Mean change in EDSS: 0.48 (SD 1.27) at 2 yrs Mean change in AI: 0.44 (SD 1.30) at 2 yrs

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Liu 1999 PRISMS (Re-analysis of PRISMS)	NR	On outcome: Subgroup analyses: EDSS ≤3.5: 22 µg was better than placebo for both "2 yr EDSS difference" (P=0.016) and AUC(sum) analyses (P=0.043). For AUC(change), both treatment doses were favored compared with placebo (P=0.036 and 0.016 for 44 µg and 22 µg IFN). On population: PRISMS (1) 1998, N=466 for those with BL EDSS ≤3.5; N=94 for those with BL EDSS >3.5
Liu 1999 PRISMS (Re-analysis of PRISMS)	NR	
Liu 1999 PRISMS (Re-analysis of PRISMS)	NR	

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Liu (2) 2002 PRISMS (Re-analysis of PRISMS)	IFN β-1a (Rebif) 44 µg/22µg/Placebo	Data was not included in this post-hoc analysis	See comments
Miller 2006 USA, Canada IMPACT (Subgroup analysis of IMPACT data)	IFN β-1a (Avonex) Injection 60 µg weekly, over 24 mos N=162 Male: 57 (35%) Female: 105 (65%) Mean age (SD): 48 (7.8)	NR	NR

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Liu (2) 2002 PRISMS (Re-analysis of PRISMS)	NR	On outcome: On total cohort: combined data (N=533), Treatment effect: P=0.002 Total cohort: scheduled visits data (N=533), Treatment effect: P=0.018 Entry EDSS ≤3.5: combined data (N=444), Treatment effect: P=0.010 Entry EDSS >3.5: combined data (N=89), Treatment effect: P=0.018 On intervention: Results reflect the combined groups of IFN β-1a 22 µg and 44 µg vs. placebo. The outcomes are not the typically outcomes so results were included as narrative under outcomes.
Miller 2006 USA, Canada IMPACT (Subgroup analysis of IMPACT data)	NR	On outcome: The only demographic difference noted in BL MSQLI scores were that males reported worse satisfaction with sexual function (female 10.39 vs. male 12.29, *P*=0.02). The correlations between BL MSQLI components and disease characteristics were generally NS. On intervention: mean BL values, IFN β-1a vs placebo EDSS: 5.2 vs 5.3 Relapses in 3 yrs preceding study: 1.6 vs 1.4 Disease duration: 17.0 vs 17.0 General comments: Numerous tables included that reflects Pearson correlations between BL to mo 234 change in the MSQLI, MSFC and its components, EDSS

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
MS Collaborative Research Group (2) 1995 USA	IFN β-1a (Avonex) 30 µg (6 MIU) weekly/Placebo	NR	NR
MS Collaborative Research Group (3) 1997 USA MSCRG (Post-hoc analysis)	IFN β-1a (Avonex) 30 µg (MIU) weekly, up to 104 weeks	See comments	Probability of patients progressing by 2 yrs: 21.9% at sustained 6 mos, at least 1 point, P=0.024 Probability of patients progressing by 2 yrs: 11.5% at sustained 1 yr, at least 1 point, P=0.002 Probability of patients progressing by 2 yrs: 6.1% at sustained 6 mos, at least 2 points, P=0.028 Mean EDSS scores: 2.4 at BL, P=0.576 Mean EDSS scores: 2.4 at week 26 Mean EDSS scores: 2.5 at week 52 Mean EDSS scores: 2.6 at week 78, P=0.333 Mean EDSS scores: 2.5 at week 104, P=0.013 Mean EDSS scores: 2.7 at week 130, P=0.014

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
MS Collaborative Research Group (2) 1995 USA	NR	On outcome: Other outcomes conducted but not reported in the main publication included visual function, upper and lower extremity function (NHPT) and the box and block test (BBT), AI, emotional status, etc. On population: Pre-study exacerbation rates ranged from 0.67 to 3.7 exacerbations per yr (mean 1.2 exacerbations per yr). Mean and median pre-study duration of disease were 6.5 yrs and 4.5 yrs respectively. On the reviewer: This article was a review of design and BL characteristics of patients of the MSCRG trial.
MS Collaborative Research Group (3) 1997 USA MSCRG (Post-hoc analysis)	NR	On outcome: Time to disability progression was calculated as the number of days from randomization until the onset of sustained worsening from BL EDSS. On WDs: 5 patients, all IFN β-1a, prematurely withdrew from the study while still at risk to progress (i.e. at least 2 scheduled visits left in their treatment course). 8 patients (5 IFN β-1a and 3 placebo) failed on the primary endpoint or were beyond the date when they could have reached the primary endpoint (one scheduled visit left in their treatment course and the EDSS had not increased by at least 1.0 point from BL)

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
MS Collaborative Research Group (3) 1997 USA (Post-hoc analysis)	Placebo	NR	Probability of patients progressing by 2 yrs: 18.3% at sustained 6 mos, at least 2 points Probability of patients progressing by 2 yrs: 29.8% at sustained 1 yr, at least 1 point Probability of patients progressing by 2 yrs: 34.9% at sustained 6 mos, at least 1 point Mean EDSS scores: 2.3 at BL Mean EDSS scores: 2.5 at week 26 Mean EDSS scores: 2.8 at week 52 Mean EDSS scores: 3.0 at week 78 Mean EDSS scores: 3.1 at week 104 Mean change in EDSS: 3.4 at week 130
Oger 2005 PRISMS (Analysis of PRISMS data)	IFN β-1a (Rebif) 22 µg 3x/week, over two yrs N=85 Male: 23 (27%) Female: 62 (73%) Mean age: 36	Total WDs: 12 (14%) AE WDs: 3 (4%)	Percentage progression-free: 72% at yrs 3-4, *P*=0.170 Annual rate of 1-point EDSS progressions: 0.3 at yrs 3-4, *P*=0.001 AUC of the EDSS (EDSS step-yrs): 110 at yrs 3-4, *P*=0.118 Annualized relapse rate: 0.6 at yrs 3-4 Proportion of relapse-free patients: 40% at yrs 3-4, *P*≤0.001 Total number of relapses: 1.2 at yrs 3-4, *P*≤0.001

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
MS Collaborative Research Group (3) 1997 USA (Post-hoc analysis)	NR	
Oger 2005 PRISMS (Analysis of PRISMS data)	Fatigue/tiredness: 29/85 (34.1%) Flu-like illness: 36/85 (42.4%) ISR (e.g. bleeding): 24/85 (28.2%) Lymphopenia: 44/85 (51.8%) Weakness/muscle weakness: 18/85 (21.2%)	On outcome: Relapse count in the 2 yrs prior to PRISMS was 3.0, while during the first 2 yrs the relapse count was 2.6 (13% RR). Once IFN treatments were started, a 54% RR in relapses in yrs 3 and 4 for patients in both 22 and 44 µg groups compared with yrs on placebo (P<0.001). On intervention: mean BL values, IFN-1a 22 µg vs IFN-1a 44 µg EDSS: 3.0 vs 2.6 Disease duration: 8.5 yrs vs 7.6 yrs

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Oger 2005 PRISMS (Analysis of PRISMS data)	IFN β-1a (Rebif) 44 µg 3x/week, over two yrs N=87 Male: 19 (22%) Female: 68 (78%) Mean age: 37	Total WDs: 25 (29%) AE WDs: 13 (15%)	Percentage progression-free: 76% at yrs 3-4, *P*=0.019 Annual rate of 1-point EDSS progressions: 0.2 at yrs 3-4, *P*≤0.001 AUC of the EDSS (EDSS step-yrs): 56 at yrs 3-4, *P*=0.118 Annualized relapse rate: 0.7 at yrs 3-4 Proportion of relapse-free patients: 28% at yrs 3-4, *P*=0.007 Total number of relapses: 1.2 at yrs 3-4, *P*≤0.001
OWIMS Study Group 1999 Efficacy quality: Good AE quality: Fair	IFN β-1a (Rebif) 22 µg every week, over 48 weeks N=95 Male: 26 (27%) Female: 69 (73%)	Total WDs: 8 (8.42%) AE WDs: 1 (1.05%)	Use of rescue medication in relapsing patients: 0.58 (range 0-4) at 48 weeks (1 yr) Mean relapse rate: 1.08 (SD 1.04) at 48 weeks Median Time to first relapse (days): 152 at 48 weeks Percentage of patients with moderate/severe relapses: 36% at 48 weeks Proportion of relapse-free patients: 33% at 48 weeks

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Oger 2005 PRISMS (Analysis of PRISMS data)	Fatigue/tiredness: 32/87 (36.8%) Flu-like illness: 53/87 (60.9%) ISRs (e.g. bleeding): 33/87 (37.9%) Lymphopenia: 49/87 (56.3%) Weakness/muscle weakness: 20/87 (23%)	
OWIMS Study Group 1999 Efficacy quality: Good AE quality: Fair	Abnormal LFT: 4/95 (4.2%) Chills: 7/95 (7.4%) Depression: 4/95 (4.2%) Fever: 8/95 (8.4%) Flu-like illness: 39/95 (41.1%) Headache: 46/95 (48.4%) Injection site inflammation: 68/95 (71.6%) Injection site necrosis: 0/95 (0%) ISP: 13/95 (13.7%) Weakness/muscle weakness: 17/95 (17.9%)	On intervention: Dose adjustments were allowed for management of symptomatic or laboratory-identified AE. APAP was recommended for prophylactic use and to ameliorate constitutional symptoms as required throughout the study.

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
OWIMS Study Group 1999 Efficacy quality: Good AE quality: Fair	IFN β-1a (Rebif) 44 µg every week, over 48 weeks N=98 Male: 28 (29%) Female: 70 (71%)	Total WDs: 13 (13.26%) AE WDs: 5 (5.1%)	Use of rescue medication in relapsing patients: 0.38 (range 0-3) at 48 weeks (1 yr), *P*=0.014 vs placebo Mean relapse rate: 0.87 (SD 0.96) at 48 weeks Median time to first relapse (days): 239 at 48 weeks Percentage of patients with moderate/severe relapses: 32% at 48 weeks Proportion of relapse-free patients: 40% at 48 weeks
OWIMS Study Group 1999 **OWIMS Study** Efficacy quality: Good AE quality: Fair	Placebo Every week, over 48 weeks N=100 Male: 26 (26%) Female: 74 (74%)	Total WDs: 3 (3%) AE WDs: 0 (0%)	Use of rescue medication in relapsing patients: 0.76 (range 0-7) at 48 weeks (1 yr) Mean relapse rate: 1.08 (SD 1.15) at 48 weeks Median time to first relapse (days): 189 days at 48 weeks Percentage of patients with moderate/severe relapses: 41% at 48 weeks Proportion of relapse-free patients: 36% at 48 weeks

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
OWIMS Study Group 1999 Efficacy quality: Good AE quality: Fair	Abnormal LFT: 4/98 (4.1%) Chills: 12/98 (12.2%) Depression: 8/98 (8.2%) Fever: 24/98 (24.5%) Flu-like illness: 59/98 (60.2%) Headache: 49/98 (50%) Injection site inflammation: 68/98 (69.4%) Injection site necrosis: 0/98 (0%) ISP: 17/98 (17.3%) Weakness/muscle weakness: 20/98 (20.4%)	
OWIMS Study Group 1999 **OWIMS Study** Efficacy quality: Good AE quality: Fair	Abnormal LFT: 1/100 (1%) Chills: 3/100 (3%) Depression: 8/100 (8%) Fever: 7/100 (7%) Flu-like illness: 33/100 (33%) Headache: 34/100 (34%) Injection site inflammation: 12/100 (12%) Injection site necrosis: 0/100 (0%) ISP: 17/100 (17%) Weakness/muscle weakness: 11/100 (11%)	

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	IFN β-1a (Rebif) Injection 22 µg 2x/week, over 3 yrs	NR	See SPECTRIMS, 2001
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	IFN β-1a (Rebif) Injection 44 µg 3x/week, over 3 yrs N=98	NR	See SPECTRIMS, 2001
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	Placebo Injection 3x/week, over 3 yrs N=104	NR	See SPECTRIMS, 2001

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	Depression, based on CES-D score: 8/46 (17.4%) Suicide risk, based on BHS ratings: 17/79 (21.5%)	On population: 365 (sample size) represented 59.1% of the 618 SPECTRIMS participants. Median date of onset of MS in this sample was 12.3 yrs prior to enrollment in the study. The median time since onset of the secondary progressive phase was 3.1 yrs. Both time since onset of MS and mean time since onset of progression were comparable between the 3 groups.
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	Depression, based on CES-D score: 17/57 (29.8%) Suicide risk, based on BHS ratings: 9/76 (11.8%)	
Patten 2002 SPECTRIMS Trial (Re-analysis of SPECTRIMS)	Depression, based on CES-D score: 17/53 (32.1%) Suicide risk, based on BHS ratings: 16/78 (20.5%)	

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
PRISMS (1) 1998 Multiple (Europe, North American & Australia) Efficacy quality: Good AE quality: Good	IFN β-1a (Rebif) Injection 22 µg (6 MIU) 3x/weekly, 66 µg/wk over 2 yrs N=189 Male: 62 (33%) Female: 127 (67%) Mean age: 35	Total WDs: 22 (11.6%) AE WDs: 6 (3.2%)	Time to confirmed progression: RR=0.68 at 2 yrs, *P*<0.05; 95% CI, 0.48 to 0.98 Mean change in EDSS: 0.23 (SD 1.3) at 2 yrs, *P*≤0.05 Use of rescue medication in relapsing patients: 0.97 at 2 yrs, *P*≤0.05 Mean moderate and severe exacerbations per person-yr, N: 0.71 at 2 yrs, *P*<0.005 Mean relapse rate per patient: 1.82 at 2 yrs, *P*<0.005 Relapse requiring hospitalization: 0.38 at 2 yrs
PRISMS (1) 1998 Multiple (Europe, North American & Australia) Efficacy quality: Good AE quality: Good	IFN β-1a (Rebif) Injection 44 µg (12 MIU) 3x/weekly, 132 µg/wk over 2 yrs N=184 Male: 63 (34%) Female: 121 (66%) Mean age: 36	Total WDs: 19 (10.3%) AE WDs: 9 (4.8%)	Time to confirmed progression: RR=0.62 at 2 yrs, *P*<0.05; 95% CI, 0.43 to 0.91 Mean change in EDSS: 0.24 (SD 1.1) at 2 yrs, *P*≤0.05 Use of rescue medication in relapsing patients: 0.75 at 2 yrs, *P*<0.005 Mean moderate and severe relapses per person-yr, N: 0.62 at 2 yrs, *P*<0.005 Mean relapse rate per patient: 1.73 at 2 yrs, *P*<0.005 Relapse requiring hospitalization: 0.25 at 2 yrs, *P*<0.005

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
PRISMS (1) 1998	Depression: 39/189 (20.6%)	On outcome: Disease progression: placebo vs 22 µg group vs 44 µg group
Multiple (Europe, North American & Australia)	Fatigue/tiredness: 27/189 (14.3%)	Groups with high BL EDSS (>3.5): First quartile time to progression: 7.3 mos vs 7.5 mos, RR 0.75 (0.35-1.56) vs 21.3 mos, 0.42 (0.18-0.99) (P <0.05)
	Fever: 25/189 (13.2%)	
	Flu-like illness: 47/189 (24.9%)	
Efficacy quality: Good	Headache: 89/189 (47.1%)	On population: BL data: Median age: 34.9
AE quality: Good		Median history of MS: 5.3 yrs
	ISRs (e.g. bleeding): 128/189 (67.7%)	Mean number of relapses in previous 2 yrs: 3 Mean EDSS: 2.5
	Lymphopenia: 9/189 (4.8%)	
	Weakness/muscle weakness: 24/189 (12.7%)	On intervention: The age entered is median age. Relapses could be treated with a standard regimen of 1.0 g IV methylprednisolone for 3 consecutive days.
PRISMS (1) 1998	Depression: 44/184 (23.9%)	
Multiple (Europe, North American & Australia)	Fatigue/tiredness: 34/184 (18.5%)	
	Fever: 22/184 (12%)	
	Flu-like illness: 50/184 (27.2%)	
Efficacy quality: Good	Headache: 83/184 (45.1%)	
AE quality: Good		
	ISRs (e.g. bleeding): 114/184 (62%)	
	Lymphopenia: 23/184 (12.5%)	
	Weakness/muscle weakness: 25/184 (13.6%)	

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
PRISMS (1) 1998 Multiple (Europe, North American & Australia) Efficacy quality: Good AE quality: Good	Placebo Injection 3x/weekly N=187 Male: 47 (25%) Female: 140 (75%) Mean age: 35	Total WDs: 17 (9.1%) AE WDs: 2 (1.0%)	Time to confirmed progression: RR=1.00 at 2 yrs Mean change in EDSS: 0.48 (SD 1.3) at 2 yrs Use of rescue medication in relapsing patients: 1.39 at 2 yrs Mean moderate and severe exacerbations per person-yr, N: 0.99 at 2 yrs Mean relapse rate per patient: 2.56 at 2 yrs Relapse requiring hospitalization: 0.48 at 2 yrs

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
PRISMS (1) 1998 **Multiple (Europe, North American & Australia)** Efficacy quality: Good AE quality: Good	Depression: 52/187 (27.8%) Fatigue/tiredness: 29/187 (15.5%) Fever: 12/187 (6.4%) Flu-like illness: 45/187 (24.1%) Headache: 82/187 (43.9%) ISRs (e.g. bleeding): 41/187 (21.9%) Lymphopenia: 7/187 (3.7%) Weakness/muscle weakness: 15/187 (8%)	

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
SPECTRIMS 2001 Efficacy quality: Good AE quality: Good	IFN β-1a (Rebif) Injection 44 µg 3x/week, over 3 yrs N=204 Male: 229 (37%) Female: 389 (63%) Mean age (SD): 43 (7.1)	Total WDs: 43 (21%) AE WDs: 18 (8.8%)	Time to confirmed progression at 3 yrs: HR=0.93 (patents without pre-study relapse, N=325), *P*=0.688; 95% CI, 0.65 to 1.33 HR=0.76 (patients with pre-study relapse, N=293), *P*=0.142; 95% CI, 0.53 to 1.10 HR=1.30 (male patients), *P*=0.226; 95% CI, 0.85 to 2.01 HR=0.63 (female patients), *P*=0.006; 95% CI, 0.45 to 0.87 (adjusted analysis): HR=0.78 (adjusted for center), P=0.046; 95% CI, 0.60 to 1.00 In disability: HR=0.83 at 3 yrs, *P*=0.146; 95% CI, 0.65 to 1.07 Exacerbation requiring hospitalization: 0.15 at 3 yrs (per person-yr); 95% CI, 0.12 to 0.18 Mean exacerbations per person-yr: 0.50 at 3 yrs; 95% CI, 0.45 to 0.56 Mean moderate and severe exacerbations per person-yr, N: 0.27 at 3 yrs; 95% CI, 0.23 to 0.31 Mean steroid courses per person-yr: 0.34 at 3 yrs; 95% CI, 0.30 to 0.39 Median time between first and second exacerbation (days): 511 at 3 yrs; 95% CI, 314 to 708 Median time to first exacerbation (days): 494 at 3 yrs; 95% CI, 303 to 685

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
SPECTRIMS 2001 Efficacy quality: Good AE quality: Good	Depression: 71/204 (34.8%) Flu-like illness: 102/204 (50%) Injection site necrosis: 18/204 (8.8%) ISRs (e.g. bleeding): 177/204 (86.8%)	On population: 506 (82%) completed 3 yrs of treatment, and an additional 65 who stopped therapy were followed for the remainder of the 3 yrs, providing full data for 92.4% of patients. BL data: Mean EDSS: placebo 5.4 vs IFN-1a 22 µg 5.5 vs IFN-1a 44 µg 5.3 Relapses 2 yrs preceding study entry: 0.9 Disease duration: 13.3 yrs AI: 3.6

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Dosage, Population	Withdrawals	Outcomes
SPECTRIMS 2001 Efficacy quality: Good AE quality: Good	IFN β-1a (Rebif) Injection 22 µg 3x/week, over 3 yrs N=209	Total WDs: 37 (17.7%) AE WDs: 15 (7.1%)	Exacerbation requiring hospitalization: 0.14 at 3 yrs; 95% CI, 0.11 to 0.17 Mean exacerbations per person-yr: 0.50 at 3 yrs; 95% CI, 0.44 to 0.56 Mean moderate and severe exacerbations per person-yr, N: 0.26 at 3 yrs; 95% CI, 0.22 to 0.31 Mean steroid courses per person-yr: 0.31 at 3 yrs; 95% CI, 0.27 to 0.36 Median time between first and second exacerbation (days): 572 at 3 yrs; 95% CI, 241 to 903 Median time to first exacerbation (days): 476 at 3 yrs; 95% CI, 307 to 645
SPECTRIMS 2001 Efficacy quality: Good AE quality: Good	Placebo Injection 3x/week, over 3 yrs N=205	Total WDs: 32 (15.6%) AE WDs: 5 (2.4%)	Exacerbation requiring hospitalization: 0.22 at 3 yrs; 95% CI, 0.18 to 0.26 Mean exacerbations per person-yr: 0.71 at 3 yrs; 95% CI, 0.65 to 0.78 Mean moderate and severe exacerbations per person-yr, N: 0.39 at 3 yrs; 95% CI, 0.34 to 0.44 Mean steroid courses per person-yr: 0.52 at 3 yrs; 95% CI, 0.46 to 0.58 Median time between first and second exacerbation (days): 279 at 3 yrs; 95% CI, 181 to 377 Median time to first exacerbation (days): 281 at 3 yrs; 95% CI, 167 to 395

Evidence Table 6. Effectiveness and adverse events in active-control and placebo-controlled trials of interferon beta 1a

Study	Adverse events	Comments
SPECTRIMS 2001 Efficacy quality: Good AE quality: Good	Depression: 67/209 (32.1%) Flu-like illness: 107/209 (51.2%) ISRs (e.g. bleeding): 170/209 (81.3%)	
SPECTRIMS 2001 Efficacy quality: Good AE quality: Good	Depression: 59/205 (28.8%) Flu-like illness: 107/205 (52.2%) ISRs (e.g. bleeding): 84/205 (41%)	

Evidence Table 7. Placebo-controlled trials of interferon beta 1b

Study	Population type	Design	Recruitment	Eligibility
European Study Group on Interferon (ESG) 1998 Europe-Switzerland	SPMS	DB Parallel Multicenter Setting: NR	Screened: 768 Eligible: NR Enrolled: 718 Withdrawn: 187 Lost to FU: 57 Analyzed: 711	Clinically or laboratory supported definite diagnosis of MS, secondary progression defined as a period of deterioration, independent of relapses, sustained for at least 6 mos and that followed a period of RRMS, ages 18-55 yrs, baseline EDSS score of 3.0-6.5, recorded history of either two relapses or more or 1.0 point or more increase in EDSS in the previous two yrs
Freeman 2001 Europe	Same as European Study Group, 1998	DB Multicenter Setting: NR	Same as European Study Group, 1998	Same as European Study Group, 1998
IFNB MS Study Group 1993 USA and Canada	RRMS	DB Parallel Multicenter Setting: Research Center	Screened: NR Eligible: NR Enrolled: 372 Withdrawn: 65 Lost to FU: NR Analyzed: 338	Ages 18-50 yrs, EDSS scores of 5.5 or less, at least two acute exacerbations during the previous 2 yrs, clinically stable for at least 30 days before study entry and received no steroids during this period
INFB MS Study Group (1) 1995	Same as IFNB, 1993	Same as IFNB, 1993	Same as IFNB, 1993	Same as IFNB, 1993

Evidence Table 7. Placebo-controlled trials of interferon beta 1b

Study	Exclusion	Sample size, Age, Gender, Ethnicity
European Study Group on Interferon (ESG) 1998 Europe-Switzerland	Immunosuppressive treatment or other putative treatments for MS for defined periods before entry	N=718 38.86% male 61.14% female
Freeman 2001 Europe	Same as European Study Group, 1998	Same as European Study Group, 1998
IFNB MS Study Group 1993 USA and Canada	Patients taking AZA or CPA	N=372 Mean age (SD): 35.5 (0.63) 30.38% male 69.62% female 93.5% white 6.5% other
INFB MS Study Group (1) 1995	Same as IFNB, 1993	Same as IFNB, 1993

Evidence Table 7. Placebo-controlled trials of interferon beta 1b

Study	Population type	Design	Recruitment	Eligibility
Kappos 2001 Europe-Switzerland	Same as European Study Group, 1998	DB Parallel Multicenter Setting: NR	Same as European Study Group, 1998	Same as European Study Group, 1998
Kappos 2006 Multiple European Countries; Canada; Israel BENEFIT	CIS	DB Parallel Multicenter Setting: NR	Screened: 603 Eligible: 511 Enrolled: 487 Withdrawn: 62 Lost to FU: 31 Analyzed: 468	Patients with a CIS—defined as a first neurologic event suggestive of MS lasting for at least 24 hours and with symptoms and signs indicating either a single lesion (monofocal) or more than one lesion (multifocal) within the CNS; age 18 and 45 yrs; have presented with a first neurologic event suggestive of MS that lasted for at least 24 hours, and had to have at least two clinically silent lesions on their T2-weighted brain MRI scan with a size of at least 3 mm, at least one of which being ovoid, periventricular, or infratentorial; BL EDSS 0-5
Knobler 1990	RRMS	DB Parallel Single Center Setting: Research Center	Screened: NR Eligible: NR Enrolled: 31 Withdrawn: 1 Lost to FU: NR Analyzed: NR	Ages 18-50 yrs with clinically definite RRMS for not less than 1 yr and not more than 15 yrs and had at least two exacerbations in the previous 2 yrs; in clinical remission at the time of study entry; contraception for women of child-bearing potential; EDSS
Montalban 2004 Europe	PPMS	Blinding NR Setting: NR	Screened: NR Eligible: NR Enrolled: 73 Withdrawn: 5 Lost to FU: NR Analyzed: NR	Ages 18-65 yrs; EDSS score of 3.0-7.0

Evidence Table 7. Placebo-controlled trials of interferon beta 1b

Study	Exclusion	Sample size, Age, Gender, Ethnicity
Kappos 2001 Europe-Switzerland	Same as European Study Group, 1998	Same as European Study Group, 1998
Kappos 2006 Multiple European Countries; Canada; Israel BENEFIT	Patients in whom any disease other than MS could explain their signs and symptoms; any previous episode that could possibly be attributed to an acute demyelinating event; patients with complete transverse myelitis or bilateral optic neuritis; patients who had received prior immunosuppressive therapy	N=468 Mean age: 30 (range 24-37.5) 29.27% male 70.73% female 98% white 2% other
Knobler 1990	NR	N=31 Others NR
Montalban 2004 Europe	Previous immunosuppressive or immunomodulatory therapy	N=73 Mean age: NR Gender NR

Evidence Table 7. Placebo-controlled trials of interferon beta 1b

Study	Population type	Design	Recruitment	Eligibility
North American Study Group on SPMS (1) 2004	SPMS	DB Parallel Multicenter Setting: NR	Screened: NR Eligible: NR Enrolled: 939 Withdrawn: 229 Lost to FU: 73 Analyzed: 939	Ages 18-65 yrs; clinically definite or laboratory supported definite MS of at least 2 yrs duration; history of at least one relapse followed by progressive deterioration sustained for at least 6 mos; an EDSS score at screening of 3.0-6.5 inclusive
Sibley 1996 US/Canada	Same as IFNB, 1993	Same as IFNB, 1993	Same as IFNB, 1993	Same as IFNB, 1993

Evidence Table 7. Placebo-controlled trials of interferon beta 1b

Study	Exclusion	Sample size, Age, Gender, Ethnicity
North American Study Group on SPMS (1) 2004	Received treatment with systemic corticosteroids or ACTH within 60 days before the screening visit; previous treatment with any IFN β, monoclonal antibody, cladribine, or total lymphoid radiation; received cytotoxic or immunosuppressive therapy, GA, or other investigational drug within 6 mos before screening visit	N=939 37.38% male 62.62% female
Sibley 1996 US/Canada	Same as IFNB, 1993	Same as IFNB, 1993

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes
European Study Group on Interferon (ESG) 1998 **Europe-Switzerland** Efficacy quality: Good AE quality: Good	IFN β-1b (Betaseron) Injection 8 MIU qod, over 36 mos N=360 Male: 151 (42%) Female: 209 (58%) Mean age (SD): 41 (7.2)	Total WDs: 90 (25%) AE WDs: 45 (12.5%)	Proportion of patients with confirmed progression: 38.9% at 33 mos, *P*=0.0048 Time to confirmed progression: 893 days at 33 mos; 95% CI, 726 to undetermined Mean change in EDSS: 0.47 at 33 mos, *P*=0.0299 Loss of mobility: 0.77 at 33 mos, *P*=0.0133 Mean Annual Relapse Rate: 0.44 at 33 mos, *P*=0.0002 Median time to first exacerbation (days): 644, *P*=0.0030
European Study Group on Interferon (ESG) 1998 **Europe-Switzerland** Efficacy quality: Good AE quality: Good	Placebo N=358 Male: 129 (36%) Female: 229 (64%) Mean age (SD): 41 (7.2)	Total WDs: 97 (27.1%) AE WDs: 15 (4.2%)	Proportion of patients with confirmed progression: 49.7% at 33 mos Time to confirmed progression: 549 days at 33 mos; 95% CI, 463 to 642 Mean change in EDSS: 0.60 at 33 mos Loss of mobility: 0.66 at 33 mos Mean Annual Relapse Rate: 0.64 at 33 mos Median time to first relapse (days): 403
Freeman 2001 **Europe** (Additional analysis of ESG data. Not quality assessed.)	IFN β-1b Injection 8 MIU qod, over 36 mos	Same as European Study Group on IFN β-1b in SPMS, 1998	Sickness Impact Profile: 15.9 at BL -0.1 at 6 mo -0.3 at 12 mo -0.4 at 18 mo 0.2 at 24 mo 0.3 at 30 mo 1.8 at 36 mo 0.4 at Final

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Adverse events	Comments
European Study Group on Interferon (ESG) 1998 Europe-Switzerland Efficacy quality: Good AE quality: Good	Flu-like illness: 213/360 (59.2%) Hypertension: 14/360 (3.9%) Injection site inflammation: 180/360 (50%) Injection site necrosis: 17/360 (4.7%) Suicide or suicide attempts: 3/360 (0.8%)	On intervention: Mean BL values, IFN-1b vs placebo: EDSS: 5.1 vs 5.2 Time since evidence of progressive deterioration: 3.8 vs 3.8 Disease duration SPMS course: 2.2 yrs vs 2.1 yrs Disease duration RRMS: 8.1 yrs vs 8.2 yrs
European Study Group on Interferon (ESG) 1998 Europe-Switzerland Efficacy quality: Good AE quality: Good	Flu-like illness: 133/358 (37.2%) Hypertension: 3/358 (0.8%) Injection site inflammation: 15/358 (4.2%) Injection site necrosis: 0/358 (0%) Suicide or suicide attempts: 5/358 (1.4%)	
Freeman 2001 Europe (Additional analysis of ESG data. Not quality assessed.)	Same as European Study Group on IFN β-1b in SPMS, 1998	On outcome: Sickness Impact Profile scale 0-100, with 0 as best possible HRQOL and 100 as worst possible HRQOL. After BL, Sickness Impact Profile is reported as mean change.

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes
Freeman 2001 Europe (Additional analysis of ESG data. Not quality assessed.)	Placebo	Same as European Study Group on IFN β-1b in SPMS, 1998	Sickness Impact Profile: 16.1 at BL 0.4 at 6 mo 0.7 at 12 mo 1.0 at 18 mo 0.5 at 24 mo 1.7 at 30 mo 2.1 at 36 mo 1.8 at Final
IFNB MS Study Group 1993 USA and Canada Efficacy quality: Good AE quality: Poor/Fair	IFN β-1b Injection 1.6 MIU qod, over 2 yrs N=125 Female: 85 (68%) Male: 40 (32%) Mean age: 35	Total WDs: 24 (19%) AE WDs: 10 (8%)	Annualized relapse rate: 1.17 at 2 yrs, *P*=0.0001 Annualized relapse rate: 1.05 at 3 yrs, *P*=0.0004 Exacerbation requiring hospitalization: 53 at 3 yrs Median time to first exacerbation (days): 199 at 3 yrs, *P*=0.028 Median time to first exacerbation (days): 180 at 2 yrs, *P*=0.015 Proportion of relapse-free patients: 21% at 2 yrs Proportion of relapse-free patients: 18% at 3 yrs, *P*=0.097
IFNB MS Study Group 1993 USA and Canada Efficacy quality: Good AE quality: Poor/Fair	IFN β-1b Injection 8.0 MIU qod, over 2 yrs N=124 Male: 38 (31%) Female: 86 (69%) Mean age: 35	Total WDs: 18 (15%) AE WDs: 5 (4%)	Annualized relapse rate: 0.84 at 2 yrs, *P*=0.0001 Annualized relapse rate: 0.84 at 3 yrs, *P*=0.0004 Exacerbation requiring hospitalization: 37 at 3 yrs, *P*=0.046 Median time to first exacerbation (days): 264 at 3 yrs, *P*=0.028 Median time to first exacerbation (days): 295 at 2 yrs, *P*=0.015 Proportion of relapse-free patients: 31% at 2 yrs Proportion of relapse-free patients: 22% at 3 yrs, *P*=0.097

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Adverse events	Comments
Freeman 2001 Europe (Additional analysis of ESG data. Not quality assessed.)	Same as European Study Group on IFN β-1b in SPMS, 1998	
IFNB MS Study Group 1993 USA and Canada Efficacy quality: Good AE quality: Poor/Fair	Fever: 44/111 (39.6%) Injection site inflammation: 70/111 (63.1%) Myalgia: 27/111 (24.3%)	On intervention: Mean BL values, 1.6 MIU vs 8 MIU vs placebo EDSS: 2.9 vs 3.0 vs 2.8 Relapses 2 yrs preceding study entry: 3.3 vs 3.4 vs 3.6 Disease duration: 4.7 yrs vs 4.7 yrs vs 3.9 yrs On AE: AEs reported in percentage, calculated with total n for 2 yrs
IFNB MS Study Group 1993 USA and Canada Efficacy quality: Good AE quality: Poor/Fair	Fever: 67/115 (58.3%) Injection site inflammation: 79/115 (68.7%) Myalgia: 47/115 (40.9%)	

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes
IFNB MS Study Group 1993 **USA and Canada** Efficacy quality: Fair AE quality: Poor/Fair	Placebo N=123 Male: 35 (28%) Female: 88 (72%) Mean age (SD): 36	Total WDs: 23 (19%) AE WDs: 1 (1%)	Annualized relapse rate: 1.21 at 3 yrs, *P*=0.0004 Annualized relapse rate: 1.27 at 2 yrs, *P*=0.0001 Exacerbation requiring hospitalization: 65 at 3 yrs, *P*=0.046 Median time to first exacerbation (days): 153 at 2 yrs, *P*=0.015 Median time to first exacerbation (days): 147 at 3 yrs, *P*=0.028 Proportion of relapse-free patients: 14% at 3 yrs, *P*=0.097 Proportion of relapse-free patients: 16% at 2 yrs
IFNB MS Study Group (1) **1995** (5 year data from IFNB trial)	IFN β-1b (Betaseron) Injection 1.6 MIU qod, over 5 yrs N=125	Total WDs: 57 (46%)	Median annual change in EDSS: 0.20 at 5 yrs Annualized relapse rate: 1.22 at yr 1 1.04 at yr 2 0.80 at yr 3 0.68 at yr 4 0.66 at yr 5

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Adverse events	Comments
IFNB MS Study Group 1993 **USA and Canada** Efficacy quality: Fair AE quality: Poor/Fair	Fever: 38/112 (33.9%) Injection site inflammation: 7/112 (6.2%) Myalgia: 27/112 (24.1%)	
IFNB MS Study Group (1) **1995** (5 year data from IFNB trial)	See comments	On AEs: reported as percentages only; unclear total number of patients 1.6 MIU vs 8 MIU vs placebo Depressive symptoms at yr 5: 5.5% vs 11.1% vs 5.1% Suicide attempts: 0% vs 0% vs 0% On outcome: *P* values are 8 MIU versus Placebo. Subgroups: 1.6 MIU vs 8 MIU vs placebo Patients with confirmed progression - BL EDSS <3.0: 30/59 (51%) vs 20/55 (36%) vs 26/58 (45%) Patients with confirmed progression - BL EDSS >3.0: 29/66 (44%) vs 23/67 (34%) vs 30/64 (47%)

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes
IFNB MS Study Group (1) 1995 (5 year data from IFNB trial)	IFN β-1b (Betaseron) Injection 8 MIU qod, over 5 yrs N=124	Total WDs: 48 (39%)	Median annual change in EDSS: 0.00 at 5 yrs Annualized relapse rate: 0.96 at yr 1, *P*≤0.001 0.85 at yr 2, *P*=0.030 0.66 at yr 3, *P*=0.084 0.67 at yr 4, *P*=0.166 0.57 at yr 5, *P*=0.393
IFNB MS Study Group (1) 1995 (5 year data from IFNB trial)	Placebo N=123	Total WDs: 49 (40%)	Median annual change in EDSS: 0.11 at 5 yrs Annualized relapse rate: 1.44 at yr 1 1.18 at yr 2 0.92 at yr 3 0.88 at yr 4 0.81 at yr 5
Kappos 2001 **Europe-Switzerland** (Additional data from ESG trial)	IFN β-1b N=360	Total WDs: 143 (39.7%) AE WDs: NR	Proportion of patients with confirmed progression: 37.3% (EDSS <3.5) Proportion of patients with confirmed progression: 47.7% (EDSS >6.0) Proportion of patients with confirmed progression: 46.4% (EDSS 4.0-5.5) Mean change in EDSS: 0.47 at 33 mos, *P*=0.003 Mean EDSS scores: 5.58 at 33 mos, *P*=0.007 Proportion of patients becoming wheelchair bound: 18.6% at 33 mos, *P*=0.007 Mean Annual Relapse Rate: 0.42, *P*=0.003

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Adverse events	Comments
IFNB MS Study Group (1) 1995 (5 year data from IFNB trial)	See comments	
IFNB MS Study Group (1) 1995 (5 year data from IFNB trial)	See comments	
Kappos 2001 Europe-Switzerland (Additional data from ESG trial)	Same as European Study Group on IFN β-1b in SPMS, 1998	

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes
Kappos 2001 **Europe-Switzerland** (Additional data from ESG trial)	Placebo N=358	Total WDs: 165 (46.1%) AE WDs: NR	Proportion of patients with confirmed progression: 54.9% (EDSS 4.0-5.5) Proportion of patients with confirmed progression: 44.7% (EDSS <3.5) Proportion of patients with confirmed progression: 55.6% (EDSS >6.0) Mean change in EDSS: 0.69 at 33 mos, *P*=0.003 Mean EDSS scores: 5.93 at 33 mos, *P*=0.007 Proportion of patients becoming wheelchair bound: 28.5% at 33 mos, *P*=0.007 Mean Annual Relapse Rate: 0.57, *P*=0.003
Kappos 2004 (Reanalysis. Not quality assessed.)	See original trials for details of populations, comparison of trial populations; European group had significantly lower age at entry, lower age at onset, lower duration of MS, greater number of relapses in prior 2 yrs, greater change in EDSS in prior 2 yrs, and lower percentage of patients that were relapse free in prior 2 yrs when compared to North American trial population. There were no significant differences in duration of SPMS, or BL EDSS.	NR	Combined Subgroup Analysis, comparison between treatment groups: All patients: 0.79, *P*=0.0076 Patients with relapses: 0.70, *P*=0.0024 Patients with change in EDSS >1: 0.63, *P*=0.0006 Patients with relapses or change in EDSS >1: 0.72, *P*=0.0011 Patients with relapses and change in EDSS >1: 0.53, *P*=0.0006 NSD for relapses and change in EDSS <1 or without relapses but change in EDSS >1 Pooled analysis population: Patients with at least one relapse in the 2 yrs before study entry or pronounced EDSS progression had a risk reduction to experience disability progression of 30-40%

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Adverse events	Comments
Kappos 2001 Europe-Switzerland (Additional data from ESG trial)	Same as European Study Group on IFN β-1b in SPMS, 1998	
Kappos 2004 (Reanalysis. Not quality assessed.)	NR	Pooled analysis of the European-SPMS and North American-SPMS trials, see original trials for inclusion and exclusion criteria

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes
Kappos 2006 **Kappos 2007, Kappos 2009** **Polman 2008** **Multiple European; Canada; Israel** **BENEFIT** Efficacy Quality: Good AE Quality: Fair/Good	IFN β-1b (Betaseron) 250 µg, SQ, qod up to 2 yrs N=292 Male: 85 (29%) Female: 207 (71%) Mean age: 30	Total WDs: 65 (22%) AE WDs: 32 (11%)	Patients progressing to Clinically Definite Multiple Sclerosis: 75 patients Patients progressing to McDonald criteria MS: 191 patients Early vs delayed IFN β-1b The difference in the mean EDSS score at yr 3 was lower in the early IFN β-1b group vs delayed IFN β-1b group, *P*=0.0475 Percentage of patients with Clinically Definite Multiple Sclerosis at yr 3: 34% vs 48%, HR 0.59 (0.44 to 0.80), *P*=0.0011, AAR 14% Percentage of patients with EDSS progression excluding unscheduled visits: 14% vs 23%, HR 0.60 (0.39 to 0.92), *P*=0.022, ARR: 8% Annualized relapse rates: Significant (*P*=0.011) at yr 1 in favor of early treatment group and NS at yr 2 and 3 Change in EDSS from BL to yr 5; mean (SD), Median (Interquartile range): -0.03 (1.19), 0.0 (-1.0 to 0.5) vs 0.07 (1.08), 0.0 (-0.5 to 0.5) Recurrent relapses: 44% vs 56% Relapse rates lower in early versus delayed treatment group in the first yr and yr 1-5 together (*P*=0.014), but NS from yr 2 onwards. MSFC improved over 5 yrs and no significant improvement between groups, P=0.608 QOL assessed with EuroQoL-5 dimensional questionnaire and functional assessment of MS trial outcome index-TOI in early vs delayed treatment groups remained high and without significant differences between the two groups.
Kappos 2006 **Multiple European; Canada; Israel** **BENEFIT** Efficacy Quality: Good AE Quality: Fair/Good	Placebo SQ, qod up to 2 yrs N=176 Male: 2 (1%) Female: 174 (99%) Mean age: 30	Total WDs: 28 (16%) AE WDs: 1 (0.5%)	Patients progressing to Clinically Definite Multiple Sclerosis: 77 patients Patients progressing to McDonald criteria MA: 142 patients

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Adverse events	Comments
Kappos 2006 **Kappos 2007, Kappos 2009** **Polman 2008** **Multiple European; Canada; Israel** **BENEFIT** Efficacy Quality: Good AE Quality: Fair/Good	ISR: 141/292 (48.3%) Flu-like illness: 129/292 (44.2%) Depression: 30/292 (10.3%) Abnormal LFT (ALT): 52/292 (18%) Abnormal LFT (AST): 18/292 (6.2%)	On design: 13 IFN β-1b and 6 placebo patients were randomized but never received treatment. On population: Only white race reported. Other 2% of patients not described by race. On WDs: Includes patients lost to FU and WDs.
Kappos 2006 **Multiple European; Canada; Israel** **BENEFIT** Efficacy Quality: Good AE Quality: Fair/Good	ISR: 15/176 (9%) Flu-like illness: 32/176 (18.2%) Depression: 20/176 (11.4%) Abnormal LFT (ALT): 8/176 (5%) Abnormal LFT (AST): 1/176 (0.56%)	

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes
Knobler 1990 Efficacy quality: Fair AE quality: Fair	IFN β-1b (Betaseron) Injection 0.8 MIU 3 times per week, over 24 weeks N=6 Male: 2 (33%) Female: 4 (67%) Mean age: 34	Total WDs: 1 (16.7%) AE WDs: 1 (16.7%)	Annualized relapse rate: 0.8 at 24 weeks; 95% CI, 0.1 to 2.5 Total number of patients experiencing an exacerbation: 2 at 24 weeks
Knobler 1990 Efficacy quality: Fair AE quality: Fair	IFN β-1b (Betaseron) injection 4 MIU 3 times per week, over 24 weeks N=6 Male: 4 (67%) Female: 2 (33%) Mean age: 38	Total WDs: 0 (0%) AE WDs: 0 (0%)	Annualized relapse rate: 2.2 at 24 weeks; 95% CI, 0.9 to 4.3 Total number of patients experiencing an exacerbation: 4 at 24 weeks
Knobler 1990 Efficacy quality: Fair AE quality: Fair	IFN β-1b (Betaseron) Injection 8 MIU 3 times per week, over 24 weeks N=6 Male: 4 (67%) Female: 2 (33%) Mean age: 35	Total WDs: 1 (16.7%) AE WDs: 0 (0%)	Annualized relapse rate: 0.9 at 24 weeks; 95% CI, 0.2 to 2.7 Total number of patients experiencing an exacerbation: 4 at 24 weeks

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Adverse events	Comments
Knobler 1990 Efficacy quality: Fair AE quality: Fair	AE rates apply to first 3 yrs. Rates are only stratified by placebo and Betaseron; there is no AE information by dose. AE reported under 8 MIU arm and placebo arm.	On intervention: Mean BL values: 0.8 MIU vs 4 MIU vs 8 MIU vs 16 MIU vs placebo EDSS: 2.8 vs 4.0 vs 2.7 vs 2.9 vs 3.1 Relapses 2 yrs preceding study: 2.7 vs 3.3 vs 4.0 vs 2.0 vs 2.3 Disease duration: 6.2 vs 8.2 vs 4.2 vs 7.3 vs 7.0
Knobler 1990 Efficacy quality: Fair AE quality: Fair	AE rates apply to first 3 yrs. Rates are only stratified by placebo and Betaseron; there is no AE information by dose. AE reported under 8 MIU arm and placebo arm.	
Knobler 1990 Efficacy quality: Fair AE quality: Fair	Depression: 12/24 (50%) Flu-like illness: 4/24 (16.7%) Headache: 18/24 (75%) Injection site inflammation: 23/24 (95.8%) ISP: 20/24 (83.3%)	

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes
Knobler 1990 Efficacy quality: Fair AE quality: Fair	IFN β-1b (Betaseron) Injection 16 MIU 3 times per week, over 24 weeks N=6 Male: 4 (67%) Female: 2 (33%) Mean age: 36	Total WDs: 1 (16.7%) AE WDs: 1 (16.7%)	Annualized relapse rate: 0 at 24 weeks; 95% CI, 0.0 to 1.2 Total number of patients experiencing an exacerbation: 0 at 24 weeks
Knobler 1990 Efficacy quality: Fair AE quality: Fair	Placebo N=7 Male: 2 (29%) Female: 5 (71%) Mean age: 34	Total WDs: 1 (16.7%) AE WDs: 0 (0%)	Annualized relapse rate: 1.8 at 24 weeks; 95% CI, 0.7 to 3.7 Total number of patients experiencing an exacerbation: 4 at 24 weeks
Montalban 2004 Europe Efficacy quality: Poor AE quality: Poor	IFN β-1b 8 MIU qod, over 2 yrs N=36	NR	See comments on outcome

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Adverse events	Comments
Knobler 1990 Efficacy quality: Fair AE quality: Fair	AE rates apply to first 3 yrs. Rates are only stratified by placebo and Betaseron; there is no AE information by dose. AE reported under 8 MIU arm and placebo arm.	
Knobler 1990 Efficacy quality: Fair AE quality: Fair	Depression: 2/6 (33.3%) Flu-like illness: 4/6 (66.7%) Headache: 6/6 (100%) Injection site inflammation: 2/6 (33.3%) ISP: 3/6 (50%)	
Montalban 2004 Europe Efficacy quality: Poor AE quality: Poor	No details reported, only that frequency of treatment-related AEs (flu-like symptoms, leucopenia and ISR) were greater in the IFN group.	On outcome: Primary outcome- sustained progression defined as EDSS of at least 1.0 or more for 6 mos in patients with BL 5.0 or less and 0.5 or more for 6 mos in patients with BL of 5.5 or more. No primary outcome values reported. On population: Population included 49 with PPMS and 24 with transitional MS, defined as progressive disease with history of a single episode of relapse prior to, at the onset of, or during the progressive phase.

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes
North American Study Group on SPMS (1) 2004 Efficacy quality: Good AE quality: Fair	IFN β-1b Injection 5 MIU qod, over 3 yrs N=314 Male: 121 (39%) Female: 193 (61%) Mean age (SD): 47 (0.47)	Total WDs: 75 (24%) AE WDs: 23 (7%)	Time to confirmed progression: 668 days at 6 mos or more, *P*=0.261
North American Study Group on SPMS (1) 2004 Efficacy quality: Good AE quality: Fair	IFN β-1b Injection 8 MIU qod, over 3 yrs N=317 Male: 107 (34%) Female: 210 (66%) Mean age (SD): 46 (0.45)	Total WDs: 79 (25%) AE WDs: 22 (7%)	Time to confirmed progression: 981 days at 6 mos or more, *P*=0.606

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Adverse events	Comments
North American Study Group on SPMS (1) 2004 Efficacy quality: Good AE quality: Fair	Headache: 182/314 (58%) ISR: 173/314 (55%) Flu-like illness: 141/314 (50%) Injection site inflammation: 165/314 (53%) Chills: 69/314 (22%) Myalgia: 75/314 (24%)	On outcome: Confirmed progression was number of days from the start of treatment to the first recorded increase of 1.0 point or more from the BL EDSS score (0.5 point EDSS score for BL 6.0-6.5) confirmed at two scheduled examinations spanning 6 mos or more from the onset of progression. P-values for time to progression are compared to placebo. Other secondary outcomes are measured as placebo vs pooled IFN β-1b group. The study reported a significant treatment benefit for reduction in annual relapse rate 36% vs 43%, placebo vs 8 MIU respectively. On intervention: Mean BL values: IFN-1b 250 µg vs IFN-1b 160 µg vs placebo EDSS: 5.2 vs 5.1 vs 5.1 Relapses 2 yrs preceding study: 0.8 vs 0.9 vs 0.8 Disease duration SPMS course: 4.0 yrs vs 4.0 yrs vs 4.1 yrs Disease duration MS diagnosis: 14.6 yrs vs 14.5 yrs vs 14.9 yrs
North American Study Group on SPMS (1) 2004 Efficacy quality: Good AE quality: Fair	Headache: 174/317 (55%) ISR: 165/317 (52%) Flu-like illness: 137/317 (43.2%) Injection site inflammation: 160/317 (50%) Chills: 70/317 (22%) Myalgia: 92/317 (29%)	

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Dosage, Population	Withdrawals	Outcomes
North American Study Group on SPMS (1) 2004 Efficacy quality: Good AE quality: Fair	Placebo N=308 Male: 123 (40%) Female: 185 (60%) Mean age (SD): 48 (0.46)	Total WDs: 75 (24.3%) AE WDs: 28 (9%)	Time to confirmed progression: 750 days at 6 mos or more
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	IFN β-1b 8 MIU	NR	Annualized relapse rate: 0.96 at 3 yrs
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	IFN β-1b 1.6 MIU	NR	Annualized relapse rate: 0.96 at 3 yrs
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	Placebo	NR	Annualized relapse rate: 1.12 at 3 yrs

Evidence Table 8. Effectiveness and adverse events in placebo-controlled trials of interferon beta 1b

Study	Adverse events	Comments
North American Study Group on SPMS (1) 2004 Efficacy quality: Good AE quality: Fair	Headache: 141/308 (46%) ISR: 43/308 (14%) Flu-like illness: 102/308 (33%) Injection site inflammation: 20/308 (6%) Chills: 36/308 (12%) Myalgia: 57/308 (19%)	
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	NR	On outcome: These data represent pooled "annual exacerbation rates" however they do not match the data in IFN β 1993 (the main publication for this trial). For "exacerbation rate" at 3 yrs, those data are (1.6 MIU vs 8 MIU vs placebo): 1.05 vs 0.84 vs 1.21. The reason for these discrepant figures is unclear.
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	NR	
Sibley 1996 US/Canada (Additional analysis of IFNB 1993)	NR	

Evidence Table 9. Placebo-controlled trials of glatiramer acetate

Study	Population type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Bornstein 1987	RRMS	DB Parallel Center: NR Setting: NR	Screened: 140 Eligible: NR Enrolled: 50 Withdrawn: 7 Loss to FU: 2 Analyzed: 48	Definite MS diagnosis; age 20-35; at least 2 'well-demarcated' and well-documented exacerbations 2 yr prior to study entry; EDSS ≤6; emotionally stable as determined by psychosocial evaluation	NR; authors report screened patients excluded for the following reasons: age, low frequency of exacerbations, lack of documentation, psychosocial inadequacy, transition to a chronic progressive course, distance from the clinic, and pregnancy	N=50 Mean age : 30.5 42% male 58% female 96% white 4% other
Comi 2001 **6 European countries; Canada**	RRMS	DB Parallel Multicenter Setting: NR	Screened: 485 Eligible: 272 Enrolled: 239 Withdrawn: 14 Loss to FU: 2 Analyzed: Unclear	RRMS diagnosis for at least 1 yr; at least 1 documented relapse in 2 yrs preceding study entry; age 18-50 yrs; baseline EDSS 0-5; at least on enhancing lesion on MRI; clinically relapse-free and without steroid treatment 30 days prior to MRI	Previous use of GA or oral myelin; prior lymphoid irradiation, use of immunosuppressant or cytotoxic agents in 2 yrs preceding study entry; use of AZA, cyclosporine, IFNs, deoxyspergualin or chronic corticosteroid use during 6 mos prior to study entry; concomitant therapy with an experimental MS drug; serious intercurrent systemic or psychiatric illnesses; pregnancy or unwilling/unable to practice contraception during study enrollment; known hypersensitivity to gadolinium-DTPA; unable to undergo repeated MRI scans	N=239 Mean age (SD): 34.0 (7.5) Gender NR

Evidence Table 9. Placebo-controlled trials of glatiramer acetate

Study	Population type	Design	Recruitment	Eligibility	Exclusion	Sample size, Age, Gender, Ethnicity
Johnson 1995	RRMS	DB Parallel Multicenter Setting: Research Center	Screened: 284 Eligible: NR Enrolled: 251 Withdrawn: 36 Loss to FU: 0 Analyzed: 251	Clinically definite or lab supported RRMS; age 18-45 yrs; baseline EDSS 0-5; at least two relapses in 2 yrs prior to study entry; onset of 1st relapse at least 1 yr prior to randomization; period of neurologic stability; no use of steroids 30 days prior	Previous use of Cop 1 (GA), immunosuppressive therapy with cytotoxic chemotherapy or lymphoid irradiation; pregnancy or lactation; insulin-dependent diabetes; HIV or HTLV-1 positive; evidence of Lyme disease; required use of aspirin or chronic NSAIDs	N=251 Mean age (SD): 34.4 (6.3) 26.69% male 73.31% female 94% white 6% other
Wolinsky, 2007	PPMS	DB Parallel Multicenter Setting: Research Center	Screened: 1050 Eligible: NR Enrolled: 943 Withdrawn: 197 Loss to FU: 25 Analyzed: 943	PPMS; age 30-65 yrs; EDSS 3.0-6.5; progressive neurological symptoms including evidence of myelopathy for ≥6 mos before screening; objective evidence of pyramidal damage on neurological examination including a functional system score for the pyramidal system of ≥2; evidence of multilevel CNS disease based on examination or supplemented by MRI findings or visual or auditory evoked responses	Lymphopenia <3000 cells/mL; use of IFN β drug, immunosuppressant, immunomodulating agent, corticosteroid or investigational drug within 3 mos of study entry; any known life-threatening, clinically significant, or uncontrolled illness; allergy to gadolinium or other condition that would preclude MRI; pregnant or lactating; major competing causes of progressive neurological disease	N=943 Mean age (SD): 50.4 (8.3) 51% female 49% male 90% white EDSS (SD): 4.9 (1.2)

Evidence table 10. Effectiveness and adverse events in placebo-controlled trials of glatiramer acetate

Source	Dosage, population	Withdrawals	Outcomes	Adverse events	Comments
Bornstein (1) 1987 Efficacy Quality: Fair AE Quality: Fair	GA (Copolymer 1) Self-injection 20 mg qd n=25	NR	Proportion of patients with confirmed progression: 20% at 2 yrs, P≤0.005 Mean relapse rate: 0.6 at 2 yrs Proportion of relapse-free patients: 56% at 2 yrs Total number of relapses: 16 at 2 yrs	Arthralgia (joint pain): 10/25 (40%) Headache: 8/25 (32%) Injection site itching: 16/25 (64%) Injection site redness: 19/25 (76%) Injection site soreness: 23/25 (92%) Injection site swelling: 22/25 (88%) Patterned reaction: 2/25 (8%)	On population: Population reported as 'exacerbating-remitting' by study authors - here reported as 'RRMS'; Black/Hispanic reported as a single group by study authors - here reported as 'Other'; BL EDSS: 2.9 GA vs 3.1 placebo On outcome: Subgroup analyses found that BL EDSS and treatment group both significantly affected likelihood that a patient would be relapse-free (*P*=0.003 for BL EDSS; *P*=0.036 for treatment group) On AE: Patterned reactions consist of flushing, sweating, palpitations, tightness in the chest, difficulty breathing, anxiety beginning during/immediately after injection and lasting 5-15 minutes On WD: 7 patients identified as having stopped treatment, including 2 in placebo group whose data was deemed unusable. Other 5 patients not identified by treatment group.
Bornstein (1) 1987 Efficacy Quality: Fair AE Quality: Fair	Placebo Self-injection qd n=25	NR	Proportion of patients with confirmed progression: 48% at 2 yrs Mean relapse rate: 2.7 at 2 yrs Proportion of relapse-free patients: 26% at 2 yrs Total number of relapses: 62 at 2 yrs	Arthralgia (joint pain): 9/23 (39.1%) Headache: 9/23 (39.1%) Injection site itching: 5/23 (21.7%) Injection site redness: 11/23 (47.8%) Injection site soreness: 8/23 (34.8%) Injection site swelling: 4/23 (17.4%) Patterned reaction: 0/23 (0%)	

Evidence table 10. Effectiveness and adverse events in placebo-controlled trials of glatiramer acetate

Source	Dosage, population	Withdrawals	Outcomes	Adverse events	Comments
Comi 2001 **6 European countries; Canada** Efficacy Quality: Fair AE Quality: Fair/Good	GA (Copolymer 1) Injection 20 mg qd n=119 Mean age (SD): 34 (7.4)	Total WDs: 7 (5.8%) AE WDs: 3 (2.5%)	Use of rescue medications: 33.6% at 9 mos Annualized relapse rate: 0.81 at 1 yr (projection) Exacerbation requiring hospitalization: 16/119 at 9 mos Mean relapse rate: 0.51 at 9 mos, *P*=0.012 Proportion of relapse-free patients: 55.5% at 9 mos, *P*=0.175	ISRs: 84/119 (70.6%) Patterned reaction: 45/119 (37.8%)	On population: BL EDSS (SD): 2.4 (1.2)
Comi 2001 **6 European countries; Canada** Efficacy Quality: Fair AE Quality: Fair/Good	Placebo N=120 Mean age (SD): 34 (7.5)	Total WDs: 7 (5.8%) AE WDs: 2 (1.7%)	Use of rescue medications: 39.2% at 9 mos Annualized relapse rate: 1.21 at 1 yr (projection) Exacerbation requiring hospitalization: 30/120 at 9 mos Mean relapse rate: 0.76 at 9 mos Proportion of relapse-free patients: 49.2% at 9 mos	ISRs: 34/120 (28.3%) Patterned reaction: 16/120 (13.3%)	
Johnson 1995 Efficacy quality: Good AE quality: Fair	GA (Copolymer 1) Injection 20 mg qd N=125 Male: 37 (30%) Female: 88 (70%) Mean age (SD): 35 (6.0)	Total WDs: 19 (15%) AE WDs: 4 (3%)	Mean change in EDSS (SD): -0.05 (1.13) at 2 yrs, *P*=0.023 Proportion of patients EDSS progression-free: 78.4% at 2 yrs, *P*=NS Ambulation index (SD): 0.27 (0.94) at 2 yrs, *P*=NS Annualized relapse rate: 0.59 Mean relapse rate: 1.19 at 2 yrs, *P*=0.007 Median Time to first relapse (days): 287, *P*=0.097 Proportion of relapse-free patients: 33.6% at 2 yrs, *P*=0.098	ISRs: 113/125 (90.4%) Patterned reaction: 19/125 (15.2%)	On population: Race only listed as 'white' and 'other' Mean BL EDSS (SD): 2.6 (1.3) 2-yr relapse rate preceding study: 2.9

Evidence table 10. Effectiveness and adverse events in placebo-controlled trials of glatiramer acetate

Source	Dosage, population	Withdrawals	Outcomes	Adverse events	Comments
Johnson 1995 Efficacy quality: Good AE quality: Fair	Placebo n=126 Male: 30 (24%) Female: 96 (76%) Mean age (SD): 34 (6.5)	Total WDs: 17 (14%) AE WDs: 1 (0.8%)	Mean change in EDSS (SD): 0.21 (0.99) at 2 yrs Proportion of patient EDSS progression-free: 75.4% at 2 yrs Ambulation index (SD): 0.28 (0.93) at 2 yrs Annualized relapse rate: 0.84 Mean relapse rate: 1.68 at 2 yrs Median time to first relapse (days): 198 Proportion of relapse-free patients: 27.0% at 2 yrs	ISRs: 74/126 (58.7%) Patterned reaction: 4/126 (3.2%)	
Wolinsky 2007 Efficacy Quality: Fair AE quality: Fair Wolinksy 2009	Stratum I - EDSS 3.0-5.0 GA n=341, Placebo n=169 Stratum II - EDSS 5.5-6.5 GA n=286, Placebo n=147 Mean age: 49 90% white Mean EDSS: stratum I 3.9, stratum II 6.15	Total WDs: 197 AE WDs: 41 (GA 31, placebo 10)	Delay in time to sustained progression HR 0.87; 95% CI, 0.71 to 1.07 No difference in mean EDSS increase from BL (GA 0.58 +/- 1.0, Placebo 0.61 +/- 1.13) Males randomized to GA was associated with significant delayed time to progression of disability HR 0.71; 95% CI 0.53 to 0.95; P=0.0193 Median progression free survival for males was 952 days Significant HRs (HR 0.70-0.71) when adjusted for Center, BL EDSS, age and disease duration, but NS when days to study was added to the list of covariates	Most common AE is ISR more frequent in GA group GA vs placebo: Edema: 14.2 vs 3.5% Erythema: 57.1% vs 10.4% Hemorrhage: 20.7% vs 28.5% Inflammation: 8.6% vs 1.3% Mass: 35.6% vs 4.7% Pain: 48.8% vs 17.1% Pruritus: 26.8% vs 28.8%	

Evidence Table 11. Placebo-controlled trials of natalizumab

Study	Population type	Design	Recruitment	Eligibility
Miller (2) 2003 US, Canada, UK	RRMS, SPMS	DB Parallel Multicenter Setting: Specialty Clinic	Screened: NR Eligible: NR Enrolled: 213 Withdrawn: 18 Lost to FU: 10 Analyzed: 205	Age 18-65 yrs, clinically or lab supported diagnosis of RRMS or SPMS with at least 2 relapses within previous 2 yrs, EDSS 2.0-6.5 with a minimum of 3 brain lesions on MRI
O'Connor 2004	RRMS, SPMS	DB RCT Multicenter	Screened: NR Eligible: NR Enrolled: 180 Randomized: 180 Withdrawn: 1 Lost to FU: 3 Analyzed: 180	Age 18-65 yrs, EDSS ≤5.5, stable FSS for ≥30 days prior to onset of study qualifying acute relapse; symptoms of acute relapse for >24 hours but <96 hours prior to receiving the study medication with EDSS at study entry of >3.0
Polman 2006 AFFIRM	RRMS	DB Parallel Multicenter Setting: Specialty Clinic	Screened: NR Eligible: NR Enrolled: 942 Withdrawn: 83 Lost to FU: 12 Analyzed: 942	Adults age 18-50 yrs, diagnosis of RRMS and EDSS score 0-5, MRI lesions consistent with MS diagnosis, at least 1 relapse in preceding 12 mos

Evidence Table 11. Placebo-controlled trials of natalizumab

Study	Exclusion	Sample Size, Age, Gender, Ethnicity
Miller (2) 2003 US, Canada, UK	Use of immunosuppressive or immunomodulating treatments within 3 mos prior to study entry, relapse within 30 days, use of systemic corticosteroids within 30 days	N=213 Mean age: 43.6 (range 22-66) 28.64% male 71.36% female
O'Connor 2004	Patients whose study-qualifying relapse improved prior to administration of study medication; unable to tolerate MRI or gadolinium contrast agent; signs and symptoms of study-qualifying exacerbation were related only to changes in sensory, bladder/bowel, or cognitive function; prior exposure to any murine proteins or monoclonal antibodies, immunomodulating or investigational drug therapies within 3 mos prior to study entry; systemic corticosteroid treatment within 30 days of study entry; concomitant use of immunomodulatory treatments during the study	N=180 Mean age: 39.5 82% female 79% EDSS ≤5.5
Polman 2006 AFFIRM	PPMS, SPMS or PRMS diagnosis; relapse within 50 days prior to drug administration; treatment with CPA or MITO within previous yr; treatment with IFN β, GA, cyclosporine, AZA, methotrexate or intravenous immune globulin within 6 mos; previous treatment with IFN β, GA or both for more than 6 mos	N=942 Mean age (SD): 36.0 (8.3) (range 18-50) 29.94% male 70.06% female 95% white 5% other

Evidence Table 11. Placebo-controlled trials of natalizumab

Study	Population type	Design	Recruitment	Eligibility
Rudick 2006 US, Europe SENTINEL	RRMS	DB Parallel Multicenter Setting: Specialty Clinic	Screened: NR Eligible: NR Enrolled: 1196 Withdrawn: 168 Lost to FU: 9 Analyzed: 1171	Age 18-55 yrs, diagnosis of RRMS, EDSS 0-5.0, MRI confirmed brain lesions consistent with MS diagnosis, previous use of IFN β-1a for at least 12 mos prior to study entry, at least 1 relapse in 12 mos preceding randomization
Sheremata 1999 US	RRMS, SPMS	NR	Screened: NR Eligible: NR Enrolled: 28 Withdrawn: 0 Loss to FU: 0 Analyzed: 28	Clinically-definite RRMS or SPMS, age 19-55 yrs, within 15% ideal body weight range, baseline EDSS ≤5.5
Tubridy 1999 UK	RRMS, SPMS	DB Parallel Multicenter Setting: Specialty Clinic	Screened: NR Eligible: NR Enrolled: 72 Withdrawn: 2 Loss to FU: 0 Analyzed: 70	Clinically definite RRMS or SPMS, age 18-55 yrs, <90kg (198 lbs), EDSS 2.0-7.0, 2 or more exacerbations in 18 mos preceding study, >4 weeks since last exacerbation

Evidence Table 11. Placebo-controlled trials of natalizumab

Study	Exclusion	Sample Size, Age, Gender, Ethnicity
Rudick 2006 **US, Europe** **SENTINEL**	Diagnosis of PPMS, SPMS or PRMS; relapse within 50 days of study entry; treatment with any disease-modifying therapy other than β-1a within 12 mos prior to randomization	N=1171 Mean age (SD): 38.9 (7.7) (range 18-55) 26.39% male 73.61% female 93% white 7% other
Sheremata 1999 **US**	Patients with MS exacerbations or infections; immunomodulatory or investigational drug recipients; pregnancy, breastfeeding or failure to use adequate birth control; regular blood donors, heavy smokers, drinkers other medical disorders; known drug hypersensitivity	N=28 Mean age (SD): 40.8 (9.1) 53.57% male 46.43% female
Tubridy 1999 **UK**	PPMS; pregnant, breastfeeding or women of childbearing age not using birth control; normal T2 weighted MRI at week -4; use of immunosuppressive drug within 6 mos (including AZA, CPA and IFN β); use of methylprednisolone and/or oral prednisone in 4 weeks preceding first visit; previous treatment with anti-CD4 antibodies, other monoclonal antibodies or total lymphoid irradiation at any time; previous exposure to products containing murine protein; alcohol consumption >21 units/week or abuse of other drugs	N=72 Mean age: 40.3 (range 25-55) 36.11% male 63.89% female

Evidence Table 12. Effectiveness and adverse events in placebo-controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse events	Comments
Miller (2) 2003 **US, Canada, UK** Efficacy quality: Good AE quality: Fair	Nat IV 3 mg/kg every 28 days, over 6 mos N=68 Male: 21 (31%) Female: 47 (69%) Mean age: 43	Total WDs: 5 (7.4%) AE WDs: 4 (5.9%)	Mean change in EDSS: -0.14 Visual-analogue scale score, mean change: 9.49 mm, *P*=0.04 Use of rescue medication in relapsing patients: 5/13, *P*<0.001 Total number of relapses (physician assessed): 3, *P*=0.004	Headache: 27/68 (39.7%) Infections: 15/68 (22.1%) UTI: 15/68 (22.1%) Weakness/muscle weakness: 12/68 (17.6%)	On intervention: Other BL values: 3mg/kg vs 6 mg/kg vs placebo Mean EDSS: 4.2 vs 4.3 vs 4.4 Mean relapses 2 yrs prior to study entry: 2.9 vs 3.1 vs 3.0 RRMS course: 47 (69%) vs 52 (70%) vs 45 (63%) SPMS course: 21 (31%) vs 22 (30%) vs 26 (37%) On outcome: Relapse rates were measured 6 mos after stopping treatment; NSD found among three treatment groups. P-values are versus placebo.
Miller (2) 2003 **US, Canada, UK** Efficacy quality: Good AE quality: Fair	Nat IV 6 mg/kg every 28 days, over 6 mos N=74 Male: 15 (20%) Female: 59 (80%) Mean age: 45	Total WDs: 8 (10.8%) AE WDs: 3 (4.1%)	Mean change in EDSS: -0.03 Visual-analogue scale score, mean change: 6.21 mm, P=0.03 Use of rescue medication in relapsing patients: 7/14, P=0.002 Total number of relapses (physician assessed): 8, P=0.11	Headache: 20/74 (27%) Infections: 14/74 (18.9%) UTI: 13/74 (17.6%) Weakness/muscle weakness: 7/74 (9.5%)	
Miller (2) 2003 **US, Canada, UK** Efficacy quality: Good AE quality: Fair	Placebo IV every 28 days, over 6 mos N=71 Male: 25 (35%) Female: 46 (65%)	Total WDs: 5 (7.0%) AE WDs: 3 (4.2%)	Mean change in EDSS: 0.03 Visual-analogue scale score, mean change: -1.38 mm Use of rescue medication in relapsing patients: 22/27 Total number of relapses (physician assessed): 18	Headache: 27/71 (38%) Infections: 11/71 (15.5%) UTI: 11/71 (15.5%) Weakness/muscle weakness: 11/71 (15.5%)	

Evidence Table 12. Effectiveness and adverse events in placebo-controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse events	Comments
O'Connor 2004	Nat Single dose 1 mg/kg vs Nat 3 mg/kg vs placebo, over 14 weeks N=180	NR	Clinical recovery after relapse EDSS, SNRS, patient assessment of well-being, steroid use for relapse: NSD	NSD between treatment groups	
Polman 2006 AFFIRM Havrdova 2009 Efficacy quality: Good AE quality: Good	Nat IV 300mg every 4 weeks, up to 116 weeks N=627 Male: 178 (28%) Female: 449 (72%) Mean age (SD): 36 (8.5)	Total WDs: 52 (8.3%) AE WDs: 15 (2.4%)	Cumulative probability of disease progression: 17%; HR 0.58 at 2 yrs, P<0.0001; 95% CI, 0.43 to 0.77 Annualized relapse rate: 0.27 at 1 yr, P<0.001; 95% CI, 0.21 to 0.33 Annualized relapse rate: 0.23 at 2 yrs, P<0.001; 95% CI, 0.19 to 0.28 Proportion of relapse-free patients: 77% at 1 yr, P<0.001 Proportion of relapse-free patients: 67% at 2 yrs, P<0.001 Nat vs placebo Relapse free: 71% vs 43% [absolute difference 27.3% (20.6-34.0)], P<0.0001 No EDSS progression (sustained at 12 weeks): 84% vs 72% [absolute difference 12.0% (5.9-17.9)], P=0.0001 Relapse-free with stable EDSS scores (Remission), yr 2: 64% vs 39% [absolute difference 25.4% (18.7-32.1)], P<0.0001 No EDSS progression (sustained at 12 weeks): absolute difference 29.3% (24.3-34.3), P<0.0001 Highly active disease at BL: 67% vs 19% [absolute difference 48.5% (36.0-61.0)], P<0.0001	Arthralgia (joint pain): 119/627 (19%) Depression: 119/627 (19%) Fatigue/Tiredness: 169/627 (27%) Headache: 238/627 (38%) ISRs (e.g. bleeding): 19/627 (3%) Respiratory infections: 107/627 (17.1%) Total patients reporting any AE: 596/627 (95.1%) UTI: 125/627 (19.9%)	On population: Mean disease duration: 5 yrs Mean EDSS at BL (SD): 2.3 (1.2) Mean relapse rate/yr at BL (SD): 1.52 (0.86) On outcome: 3 randomized patients who never received treatment were included for efficacy but not safety outcomes. On AEs: NSDs between Nat and placebo for serious AEs and non-serious AEs. Serious AEs: cholelithiasis reported in <1% of patients in both groups (P=0.435). On WDs: 24 additional Nat patients and 15 additional placebo patients discontinued drug due to AEs but completed FU; not counted as WDs by authors.

Evidence Table 12. Effectiveness and adverse events in placebo-controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse events	Comments
Polman 2002 AFFIRM **Efficacy quality: Good** **AE quality: Good**	Placebo IV every 4 weeks, up to 116 weeks N=315 Male: 104 (33%) Female: 211 (67%) Mean age (SD): 37 (7.8)	Total WDs: 31 (9.8%) AE WDs: 6 (1.9%)	Annualized relapse rate: 0.73 at 2 yrs, *P*<0.001; 95% CI, 0.62 to 0.87 Cumulative prob. of disease progression: 29% HR 0.58 at 2 yrs, *P*<0.0001; 95% CI, 0.43 to 0.77 Annualized relapse rate: 0.78 at 1 yr, *P*<0.001; 95% CI, 0.64 to 0.94 Proportion of relapse-free patients: 56% at 1 yr, *P*<0.001 Proportion of relapse-free patients: 67% at 2 yrs, *P*<0.001	Arthralgia (joint pain): 44/312 (14.1%) Depression: 50/312 (16%) Fatigue/Tiredness: 66/312 (21.2%) Headache: 103/312 (33%) ISRs (e.g. bleeding): 6/312 (1.9%) Respiratory infections: 50/312 (16%) Total patients reporting any AE: 300/312 (96.2%) UTI: 53/312 (17%)	
Rudick 2006 US, Europe SENTINEL Efficacy quality: Good AE quality: Fair	IFN β-1a (Avonex) Injection 30 ug once a week, up to 116 doses N=589 Male: 147 (25%) Female: 442 (75%) Mean age (SD): 39 (7.7)	Total WDs: 73 (12%) AE WDs: 17 (3%)	Cumulative probability of disease progression: 23% at 2 yrs, *P*=0.02 Annualized relapse rate: 0.34 at 2 yrs, *P*=0.001; 95% CI, 0.29 to 0.39 Annualized relapse rate: 0.38 at 1 yr, *P*<0.001; 95% CI, 0.32 to 0.45 Proportion of relapse-free patients: 61% at 2 yrs, *P*<0.001	Depression: 124/589 (21.1%) Flu-like illness: 118/589 (20%) Headache: 271/589 (46%) Other psychiatric event (anxiety, mania, etc.): 71/589 (12.1%) Respiratory infections: 47/589 (8%) Total patients reporting any AE: 584/589 (99.2%)	On Design: 25 post-randomization exclusions due to "data irregularities" at one study site. On Population: Population figures exclude 25 patients from one center whose data was not counted in analysis due to data irregularities. On Outcome: Proportion of relapse-free patients reported in text as 54% and 32% respectively; does not match values in Table 2 (61% and 37%). Sustained disability progression over 2 yrs: HR 0.76 (95% CI, 0.61 to 0.96; *P*=0.02) Risk of relapse: HR 0.50 (95% CI, 0.43 to 0.59; *P*<0.001)

Evidence Table 12. Effectiveness and adverse events in placebo-controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse events	Comments
Rudick 2006 **US, Europe** **SENTINEL** Efficacy quality: Good AE quality: Fair	Nat IV 300 mg every 4 weeks, up to 29 doses N=589 Male: 147 (25%) Female: 442 (75%) Mean age (SD): 39 (7.7)	Total WDs: 73 (12%) AE WDs: 17 (3%)	Cumulative probability of disease progression: 23% at 2 yrs, *P*=0.02 Annualized relapse rate: 0.34 at 2 yrs, *P*=0.001; 95% CI, 0.29 to 0.39 Annualized relapse rate: 0.38 at 1 yr, *P*<0.001; 95% CI, 0.32 to 0.45 Proportion of relapse-free patients: 61% at 2 yrs, *P*<0.001	Depression: 124/589 (21.1%) Flu-like illness: 118/589 (20%) Headache: 271/589 (46%) Other psychiatric event (anxiety, mania, etc.): 71/589 (12.1%) Respiratory infections: 47/589 (8%) Total patients reporting any AE: 584/589 (99.2%)	On Design: 25 post-randomization exclusions due to "data irregularities" at one study site. On Population: Population figures exclude 25 patients from one center whose data was not counted in analysis due to data irregularities. On Outcome: Proportion of relapse-free patients reported in text as 54% and 32% respectively; does not match values in Table 2 (61% and 37%). Sustained disability progression over 2 yrs: HR 0.76 (95% CI, 0.61 to 0.96; *P*=0.02) Risk of relapse: HR 0.50 (95% CI, 0.43 to 0.59; *P*<0.001)
Rudick 2006 **US, Europe** **SENTINEL** Efficacy quality: Good AE quality: Fair	IFN β-1a (Avonex) Injection 30 ug once a week, up to 116 weeks N=582 Male: 162 (28%) Female: 420 (72%) Mean age (SD): 39 (7.6)	Total WDs: 95 (16%) AE WDs: 14 (2%)	Cumulative probability of disease progression: 29% at 2 yrs, *P*=0.02 Annualized relapse rate: 0.75 at 2 yrs, *P*=0.001; 95% CI, 0.67 to 0.84 Annualized relapse rate: 0.81 at 1 yr, *P*<0.001; 95% CI, 0.72 to 0.92 Proportion of relapse-free patients: 37% at 2 yrs, *P*<0.001	Depression: 105/582 (18%) Flu-like illness: 111/582 (19.1%) Headache: 256/582 (44%) Other psychiatric event (anxiety, mania, etc.): 47/582 (8.1%) Respiratory infections: 41/582 (7%) Total patients reporting any AE: 578/582 (99.3%)	

Evidence Table 12. Effectiveness and adverse events in placebo-controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse events	Comments
Rudick 2006 **US, Europe** **SENTINEL** Efficacy quality: Good AE quality: Fair	Placebo IV every 4 weeks, up to 29 weeks N=582 Male: 162 (28%) Female: 420 (72%) Mean age (SD): 39 (7.6)	Total WDs: 95 (16%) AE WDs: 14 (2%)	Cumulative probability of disease progression: 29% at 2 yrs, *P*=0.02 Annualized relapse rate: 0.75 at 2 yrs, *P*=0.001; 95% CI, 0.67 to 0.84 Annualized relapse rate: 0.81 at 1 yr, *P*<0.001; 95% CI, 0.72 to 0.92 Proportion of relapse-free patients: 37% at 2 yrs, *P*<0.001	Depression: 105/582 (18%) Flu-like illness: 111/582 (19.1%) Headache: 256/582 (44%) Other psychiatric event (anxiety, mania, etc.): 47/582 (8.1%) Respiratory infections: 41/582 (7%) Total patients reporting any AE: 578/582 (99.3%)	
Sheremata 1999 **US** Efficacy quality: Fair AE quality: Poor	Nat IV 0.03-3.0 mg/kg 1x, single dose N=21	Total WDs: 0 (0%) AE WDs: 0 (0%)	NR	Total patients reporting any AE: 17/21 (81%)	On population: Other BL values: RRMS: 20/28 (71%) SPMS: 8/20 (29%) Relapse rate 2 yrs prior to study entry: 0.7-2.3 (mean NR)
Sheremata 1999 **US** Efficacy quality: Fair AE quality: Poor	Placebo IV single dose N=7	Total WDs: 0 (0%) AE WDs: 0 (0%)	NR	Total patients reporting any AE: 6/7 (85.7%)	

Evidence Table 12. Effectiveness and adverse events in placebo-controlled trials of natalizumab

Study	Dosage, Population	Withdrawals	Outcomes	Adverse events	Comments
Tubridy 1999 UK Efficacy quality: Fair AE quality: Poor/Fair	Nat IV 3 mg/kg of body weight every 4 weeks, 2 doses N=37 Male: 12 (32%) Female: 25 (68%) Mean age: 40	Total WDs: 0 (0%) AE WDs: 0 (0%)	Mean change in EDSS: -0.02 at 24 weeks Mean change in EDSS: -0.06 at 12 weeks Exacerbation requiring hospitalization: 4 at 24 weeks Exacerbation requiring hospitalization: 2 at 12 weeks Total number of patients experiencing an exacerbation: 14 at 24 weeks, *P*=0.005 Total number of patients experiencing an exacerbation: 9 at 12 weeks, *P*=0.57	Fatigue/Tiredness: 12/37 (32.4%) Total patients reporting any AE: 19/37 (51.4%)	On intervention: Nat was diluted to 100 ml with saline On Population: BL values, Nat vs placebo: Mean EDSS: 4.9 vs 4.7 RRMS: 25 (68%) vs 28 (80%) SPMS: 12 (32%) vs 7 (20%)
Tubridy 1999 UK Efficacy quality: Fair AE quality: Poor/Fair	Placebo IV 100 ml saline every 4 weeks, two doses N=35 Male: 14 (40%) Female: 21 (60%) Mean age: 41	Total WDs: 2 (6%) AE WDs: 0 (0%)	Mean change in EDSS: 0.02 at 24 weeks Mean change in EDSS: 0.18 at 12 weeks Exacerbation requiring hospitalization: 3 at 12 weeks Exacerbation requiring hospitalization: 0 at 24 weeks Total number of patients experiencing an exacerbation: 11 at 12 weeks, *P*=0.57 Total number of patients experiencing an exacerbation: 4 at 24 weeks, *P*=0.005	Fatigue/Tiredness: 4/35 (11.4%) Total patients reporting any AE: 24/35 (68.6%)	

Evidence Table 13. Active-control and placebo-controlled trials of mitoxantrone

Study	Population Type	Design	Recruitment	Eligibility
Bastianello 1994 Italy Efficacy quality: Fair AE quality: Fair	RRMS	DB Parallel Multicenter Setting: NR	Screened: NR Eligible: NR Enrolled: 52 Withdrawn: 0 Lost to FU: 0 Analyzed: 25	A definite diagnosis of MS; a relapsing-remitting disease course defined as two or more relapses occurring in the 24 mos prior to study entry; age 18-45 yrs; disease duration from 1-10 yrs; disability no less than 2 or more than 5 on the Kurtzke EDSS
Millefiorini 1996 Italy Efficacy quality: Good AE quality: Good	PRMS	Blinding: NR Parallel Multicenter Setting: NR	Screened: NR Eligible: NR Enrolled: 51 Withdrawn: 9 Lost to FU: NR Analyzed: 51	Age 18-45 yrs, clinically definite or laboratory supported RRMS, disease duration from 1-10 yrs, disability from 2 to 5 on Kurtzke EDSS with at least 2 exacerbations in the previous 2 yrs
Zipoli 2008	RRMS (active) or SPMS	Open-label Alternatively attributed with safety profiles considered	Enrolled: 162 Withdrawn: 3 (due to inefficacy, an additional 6 due to side effects) Lost to FU: 0 Analyzed: 153	RRMS or SPMS; SPMS course with decrease of ≥1 point on EDSS for BL EDSS <6 or 0.5 points for EDSS >6 in prior yr; RRMS with ≥2 relapses or 1 relapse with incomplete recovery in prior 2 yrs despite treatment with immunomodulating drugs or AZA; IM treatment stopped ≥3 mos and AZA ≥6 mos prior to start of trial

Evidence Table 13. Active-control and placebo-controlled trials of mitoxantrone

Study	Exclusion	Sample size, age, gender, ethnicity
Bastianello 1994 **Italy** Efficacy quality: Fair AE quality: Fair	HIV-positive; previous cardiovascular disease, with LVEF of less than 50% as determined by echocardiography; subjects presenting renal, liver and/or respiratory dysfunctions, diabetes, malignancy, psychiatric illness, pregnancy and women not practicing contraception; patients who had taken previous immunosuppressant medications (such as AZA, CPA, plasmapheresis) or were taking steroids during the 3 mos before entry; patients incapable of fulfilling the requirements of the study or signing the informed consent	N=25 Mean age: 29.2 40% male 60% female
Millefiorini 1996 **Italy** Efficacy quality: Good AE quality: Good	HIV-positive; previous cardiovascular disease; LVEF of less than 50% as determined by echocardiography; subjects presenting renal, liver and/or respiratory dysfunction, diabetes, malignancy, psychiatric illness, pregnancy and women not practicing contraception; patients who where taking steroids during the 3 mos before entry or previous immunosuppressant medication; patients incapable of fulfilling the requirements of the study or signing the informed consent	N=51 Mean age: 29.8 31.37% male 68.63% female
Zipoli 2008	Patients with significant post-void residual bladder volume MITO was preferred; decrease LVEF CPA preferred	N=162 (9 discontinued prior to end of yr 1; MITO 75, CPA 78) Mean age: MITO 43.3, CPA 45.3 MITO 65% female, CPA 64% female

Evidence Table 14. Effectiveness and adverse events in active-control and placebo-controlled trials of mitoxantrone

Study	Dosage, Population	Withdrawals	Outcomes	Adverse events	Comments
Bastianello 1994 **Italy** Efficacy quality: Fair AE quality: Fair	MITO IV 8 mg/m2, 30 min infusion every month, for 1 year N=13 Male: 5 (38%) Female: 8 (62%) Mean age (SD): 30 (5.2)	Total WDs: 0 AE WDs: 0	Mean change in EDSS: -0.27 at 1 year, *P*=0.18; 95% CI, NR Proportion of patients with EDSS deterioration: 8% at 1 year, *P*=0.49; 95% CI, NR Mean relapse rate: 0.54 at 1 year, *P*=0.014; 95% CI, NR Total number of patients experiencing an exacerbation: 5 at 1 year, *P*=0.02; 95% CI, NR	Amenorrhea: 1/13 (7.7%) Diarrhea, vomiting and slight fever: 1/13 (7.7%) Nausea: 7/13 (53.8%) AEs not separated by drug; AEs of 25 people all together are reported.	On intervention: Mean BL values, MITO vs placebo: EDSS: 3.7 vs 3.5 Relapses 2 years prior to study entry: 2.8 vs 3.3
Bastianello 1994 **Italy** Efficacy quality: Fair AE quality: Fair	Placebo N=12 Male: 5 (42%) Female: 7 (58%) Mean age (SD): 28 (6.5)	Total WDs: 0 AE WDs: 0	Mean change in EDSS: 0.08 at 1 year, P=0.18; 95% CI, NR Proportion of patients with EDSS deterioration: 17% at 1 year, *P*=0.49; 95% CI, NR Mean relapse rate: 1.67 at 1 year, *P*=0.014; 95% CI, NR Total number of patients experiencing an exacerbation: 10 at 1 year, *P*=0.02; 95% CI, NR	AEs not separated by treatment arm. AEs of 25 people all together are reported. (See AEs under treatment arm)	

Evidence Table 14. Effectiveness and adverse events in active-control and placebo-controlled trials of mitoxantrone

Study	Dosage, Population	Withdrawals	Outcomes	Adverse events	Comments
Millefiorini 1996 Italy Efficacy quality: Good AE quality: Good	MITO IV 8 mg/m2, once per month, for 1 year N=27 Male: 10 (37%) Female: 17 (63%) Mean age (SD): 31 (6.0)	Total WDs: 4 (15%) AE WDs: NR	Mean exacerbations per person-year: 0.44 at 2 years, *P*=0.0002; 95% CI, 0.62 to 2.84 Proportion of patients with EDSS deterioration: 7% at 2 years, *P*=0.02; 95% CI, 8 to 52 Proportion of relapse-free patients: 63% at 2 years, *P*=0.006; 95% CI, 15 to 65	Amenorrhea: 5/51 (9.8%) Headache: 3/51 (5.9%) Nausea/vomiting: 9/51 (17.6%) Respiratory infections: 2/51 (3.9%) UTI: 3/51 (5.9%) (Data not separated by treatment arms)	On intervention: Mean BL values, MITO vs placebo: EDSS: 3.6 vs 3.5 Relapses 2 years prior to study entry: 2.8 vs 2.8 Disease duration (years): 5.7 vs 5 Incomplete recruitment generated an imbalance in terms of sex.
Millefiorini 1996 Italy Efficacy quality: Good AE quality: Good	Placebo IV saline solution, once per month, for 1 year N=27 Male: 10 (37%) Female: 17 (63%) Mean age (SD): 31 (6.0)	Total WDs: 5 (21%) AE WDs: NR	Mean exacerbations per person-year: 1.31 at 2 years, *P*=0.0002; 95% CI, 0.62 to 2.84 Proportion of patients with EDSS deterioration: 37% at 2 years, *P*=0.02; 95% CI, 8 to 52 Proportion of relapse-free patients: 21% at 2 years, *P*=0.006; 95% CI, 15 to 65	Data not separated by treatment arms. See AEs under treatment arm.	

Evidence Table 14. Effectiveness and adverse events in active-control and placebo-controlled trials of mitoxantrone

Study	Dosage, Population	Withdrawals	Outcomes	Adverse events	Comments
Zipoli 2008	MITO vs CPA as second-line therapy RRMS (active) or SPMS	NR	MITO vs CPA Median time to first relapse: 2.6 years vs 2.5 years, NSD Time to progression on EDSS: 3.8 yrs vs 3.6 yrs, *P*=0.04 SPMS and shorter duration of SPMS were significantly associated with higher probability of progression; ARR: MITO 76% reduction (1.7 +/- 1.8 to 0.4 +/- 0.8, *P*=0.001)	NR Discontinued therapy: MITO 4 (5%); CPA 17 (22%), *P*=0.03 Discontinued due to nausea: MITO 20 (27%) vs 28 (36%)	

Evidence Table 15. Characteristics of trials in patients with clinically isolated syndrome

Author Year Country Trial name	Study design Setting	Inclusion/exclusion criteria	Interventions	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/analyzed	Results
Comi 2009 16 countries; 80 sites from USA, Europe, Argentina, Australia and New Zealand PreCISe Study	DB RCT (3 year) Placebo-controlled Parallel Multicenter	Inclusion: Age 18-45 years; one unifocal neurological event, and positive brain MRI at screening scan (at least 2 cerebral lesions on the T2-weighted images at least 6 mm in diameter - lesions on 2 consecutive slices each of which was 3 mm thick); enrolled within 90 days after onset of first clinical attack Exclusion: multifocal clinical presentation; diseases other than MS responsible for the clinical or MRI presentation; use of experimental or investigational drugs; any use of IFN β or chronic corticosteroids treatment within 6 months of screening; a relapse between screening and BL visits; pregnancy or breastfeeding; known sensitivity to mannitol or gadolinium	GA 2 mg daily SQ injection (n=243) Placebo daily SQ injection (n=238)	Mean age (SD): 31.2 (6.9) Median (range): 30.5 (18.1-45.8) 33% male 67% female 96% white 4% other	Mean number of T2 lesions (SD): 31.5 (30.7) Mean volume of T2 lesions (SD): 6.0 (6.9) mL Mean brain volume (SD): 1540 (105) mL Mean number of gadolinium enhancing lesions (SD): 1.5 (2.9) Mean volume of gadolinium enhancing lesions (SD): 0.3 (0.6) mL	Screened: 619 Eligible: 481 Enrolled: 481	GA (n=243) vs Placebo (n=238) WDs: 37 (15.2%) vs 21 (8.8%) Loss to FU: NR Analyzed: 243 vs 238	GA (n=243) vs Placebo (n=238) Risk of conversion to clinically definite MS: HR, 0.55; 95% CI, 0.40 to 0.77; *P*=0.0005 Time of conversion to clinically definite MS (based on 25% of patients who converted): 336 days vs 722 days; *P*=0.0041 Number of new T2 lesions: 0.7 vs 1.8; RR, 0.42; 95% CI, 0.29 to 0.61 T2 lesions volume: reduction in GA compared to P; geometric means ratio 0.75; 95% CI, 0.64 to 0.87; *P*=0.0002 Percent change from BL in brain volume: -0.33% vs -0.38%; *P*=NS Proportion of patients converted: 42.9% vs 24.7%; OR, 0.41; 95% CI, 0.28 to 0.62; *P*<0.0001
Comi; Fillipi 2001; 2004 ETOMS Multiple European Countries	DB Parallel Multicenter Setting: Specialty Clinic	Inclusion: Clinical syndromes indicating unifocal or multifocal involvement of the CNS; age 18-40 years; first neurological episode suggestive of MS in 3 months prior to study entry; one or more abnormalities in neurological exam; positive MRI brain scan Exclusion: Previous immunosuppressive or immunomodulatory treatment; participation in an experimental procedure during year before study; other serious intercurrent systemic illness or psychiatric disorders; pregnancy; unwillingness to use reliable contraception	IFN β-1a (Rebif) Placebo SQ injection once a week, for 2 years	Mean age (SD): 28 (6.1) 112 (36.2%) male 197 (63.8%) female Ethnicity: NR	Percentage treated with steroids: 70% Percentage treated with gadolinium enhancing lesions on T1: 58% Median volume of lesions on T2 weighted MRI: 4964-5542 mm2	Screened: 375 Eligible: NR Enrolled: 309	Rebif vs Placebo WDs: 13 (8%) vs 18 (11.6%) Lost to FU: NR Analyzed: 308	Rebif vs Placebo Number of patients converting to MS at 2 years: 52 (34%), *P*=0.047 vs 69 (45%), *P*=0.045 Time to conversion for CIS to MS: 5698 days, *P*=0.034 vs 252 days, *P*=NR Annualized relapse rate at 2 years: 0.33, *P*=0.045 vs 0.43, *P*=NR

Evidence Table 15. Characteristics of trials in patients with clinically isolated syndrome

Author Year Country Trial name	Method of adverse events assessment	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Comi 2009 16 countries; 80 sites from USA, Europe, Argentina, Australia and New Zealand PreCISe Study	Assessments included AEs, standard clinical laboratory tests, vital signs, weight, physical examinations, and electrocardiograph measurements	GA vs Placebo ISRs: 135 (56%) vs 56 (24%) Immediate post-injection reactions: 47 (19%) vs 12 (5%) Lymphadenopathy: 13 (5.3%) vs 1 (0.4%) Urticaria: 6 (2.5%) vs 1 (0.4%) Influenza-like illness: 10 (4.1%) vs 2 (0.8%) Constipation: 6 (2.5%) vs 2 (0.8%) Pruritus: 9 (3.7%) vs 3 (1.3%) Erythema: 9 (3.7%) vs 3 (1.3%) Vomiting: 14 (5.8%) vs 5 (2.1%) Rash: 8 (3.3%) vs 3 (1.3%) Vision blurred: 5 (2.1%) vs 0 (0%) Injection-site necrosis: 2 (0.8%) vs 0 (0%) Injection-site atrophy or lipoatrophy: 10 (3%) vs 0 (0%) Suicide: 1 (0.4%) vs 0 (0%) - occurred during day 50 of GA treatment Serious AEs occurred in 19 (8%) of patients in GA group and in 11 (5%) in the placebo group.	GA vs Placebo WDs: 37 (15.2%) vs 21 (8.8%) AE WDs: 14 (5.8%) vs 4 (1.7%); *P*=0.0184	Funded by Teva Pharmaceutical Industries The sponsor was involved in the study design, conduct, monitoring, data analysis, and writing of the report.	Efficacy Analysis: Results are findings from the interim analysis that occurred when patients had a mean overall exposure to GA of 2.32 years (SD 0.65). Note: Placebo group was stopped after reviewing data at interim analysis and the Drug Monitoring Committee recommended that patients in the placebo group receive GA in the open label extension. 193 (40%) patients were still in the DB phase at the cut-off date of the interim analysis; 230 (48%) patients completed the DB phase either because of conversion to clinically definite MS or after 3 years of treatment. No major differences between the two groups in laboratory, vital signs, and electrocardiograph findings (data NR)
Comi; Fillipi 2001; 2004 ETOMS Multiple European Countries		Rebif vs Placebo Chills: 17/154 (11%) vs 17/154 (11%) Fever: 43/154 (27.9%) vs 18/154 (11.7%) ISRs (e.g. bleeding): 92/154 (59.7%) vs 18/154 (11.7%) Myalgia: 26/154 (16.9%) vs 14/154 (9.1%)	Total WDs: 31 AE WDs: NR	Serono International SA (Geneva, Switzerland)	Subgroup analysis based on brain-volume change on MRI scan: 41/131(31%) IFN-1a vs 62/132 (47%) placebo patients converted to MS at 24 months

Evidence Table 15. Characteristics of trials in patients with clinically isolated syndrome

Author Year Country Trial name	Study design Setting	Inclusion/exclusion criteria	Interventions	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/analyzed	Results
Jacobs et al (CHAMPS Study; 3 publications) 2000, 2001 US and Canada CHAMPS	DB Parallel Multicenter Setting: Specialty Clinic	Inclusion: Age 18-50; first isolated well-defined neurologic event consistent with demyelination and involving the optic nerve, spinal cord or brain stem/cerebellum; confirmed on ophthalmologic or neurologic exam; ≥2 lesions at least 3 mm in diameter on MRI; onset of visual or neurologic symptoms no more than 14 days before corticosteroid therapy was begun Exclusion: Prior neurologic or visual event consistent with demyelination lasting longer than 48 hours	IFN β-1a (Avonex) IM 30 µg once per week, up to 3 years Placebo IM once per week	Mean age (SD): 33 (7) 24.54% male 75.46% female 86% white 8% black 1% Asian 3% Hispanic 3% other	Percentage treated with steroids: 100% Percentage treated with gadolinium enhancing lesions: 28% Median volume of lesions on T2 weighted MRI: 2051 mm2	Screened: NR Eligible: NR Enrolled: 383	Withdrawn: 57 Lost to FU: 16 Analyzed: 383	IFN β-1a Cumulative probability of conversion to MS: ARR 0.49 at 3 years, P<0.001; 95% CI, 0.33 to 0.73
Kappos 2006 Kappos 2007 3 year extension Kappos 2009 5 year extension Multiple European; Canada; Israel BENEFIT Efficacy Quality: Good AE Quality: Fair/Good	DB Parallel Multicenter Setting: NR	Inclusion: Patients with a CIS, defined as a first neurologic event suggestive of MS lasting for at least 24 hours and with symptoms and signs indicating either a single lesion (monofocal) or more than one lesion (multifocal) within the CNS; age 18-45 years; have presented with a first neurologic event suggestive of MS that lasted for at least 24 hours, and had to have at least two clinically silent lesions on their T2-weighted brain MRI scan with a size of at least 3 mm, at least one of which being ovoid, periventricular, or infratentorial; BL EDSS between 0 and 5 Exclusion: Patients in whom any disease other than MS could explain their signs and symptoms; any previous episode that could possibly be attributed to an acute demyelinating event; patients with complete transverse myelitis or bilateral optic neuritis; patients who had received prior immunosuppressive therapy	IFN β-1b (Betaseron) 250 µg, SQ, qod up to 2 years Placebo SQ qod, up to 2 years	Mean age: 30 29.27% male 70.73% female white: 98% other: 2%	Percentage treated with steroids: 71% Monofocal: 47% Percentage with gadolinium enhancing lesions on T1: 42% Median volume of T2 lesions: 1951.5-1858.5 mm2 (range 592-5029)	Screened: 603 Eligible: 511 Enrolled: 487	Withdrawn: 62 Lost to FU: 31 Analyzed: 468	Betaseron vs Placebo Patients progressing to Clinically Definite Multiple Sclerosis: 75 (26%) vs 77 (44%) HR: 0.50 (95% CI, 0.36 to 0.70), NNT 6 Patients progressing to McDonald criteria MA: 191 vs 142 HRQOL: No significant change from BL in either group

Evidence Table 15. Characteristics of trials in patients with clinically isolated syndrome

Author Year Country Trial name	Method of adverse events assessment	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Jacobs et al (CHAMPS Study; 3 publications) 2000, 2001 US and Canada CHAMPS		IFN β-1a vs placebo Depression: 20.2% vs 13% Flu-like illness: 53.9% vs 25.8%	WDs: 73 AE WDs: 8	Supported by Biogen	On outcome: Subgroup analysis of only patients presenting with optic neuritis (n=192): Conversion to clinically definite MS IFN-1a vs placebo: ARR 0.58 (0.34-1.00; *P*=0.05) On intervention: Run-in: 1 g methylprednisolone every day via IV for 3 days followed by 1 mg/kg prednisone orally every day for 11 days and a 4-day tapering period according to the following schedule: 20mg day 1; 10 mg day 2; 0 mg day 3; 10 mg day 4.
Kappos 2006 Kappos 2007 3 year extension Kappos 2009 5 year extension Multiple European; Canada; Israel BENEFIT Efficacy Quality: Good AE Quality: Fair/Good		Betaseron vs Placebo ISR: 141/292 (48.3%) vs 15/176 (9%) Flu-like illness: 129/292 (44.2%) vs 32/176 (18.2%) Depression: 30/292 (10.3%) vs 20/176 (11.4%) Abnormal LFT (ALT): 52/292 (18%) vs 8/176 (5%) Abnormal LFT (AST): 18/292 (6.2%) vs 1/176 (0.56%)	Total WDs: 93 AE WDs: 33	Funded by Schering AG	On design: 13 IFN β-1b and 6 placebo patients were randomized but never received treatment. On Population: Only white race reported. Other 2% of patients not described by race On WDs: Includes patients lost to FU and WDs

Evidence Table 15. Characteristics of trials in patients with clinically isolated syndrome

Author Year Country Trial name	Study design Setting	Inclusion/exclusion criteria	Interventions	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/analyzed	Results
Pakdaman 2007 Iran	DB RCT (3 year) Placebo-controlled Parallel Multicenter (4 centers)	Inclusion: Age 19-50 years; presented with a first neurological event consistent with demyelination of the CNS (optic neuritis, spinal cord syndrome, brain-stem or cerebellar syndrome) in the previous 3 months confirmed by neurologic examination and had an abnormal brain MRI consisting of ≥2 clinically silent lesions that were at least 3 mm in diameter and at least one had to be periventricular or ovoid Exclusion: Pregnant or desired to be pregnant during the study; if they had any serious systemic illness or psychiatric disorder or were on immunomodulatory or immunosuppressive treatment during the year before the study	IFN β-1a IM injections once weekly (n=98) Placebo IM injections once weekly (n=104)	IFN β-1a (n=98) vs P (n=102) Age: 26.4 vs 29.5 Male: 31 (31.6%) vs 32 (31.4%) Female: 67 (68.4%) vs 70 (68.6%) Iranian patients Ethnicity: NR BL characteristics was based on 200 of the 217 randomized patients	IFN β-1a vs Placebo Mean number of T2-weighted MRI lesions on screening: 4.9 vs 5.5 Number of T1 gadolinium-enhancing lesions on screening: 0.73 vs 0.63	Screened: NR Eligible: NR Enrolled: 217	WDs: 15 Lost to FU: NR Analyzed: not clear	IFN β-1a vs Placebo Proportion of patients who developed clinically definite MS at 3 years: 38/98 (36.6%) vs 57/104 (58.2%) - cumulative probability of conversion to clinically definite MS lower in IFN β-1a group (*P*<0.003) Annual relapse rate: 13% vs 22% Mean number of new and enlarging lesions on T2-weighted MRI scans at 6 months: 5.2 vs 5.9; *P*<0.001 Mean number of new and enlarging lesions on T2-weighted MRI scans at 12 months: 5.6 vs 6.6; *P*<0.003 Mean number of new and enlarging lesions on T2-weighted MRI scans at 24 months: 5.8 vs 7.7; *P*<0.002 Mean number of new and enlarging lesions on T2-weighted MRI scans at 36 months: 6.1 vs 8.9; *P*<0.001

Evidence Table 15. Characteristics of trials in patients with clinically isolated syndrome

Author Year Country Trial name	Method of adverse events assessment	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pakdaman 2007 Iran	Safety assessments, including vital signs, hematologic, and serum biochemical tests performed at the end of months 1, 6, 12, 18, 24, 30, and 36	"Over the first 6 months, an influenza-like syndrome was reported more frequently in IFN β-1a group than in the placebo group (64% vs 76%, *P*=0.002)" No description of other AEs were reported by the authors Serious AEs, none of which was reported to be treatment-related, were reported in 9 patients in the IFN β-1a group and 7 patients in the placebo group.	Total WDs: 15 AE WDs: NR	NR	Efficacy Analysis: The diagnosis of clinical definite MS was the consequence of a second demyelinating attack in all but 3 of the patients. Reporting: See Table 1: BL data on 17 patients were missing. Also, the number of patients in the placebo group (n=104) stated in the table (3rd column) does not equal the number of patients listed below it (i.e. 32 males + 70 females = 102 patients)

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Aarskog, 2009 **Norway**	Prospective cohort	N=827 (151 with IM IFN β-1a (Avonex), 186 with SC IFN β-1b (Betaferon), and 490 with SC IFN β-1a (Rebif))	IFN β-treated patients with RRMS for BAB
Baum, 2007 **International (primarily Europe)**	Prospective cohort	N=454 (306 with Betaferon, 148 with Rebif)	Patients diagnosed with RRMS who were being treated with full dose Betaferon or Rebif Patients were included according to the Product Information in the individual countries It was recommended that patients had been receiving treatment for >1 month, but <3 months at study entry, and had completed the dose-titration phase of their treatment <u>Betaferon vs Rebif</u> Mean Age (y±SD): 35.8±8.8 vs 36.1±9.9 Sex (% female): 69.6 vs 78.4

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Aarskog, 2009 **Norway**	Frequency of BAB and NAB (%): BAB positive vs NAB low to medium positive vs NAB high positive vs NAB positive (total) Betaferon (n=186): 67.2 vs 26.3 vs 18.8 vs 45.1 Rebif (n=490): 45.9 vs 10.8 vs 23.1 vs 33.9 Avonex (n=151): 8.6 vs 1.3 vs 3.3 vs 4.6 Total (n=827): 43.9 vs 12.6 vs 18.5 vs 31.1 Of 363 BAB-positive sera, NAB was present in 257 (70.8%). Of these 257, 40.5% were NAB low to moderate positive and 59.5% were NAB high positive NAB analysis using the MxA protein induction for 137 of the BAB-positive sera: NAB negative: 15.3% NAB low to medium positive: 29.2% NAB high positive: 55.5% Sera from the 28 healthy blood donors were negative in both assays	NR		Biogen Idec Norway A/S and Gerda Meyer Nyquist legacy
Baum, 2007 **International (primarily Europe)**	Rebif vs Betaferon Patients pain-free over 15 injections (%): Immediately: 4.2 vs 16.5 (P<0.0001) 30 min post-injection: 19.7 vs 42.6 (P<0.0001) 60 min post-injection: 35.6 vs 57.8 (P<0.0001) Mean proportion of pain-free injections per patient (%): Immediately: 19.8 vs 44.4 (P<0.0001) 30 min post-injection: 53.3 vs 79.0 (P<0.0001) 60 min post-injection: 71.3 vs 86.4 (P<0.0001) Patients pain-free over 15 injections (%): Immediately: 4.8 vs 16.7 (P<0.0021) 30 min post-injection: 16.2 vs 40.2 (P<0.0001) 60 min post-injection: 31.4 vs 55 (P<0.0001) Influence of needle size on proportion of pain-free injections: 25-27 G needle Immediately: 21.1 vs 41.0 (P=0.0018) 30 min post-injection: 60.9 vs 77.1 (P=0.0209) 60 min post-injection: 80.7 vs 85.0 (P=0.3136) 29-30 G needle Immediately: 19.7 vs 50.9 (P=0.0001) 30 min post-injection: 52.2 vs 82.5 (P=0.0001) 60 min post-injection: 70.1 vs 88.9 (P=0.0001)	AEs (%): Flu-like symptoms: 13.7 vs 12.8 Headache: 2.0 vs 5.4 Injection ste erythema: 13.1 vs 12.2 Total: 33.3 vs 32.4 ISRs (%) (none vs pain, itching, or erythema vs pain or swelling with inflammation or phlebitis): *Visit 1:* Betaferon: 46.9 vs 51.2 vs 1.3 Rebif: 35.2 vs 61.3 vs 3.5 **P*=0.0184 Visit 2 Betaferon: 51.8 vs 46.2 vs 2.0 Rebif: 33.8 vs 64.1 vs 2.1 **P*<0.001 (*Compares proportion of patients with and without ISRs)		Bayer Schering Pharma AG, Germany

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Boz, 2007	Prospective cohort	N=262 (119 with Betaseron 250 µgqod, 131 with Rebif 22 µgthree times weekly, and 12 with Avonex 30 µgonce weekly)	% female: 72.5% Age, yr mean (SD): 46.2 (9.3) Age at onset of MS, mean (SD): 32.7 (9.9) Pre-treatment disease duration (yrs) mean (SD): 8.8 (7.3) Total number of previous relapses: 5.3 (3.1) Pre-treatment disease duration, yrs mean (SD): 8.8 (7.3) Total number of previous relapses: 5.3 (3.1) Pre-treatment annual relapse rate: 1.18 (0.7) Pre-treatment EDSS: 2.94 (1.63) Duration of treatment: 4.9 (1.9)

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Boz, 2007	Betaseron vs Rebif vs Avonex Incidence of BAB positivity at 3 years: 60.5% vs 30.8% vs 25%, difference between Rebif and Betaseron *P*<0.001 Incidence of NAB positivity at 3 years: 15.1% vs 12.2%, vs 0%, difference between Rebif and Betaseron *P*=0.31 Betaseron vs Rebif (from graph) % of BAb positive patients at 3 yrs: 60% vs 30% % of BAb positive patients at 5 yrs:60% vs 25% % of BAb positive patients at 6-10 yrs: 58% vs 24% % of NAb positive patients at 3 yrs: 15% vs 12% % of NAb positive patients at 5 yrs: 15% vs 10% % of NAb positive patients at 6-10 yrs: 10% vs 12% Relapse rate at 3 years for negative NAb: 0.25 (0.57) vs 0.38 (0.67) Relapse rate at 3 years for positive NAb: 0.47 vs 0.38 P-value for positive vs negative NAb for Betaseron and Rebif=NS Relapse rate at 5 years for negative NAb: 0.36 (0.70) vs 0.39 (0.65) Relapse rate at 5 years for positive NAb: 0.27 (0.65) vs 0.00 (0.00) P-value for positive vs negative NAb for Betaseron and Rebif=NS Relapse rate at 6-10 years for negative NAb: 0.26 (0.48) vs 0.29 (0.48) Relapse rate at 6-10 years for positive NAb: 0.29 (0.34) vs 0.36 (0.44) P-value for positive vs negative NAb for Betaseron and Rebif=NS	NR		Study supported by the Christopher program and special therapies program supported by educational grants from Schering/Berlex, Serono, Biogen, Idec, Teva Neurosciences

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Castelli-Haley, 2008 **USA**	Retrospective cohort	Intent-to-treat' cohort: n=845 (542 with GA, 303 with IFN β-1a SC) 'Continuous use' cohort: n=410 (individuals who used either GA or IFN-β 1a SC within 28 days of the end of the 2-year post period)	Intent-to-treat' cohort: Patients were included if they had a diagnosis of MS, a procedure code or outpatient prescription for GA or IFN β-1a SC, and insurance coverage extending continuously from 6 months before through 24 months after the index date (30 months total). The index date was required to be between March 28, 2002 and July 1, 2004. 'Continuous use' cohort: subgroup of ITT cohort. Patients met all inclusion/exclusion criteria of the ITT cohort and they were required to have used no other DMT besides the ITT medication during the 2-year post-period and were also required to have received a procedure or prescription for the ITT medication in the last 28 days of the 2-year post-period. Patient Characteristics - 'Intent-to-treat' cohort: All individuals vs GA vs IFN-β 1a-SC Mean age (y±SD): 42.92±9.27 vs 43.26±9.14 vs 42.32±9.49 (P=0.1570) Female (n (%)): 670 (79.29) vs 439 (81.00) vs 231 (76.24) (P=0.1016) Patient Characteristics - 'Continuous-use' cohort: All individuals vs GA vs IFN β-1a SC Mean age (y±SD): 43.33±8.95 vs 42.91±8.56 vs 40.62±9.56 (P=0.0609) Female (n (%)): 326 (79.51) vs 220 (82.40) vs 106 (74.13) (P=0.0480)

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Castelli-Haley, 2008 **USA**	Intent-to-treat' cohort: All individuals vs GA vs IFN β-1a SQ (n (%)) Pre-period hospitalization for MS: 86 (10.06) vs 42 (7.75) vs 43 (14.19) (*P*=0.0028) Relapse: 66 (7.81) vs 33 (6.09) vs 33 (10.89) (*P*=0.0126) 'Continuous-use' cohort: All individuals vs GA vs IFN β-1a SQ (n (%)) Pre-period hospitalization for MS: 39 (9.51) vs 21 (7.87) vs 18 (12.59) (*P*=0.1204) Relapse: 21 (5.12) vs 8 (3.00) vs 13 (9.09) (*P*=0.0076) Impact of medication on probability of relapse: IFN β-1a SQ vs GA (%) 'ITT' cohort: 10.89 vs 5.92 (*P*=0.0305) 'CU' cohort: 9.09 vs 1.94 (*P*=0.0049)	NR		HealthMetrics Outcomes Research

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Cocco, 2008 **Italy**	Retrospective cohort	N=189 (107 relapsing-remitting, 77 secondary progressive, 4 primary progressive)	Women with MS treated with at least 3 cycles of MITO before age 45, in FU for a period of at least 3 months following MITO discontinuation. Mean age at time of study (y±SD): 37±7 Mean age at start of MITO (y (range)): 35 (14-45)

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Cocco, 2008 **Italy**	NR	Menstrual alterations (before/during/after) MITO treatment (n (%)): No abnormalities: 142 (75)/92 (49)/70 (37) Transient abnormalities: 47 (25)/40 (21)/28 (15) Transient amenorrhea (TA): 0 (0)/28 (15)/43 (23) Permanent amenorrhea (PA): 0 (0)/23 (12)/18 (10) Menopause: 0 (0)/6 (3)/30 (16) Median duration (months (range)): Transient amenorrhea: 5 (1-13) Permanent amenorrhea: 19 (11-57) Probability of permanent amenorrhea or menopause according to age at MITO, dose, and EP status; EP- (%)/EP+ (%): *Cumulative dose: 60 mg/m2* Age 20: 2/1 Age 25: 4/1 Age 30: 10/3 Age 35: 20/7 Age 40: 37/15 *Cumulative dose: 100 mg/m2* Age 20: 4/1 Age 25: 9/3 Age 30: 20/7 Age 35:36/15 Age 40: 57/29 *Cumulative dose: 120 mg/m2* Age 20: 6/2 Age 25: 14/5 Age 30: 27/10 Age 35: 46/21 Age 40: 67/38		NR

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Cocco, 2008 Italy (continued)			
Debouverie, 2007 France	Prospective and retrospective cohort	ATU arm Safety set: 637 Efficacy set: 512 ATU-LT arm Safety set: 205 Efficacy set: 199 Completing ATU-LT: 126	Use of GA was restricted to 2 groups of patients in France: 1) patients who INF β was contraindicated and who could start GA as first line therapy, 2) patients previous treated with INF β who developed intolerance requiring discontinuation of INF β, where GA was offered as second line therapy. Patients in whom INF β was inadequately efficacious or who were poorly adherent were not eligible. Program was from December 1997 to June 2002. In September 2002, long-term extension study to the early access program was implemented. ATU (initial program). ATU-LT (long-term extension program). Patients who discontinued GA for any reason or whose disease had converted to SPMS were excluded. Mean age (yrs): 38.5 Percent female: range 77-77.9 Time since diagnosis (yrs): 8.7 EDSS score: 3.3

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Cocco, 2008 Italy (continued)		Independent variables associated with higher risk of chemotherapy-induced amenorrhea (CIA) were represented by cumulative dose (P=0.01; OR=1.02; 95% CI, 1.01 to 1.04) that increased CIA by 2%/mg/m2 and age at the MITO beginning (P=0.01; OR=1.18; 95% CI, 1.10 to 1.27), which increased CIA of 18% for each additional year of age. CIA was less frequent (P=0.01; OR=0.31; 95% CI, 0.13 to 0.7) in patients using EP during MITO treatment. Side Effects and AEs (n (%)): Nausea: 131 (69) Anticipatory nausea: 30 (16) LVEF reduction: 8 (4) Rarefaction of hairs: 68 (36) Chemical phlebitis: 3(2) Blood cells count abnormalities: 18 (10) Fatigue: 13 (7) Other: 28 (15)		
Debouverie, 2007 France	Mean EDSS score after 1 year (SD) ATU Efficacy set: 3.3 (1.8) ATU-LT Efficacy set: 3.1 (1.7) Mean EDSS score after 5 years (SD) ATU-LT Efficacy set: 3.3 (2.1) Mean EDSS score after 7 years (SD) ATU-LT Efficacy set: 3.1 (1.5) After 5 years, 5.7% of patients progressed by at least 1 point on EDSS scale	AEs were reported in 87.3% of ATU-LT Safety Set (n=205) Local ISR: 81% Systemic reactions immediate after injection such as CP, SOB, etc: 49.3% WD due to AE: 4.9% of ATU-LT Safety Set		NR

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Durelli, 2009 **Italy**	Prospective cohort	N=147 (120 received only IFN β-1b for the entire 2 year period)	Patients were aged 18-50 years and had clinically definite RRMS, a BL EDSS score of 1.0-5.5, two clinically documented relapses during the preceding 2 years and no relapse and no corticosteroid treatment for at least 30 days before entry into the study. During a 6 month run-in phase, all patients were treated with 250 µg of INF β-1b SC qod and received serial MRI scans (at BL, and at 3, 4, 5 and 6 months). All patients vs clinical responders vs suboptimal clinical responders Mean age (y±SD): 34.8±9.4 vs 34.8±8.7 vs 34.7±10.2 Female (n (%)): 95 (65.5) vs 54 (65.9) vs 41 (65.1)

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Durelli, 2009 **Italy**	Predictivity of MRI activity or NAB+ status during the first 6 months of IFN β treatment for suboptimal treatment response (for patients always treated with IFN β for 2 years): **N / % Sensitivity / % Specificity / % PPV / % NPV / *P* value:** MRI activity at any month Relapses or progression: 120/52/80/62/73/0.002 Relapses: 120/51/77/51/77/0.02 Progression: 120/53/71/25/89/0.28 MRI activity at 6 months Relapses or progression: 120/35/84/57/67/0.03 Relapses: 120/54/74/54/74/0.01 Progression: 120/32/78/21/86/0.5 NAB positivity status Relapses or progression: 88/71/66/29/92/0.01 Relapses: 88/67/65/23/92/0.04 Progression: 88/71/63/15/96/0.08 MRI activity at any month and NAB positivity status Relapses or progression: 88/71/86/50/94/0.0003 Relapses: 88/67/84/40/94/0.008 Progression: 88/71/81/25/97/0.08 MRI activity at 6 months and NAB positivity status Relapses or progression: 88/50/91/50/90/0.0006 Relapses: 88/50/89/43/92/0.003 Progression: 88/43/92/50/89/0.07 Predictivity of MRI activity or NAB+ status during the first 6 months of IFN β treatment for suboptimal treatment response (for patients always treated with IFN β for 2 years and in all those entered in the trial (ITT population)): **N / % Sensitivity / % Specificity / % PPV / % NPV / *P* value** Always treated with IFN β (relapses or progression) 132/50/79/63/70/0.003 Always treated with IFN β (relapses) 132/51/73/51/73/0.04 Always treated with IFN β (progression) 132/52/72/28/88/0.2 All entered patients (ITT) (relapses or progression) 147/45/79/63/64/0.01 All entered patients (ITT) (relapses) 147/42/75/50/68/0.2 All entered patients (ITT) (progression) 147/44/72/30/82/0.6	NR		Bayer Schering Pharma AG, Germany

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Farrell, 2008 **England**	Prospective and retrospective chart review (from database)	N=327, however 348 were initially identified and 21 patients were excluded due to early treatment cessation or switching to a non-IFN β product	Percent women: 72% Mean age (yrs): 41.8 Time since diagnosis (yrs): 5.6 Mean relapse rate prior to treatment: 1.53 per yr Patients with RRMS: 88% Patients with SPMS: 22%
Jordy, 2008 **Brazil**	Prospective and retrospective cohort Companion to Tilbery 2006	N=390 who used immunomodulators (Rebif, Avonex, Betaferon, GA) n=390, Group 1- patients who used up to 2 yrs n=292, Group 2- patients who used from 2-3 yrs n=152, Group 3- patients who used from 3-5 yrs	Patients with RRMS continuously receiving the immunomodulator, and who had their immunomodulator changed were included. Patients who had progression to SPMS; migration due to pregnancy; migration insufficiently documented were excluded.
Koch-Henriksen **Denmark**	Retrospective cohort	N=1309 (417 with Rebif 22 µg three times weekly, 892 with Betaseron 250 µg qod)	Included patients with RRMS who started first-time treatment with Rebif 22 or Betaseron before January 1, 2003. Percent women: 65.5% Mean age: 38 Duration of disease (yrs): 5.5-7.1 Number of relapses 24 mos prior to treatment: 2.6-2.9 BL EDSS: 2.6-2.9 Observed for: 21,963 mos Overall percentage of NAbs positive: 32.3% Percent NAbs positive, Rebif vs Betaseron: 31.4 vs 33.0% (*P*=0.001)

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Farrell, 2008 **England**	NAb persistence: 23% of subject had only 1 sample available for testing and were therefore excluded from analysis. 251 had 12 or 24 mos sample. Of these, 61% remained NAb-positive at mean 4.3 yrs and 39% reverted. <u>Avonex vs Betaferon vs Rebif</u> Percentage of patients who were persistently negative: 88.5 vs 44.5 vs 53.7 Percentage of patients who were persistently positive: 5.8 vs 34.1 vs 28.7 ARR for all patients: 0.55/yr ARR for NAb-negative: 0.50/yr	Harms were identified by retrospective chart review. Comments about side effects were noted in 191 cases and were reported as present in 140 of these cases.		NR
Jordy, 2008 **Brazil**	<u>Rebif vs Betaferon vs Avonex vs GA</u> Migration rate (%): 50 vs 25 vs 18.8 vs 2.1 Mean time for migration (yrs): 2.5 vs 1.9 vs 2.1 vs 0.5 Migration because of EDSS increase (%): 62.5 vs 57.1 vs 66.6 vs NA Adherence (%): Group 1: 75 Group 2: 88% Group 3: 72%	<u>WD (%):</u> Group 1: 25% Group 2: 11% Group 3: 27% Migration because of AEs (%), Rebif vs Betaferon vs Avonex vs GA: 45.8 vs 28.5 vs 22.2 vs 100		NR
Koch-Henriksen **Denmark**	<u>Cumulative risk of being Nab positive, Rebif vs Betaseron:</u> at 12 mo: 0.19 vs 0.35 at 24 mo: 0.35 vs 0.48 at 36 mo: 0.55 vs 0.56 Overall risk of relapse higher with Betaseron than Rebif: OR 1.31, *P*=0.0002 Risk of relapse for NAb-positive months: OR 1.43; 95% CI, 1.14 to 1.78; *P*=0.0002 Risk of relapse for NAb-negative months: OR 1.22; 95% CI, 1.03 to 1.46, *P*=0.028	NR		Danish MS Society, Warwara Larsen Foundation, Danish Medical Research Council, European Union Sixth Framework Programme, Life sciences, Genomics & Biotech for health. Register is funded by Copenhagen Hosp Council and by the Assoc of Danish Regions

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Le Page, 2008 **France**	Prospective cohort (from database)	N=100 consecutive patients from European Database for MS (10 patients were included in the French British MS trial)	Patients with aggressive RRMS who were treated with MITO as induction therapy monthly for 6 months were included. Patients received their first course of MITO between September 1992 and September 2000. Because of methodological differences in MRI, authors retained single MR variable the presence of gadolinium enhancement. In 92 patients pre-treatment MRI was preformed at different time points. Pre- and post-treatment MRI were available for 76 patients. Choice of maintenance therapy was left to each patient's neurologist. 50 patients were DMT naive 11 patients were IFN non-responders 73 patients received maintenance therapy within 6 mos of the last course of MITO induction. As first line treatment: 21 received MITO every 3 mos; 25 received IFN; 15 AZA; 7 methotrexate; 5 GA. 27 patients received no DMT for mean period of 3.3 years, thereafter 13 took DMT as second line therapy for at least 1 yr. Percent women: 77% Mean age at MS onset: 27.1 Mean age at MITO onset: 32.5 Annual relapse rate 12 mo prior to MITO: 3.3 Percent with gadolinium-enhanced lesions on MRI: 84 Mean duration of MS before MITO (yrs): 5.3 Mean EDSS at BL: 4.1 Median FU time: 6.8 yrs (see Table 3 in publication for demographics of non-responders to IFN and DMT naive patients)

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Le Page, 2008 **France**	For treatment: Patients received induction treatment according to the protocol of French British trial including 6 mos courses of MITO 20 mg + methylprednisolone 1g. When WBC was abnormal, the infusion dose was reduced to 10 mg (at least once in 46 patients). Treatment administration was shortened to 3 mos in 8 patients. Effectiveness and harms data for up to 5 yrs were available for 97 patients (1 lost to FU, 2 died (suicide)) At Baseline vs At year 1 vs At year 2 vs At year 3 vs At year 4 vs At year 5 Annual relapse rates (ARR): 3.3 vs 0.30 vs 0.39 vs 0.42 vs 0.38 vs 0.30 (All ARR had *P*<0.000001) Mean EDSS: 4.1 vs 2.9 vs 3.1 vs 3.3 vs 3.5 vs 3.6 Percentage of patients relapse free (BL: 0): 0 vs 78 vs 62 vs 42.5 vs 39 vs 32 MITO rescue treatment because of exacerbation of disease was administered more often in patients with a shorter MITO induction period (i.e. 3 mo) than in patients with 6 mos induction period.	97/100 were evaluated. 3 patients presented with asymptomatic decrease in LVEF of <50% at 1 mo, 1.5 and 5 yrs after last course of MITO, persisting in the first 2 cases and transitory in the third case. A 37 year old women with acute myeloid leukaemia. 7 infectious episodes occurred during administration of MITO: 3 with severe neutropenia (<500/mm3) and 4 without severe neutropenia Grade 1 alopecia: 32.5% Moderate nausea: 24% Among the 70 women at risk for amenorrhea (≤45 years of age with menstruations at start of MITO): 9 (13%) had transitory amenorrhea 7 (10%) had persistent type 14 patients gave birth to normal babies 5 patients died at 2, 4, 5, 6 and 10 yrs after start of MITO: First 2 cases from suicide Pulmonary cancer related to smoking Last 2 cases from severe disabling MS Per authors, no death was MITO-related.	This publication is an update of an observational study (published in French) of 100 patients with aggressive RRMS followed for at least 1 yr.	NR

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Lugaresi, 2008 **Italy**	Prospective cohort	N=76 n=50 were not receiving immunomodulatory treatment prior to study (66%) n=26 switched to Rebif from other immunomodulatory drugs (34%)	RRMS patients from 19 neurological centers in Italy eligible for Rebif as first or second line therapy were included. The aim of the study was to assess the safety and tolerability of the Rebiject (autoinjector system) in patients with RRMS treated with subcut Rebif over a 1 yr period. Patients received Rebif 44 µg SC three times weekly using the Rebiject system for 1 yr. Female (%): 62 Age range (yrs): 26-50; 52.6% were ≤40 yrs % with EDSS ≤2: 55.3 Mean relapses 2 yrs prior (SD): 1.9 (1.3) Mean duration of prior treatment for all regimens (SD): 22.7 (11.5) mos

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Lugaresi, 2008 **Italy**	61/76 (80.3%) of patients who received at least 1 dose of Rebiject expressed satisfaction with periodic injections. Common advantages reported by those who expressed satisfaction (n=61) were: Convenience: 52% Easier injection: 20% Less psychological trauma: 8% Less pain: 10% Reduced skin reaction: 10% 10/71 (14.1%) of patients who received at least 1 dose with Rebiject reported dissatisfaction. Common disadvantages reported were: Cumbersome: 10% Difficult to handle: 10% Caused pain: 40% More local skin reaction: 30%	ISRs were common in 60/76 patients (78.9%) Mild intensity reaction: 85.8% Moderate intensity: 14.2% No severe reactions reported 50 patients showed persistent skin reactions 41/76 (53.9%) of patients reported at least 1 flu-like symptom requiring antipyretic treatment. 27/76 (36%) reported flu-like symptoms over entire study period. NSD in abnormal lab values before and after starting treatment.		Unclear. Industria Farmaceutica Serono edited the manuscript

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Malucchi, 2008 **Italy**	Retrospective cohort	N=137 (92 women and 45 men)	Patients with definite MS according to the McDonald criteria who were treated with one of the IFN-β products for at least 3 years, had not switched type of IFN-β, had an EDSS score of ≤6.5, and had no viral infection at least 4 weeks before and after blood sampling. IM IFN β-1a vs SC IFN β-1b vs SC IFN β-1a (22 µg) vs SC IFN β-1a (44 µg) Number of patients: 39 vs 29 vs 37 vs 32 Mean age (y±SD): 38.0±10.6 vs 39.2±12.3 vs 33.7±9.1 vs 32.0±10.1 Women: 25 vs 18 vs 27 vs 22 BL EDSS Score (mean±SD): 1.1±1.0 vs 2.2±1.4 vs 1.9±1.6 vs 1.6±1.4

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Malucchi, 2008 **Italy**	MxA, NAB, and BAB evaluation after 12±3 months of IFN β treatment: **MxA mRNA vs NABs vs BABs (number of patients (%))** IM IFN β-1a: Positive: 34 (87.2) vs 2 (5.1) vs 4 (10.5) Negative: 5 (12.8) vs 37 (94.9) vs 34 (89.5) SC IFN β-1b: Positive: 20 (69) vs 6 (20.7) vs 15 (51.7) Negative: 9 (31) vs 23 (79.3) vs 14 (48.3) SC IFN β-1a (22 µg): Positive: 33 (89.2) vs 4 (10.8) vs 5 (13.5) Negative: 4 (10.8) vs 33 (89.2) vs 32 (86.5) SC IFN β-1a (44 µg): Positive: 26 (81.2) vs 5 (15.6) vs 3 (9.7) Negative: 6 (18.8) vs 27 (84.4) vs 28 (90.3) Total: Positive: 113 (82.5)/17 (12.4)/27 (20) Negative: 24 (17.5)/120 (87.6)/108 (80) Patient categorization based on the combination of measures of MxA, BABs, and NABs: **Number of patients (% (based on MxA response))** IM IFN β-1a (MxA positive) NAB+/BAB+: 1 (2.9) NAB-/BAB-: 31 (91.2) NAB-/BAB+: 1 (2.9) NAB-: 1 (2.9) IM IFN β-1a (MxA negative) NAB+/BAB+: 1 (20) NAB-/BAB-: 3 (60) NAB-/BAB+: 1 (20) SC IFN β-1b (MxA positive) NAB+/BAB+: - (-) NAB-/BAB-: 14 (70) NAB-/BAB+: 6 (30) SC IFN β-1b (MxA negative) NAB+/BAB+: 6 (66.7) NAB-/BAB-: - (-) NAB-/BAB+: 3 (33.3)	NR		The European Community under its 6th Framework (for a specific project on NAb in MS), Fondazione per la Ricerca Biomedica ONLUS, and the S. Luigi Gonzaga ONLUS

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Malucchi, 2008 Italy (continued)			

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Malucchi, 2008 Italy (continued)	SC IFN β-1a, 22µg (MxA positive) NAB+/BAB+: 1 (3) NAB-/BAB-: 30 (91) NAB-/BAB+: 1 (3) NAB+/BAB-: 1 (3) SC IFN β-1a, 22µg (MxA negative) NAB+/BAB+: 2 (50) NAB-/BAB-: 1 (25) NAB-/BAB+: 1 (25) NAB+/BAB-: - (-) SC IFN β-1a, 44µg (MxA positive) NAB+/BAB+: - (-) NAB-/BAB-: 25 (96.1) NAB+/BAB-: 1 (3.9) SC IFN β-1a, 44µg (MxA negative) NAB+/BAB+: 2 (33.3) NAB-/BAB-: 1 (16.7) NAB-/BAB+: 1 (16.7) NAB+/BAB-: 1 (16.7) NAB+: 1 (16.7) Median time to first relapse: MxA negative: 7 months MxA positive: too long to be defined in this 3 year study (P<0.0001, HR=2.87) NAB positive: 8 months NAB negative: undefined (P=0.0013, HR=2.49) Relapse-free patients: 51% (93% were MxA positive and 7% were MxA negative)			

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Mancardi, 2008 **Italy**	Retrospective database	As of March 2008: N=909 enrolled in database	Database appeared to have been created in 2006. Centers included in the database were selected according to the following criteria: 1) clinical experience in MS treatment and immunosuppressive therapies 2) availability of MRI scanner 3) clinical expertise in PCR for research of JC virus in biological samples. These centers will add new patients to the database. On December 7, 2006, Italian Drug Agency decided for reimbursement and drug availability, they would authorize Nat as a single modifying therapy in RRMS for the following patients: 1) Group A- patients with RRMS who had not responded to full and adequate course of INF β or GA, who had at least 2 MS attacks under treatment or relapse with EDSS >2 and have at least 9 T2-hyperintense lesions on MRI or 1 gadolinium-enhancing lesion. 2) Group B- patients (even those naive to immunomodulatory drugs) with rapidly evolving RRMS, with EDSS >2, with new gadolinium-enhancing lesions on MRI or increase in T2 lesions compared with previous MRI <12 mos prior to study. <u>Group A vs Group B</u> Mean age (yrs): 35.9 vs 35.1 Mean duration of disease (yrs): 9.9 vs 5.7
Miller, 2008 **USA**	Prospective cohort (part of open-label, compassionate-use study and a pilot study)	N=46 RRMS patients who enrolled in either pilot study or open-label compassionate use study of GA Patients' neurological status has been monitored every 6 mos over many yrs. As of Oct 2004, these patients had continued to receive GA for up to 22 yrs.	Patient entry criteria were minimal since there were no immunomodulatory drugs for MS approved at the time. RRMS patients of any age, disability level, or MS treatment history could enroll provided their request was approved by the FDA under Compassionate Use Investigational New Drug. There were no restriction on other concomitant medications. Patients administered GA 20 mg/day SC.

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Mancardi, 2008 **Italy**	90% of all cases were registered as "Group A" 10% registered as "Group B"	Allergic reactions: 5% Infections: 30% In Group A, treatment was stopped in 4% of cases for the following reasons: lack of efficacy, AEs, detection of anti-Nat antibodies, no therapy. In Group B, treatment was stopped in 8% of cases for similar reasons.		Unclear how many groups were involved in creating database
Miller, 2008 **USA**	8/15 patients had progressed at least 1.0 EDSS points 6 patients remained improved or stable (EDSS change <1.0) <u>Mean duration of therapy:</u> 10.1 yrs (SE 6.6). For patients who continued with the study, mean duration of therapy 16.3 yrs (SD 3.1) <u>Annualized relapse rate</u> For all patients: from 2.9 (SE 1.4) to 0.1 (SD 0.2) For patients who continued with study: 3.06 (1.78) to 0.09 (0.21) 13/18 of those who continued (72%) were relapse-free throughout course of treatment 20/25 of those who discontinued (80%) were relapse-free	As of October 2004, 18 patients (39%) were continuing in the observational study. 28 patients (61%) discontinued. Most common reason for WD was "WD of consent": 15/28 (54%) 3 patients withdrew because wanted to alternate therapy. Most common AE: ISR ≥50% 6 patients who took GA for 22 yrs reported lipotrophy. No reports of skin necrosis over course of study.		Unclear, Teva Neuroscience?

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Minagar, 2008 **PROOF**	Prospective and retrospective cohort	N=136 had completed data up to 6 mos (69 with Avonex, 67 with Rebif 44 µg)	Adults with RRMS with 2 or more relapses within the 3-yr period prior to treatment initiation and an EDSS score from 0 to 5.5. Patients receiving Avonex 30 µg once per week and Rebif 44 µg three times weekly for 12 to 24 mos before enrollment with no interruptions or dose reductions for ≥4 weeks. Avonex vs Rebif Mean age (SD): 38 (8.3) vs 37.1 (8.6) Female (%): 85.5 vs 76.1 Median time since diagnosis (mos): 3.7 vs 4.9 Median time on INF β-1a therapy (mos): 19.9 vs 16.2 (*P*=0.003) Median time since last relapse (mos): 14.7 vs 10.8 Mean EDSS (SD): 1.8 (1.1) vs 2.2 (1.3) (*P*=0.06)
Oturai, 2009 **Denmark**	Prospective cohort	N=234 (first consecutive patients treated with Nat for RRMS) n=14 de novo patients n=175 switched from first-line disease modifying treatment n=45 switched from MITO	Per Danish regulatory provisions, Nat can be administered to: 1) patients with 2 or more documented relapses or sustained increase of 2 EDSS points on DMT in the previous yr 2) patients switching from MITO either because they approach the upper limit of cumulative MITO dose or had disease activity on MITO therapy 3) as de novo therapy to patients with very active MS as defined by the European Medicines Agency Authors included patients who had attended the planned visit 3 mos after starting therapy. Median age (yrs): 39.5 Disease duration (yrs): 8 Relapse in yr prior: 2.53 EDSS: 4.0 Median observation period: 11.3 mos

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Minagar, 2008 **PROOF**	Study was designed to assess efficacy and tolerability for up to 5 yrs but was stopped early due to slow enrollment up to 30 mos. Avonex vs Rebif Percent experiencing sustained disability progression: 25.8% vs 26.7% Annualized relapse rate: 0.35 vs 0.48 Percent requiring corticosteroids with relapse: 9% vs 15% No difference between groups for MRI endpoints.	Avonex vs Rebif: Percent with any AEs: 78.3 vs 79.1 *Common AEs* MS relapse: 20.3% vs 20.9% Nasopharyngitis: 8.7% vs16.4% Headache: 11.6% vs 6.0% Injection-site bruising: 8.7% vs 6.0% Flu-like symptoms: 5.8% vs 4.5% ISR: 2.9% vs 6.0% 1 Rebif-treated patient withdrew due to AE		Biogen Inc.
Oturai, 2009 **Denmark**	134 relapses occurred (annualized relapse rate 0.68; 95% CI, 0.57 to 0.81). 63 (47%) were treated by methylprednisolone. Annualized relapse rate: 0.83 in de novo treated patients 0.71 in patients switched from first-line DMT 0.56 in patients switched from MITO Proportion of relapse free patients: 0.63 (95% CI, 0.57 to 0.81) Proportion of patients experiencing a progression on EDSS of 1.0 point or more: 0.09 (95% CI, 0.06 to 0.13) and there was no difference between patients with EDSS ≥4 or EDSS <4 at BL (*P*=0.21)	There were no PML cases. 1 case of herpes zoster infection treated with acyclovir. 9 cases of pneumonia 45 UTI 81 other infections None of the infections were classified as serious by the treating neurologist. 9 anaphylactic reactions (2 were reported as serious)		NR

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Portaccio, 2008 **Italy**	Prospective cohort	N=939 (MS patients identified from database) Eligible patients had clinically definite RRMS and had received IFN β since 1996. Previous AZA treatment was stopped for at least 6 mos. At beginning of IFN β, subjects received training on administration technique and were educated on possible AE and their management. From 1996-Sept 2005: N=230 (46 with Betaferon 8 MUI qod, 88 with Avonex 30 µg once weekly, and 91 with Rebif 22 µg and 44 µg three times weekly; 5 patients were lost to FU)	Gender (percent female): 70% Age at disease onset (yrs): 28.6 Age at INF β onset (yrs): 36.6 Disease duration (yrs): 8 Annual relapse rate in the yr prior to INF β (SD): 1.2 (0.8) BL EDSS (SD): 1.9 (1.2) Treatment duration (yrs): 2.8 (2.2) FU duration (yrs, SD): 4.2 (2.7) There were NSD in BL characteristics with exception of mean number of relapses in the yr prior to therapy which was higher in patients treated with Betaferon and Rebif 44 µg.

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Portaccio, 2008 **Italy**	See harms	45.8% withdrew 28.9% discontinued because of perceived lack of efficacy 14.7% due to AE 2.2% due to other reasons like planning pregnancy Patients who withdrew due to AEs stopped therapy earlier than patients who stopped due to perceived lack of efficacy. WD due to perceived lack of efficacy was less in patients with a higher BL EDSS. 6 cases of flu-like syndrome 5 low compliance 5 injection reactions 5 liver function abnormalities 4 depression 3 leucopenia 3 thyroid function abnormalities 1 alopecia <u>Betaferon vs Avonex vs Rebif 22 µg vs Rebif 44 µg</u> WD due to AE: 14/46 vs 12/88 vs 6/71 vs 1/20 WD due to perceived lack of efficacy: 10/46 vs 33/88 vs 19/71 vs 3/20		NR

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Rio, 2007 **Spain**	Prospective cohort	N=146 with SPMS	Patients with SPMS who started INF β-1b (8 MUI qod) with BL EDSS score within 3 to 6.5 and a recorded history of either 2 or more relapses or increase of 1.0 or more EDSS points in the previous 2 yrs. SPMS was defined as a period of deterioration, independent of relapses, sustained for at least 6 mos followed by a period of RRMS. Mean age (SE): 45.1 (10.2) Sex (percent female): 62% Duration of MS (yrs, SD): 13 (7.8) BL EDSS (SD): 5.4 (1.2) Relapses previous 2 yrs (SD): 1.3 (1.3) Change in EDSS previous 2 yrs (SD): 1.1 (0.8) Relapse free previous 2 yrs: 58% 129 patients were followed at least 12 mos. 89 patients followed at least 3 yrs Median FU: 60 mos
Sbardella, 2009	Retrospective study	N=141 (12 with Avonex 30 µg once a week, 36 with Betaferon 8 MIU qod, 48 with Rebif 22 µg three times weekly, and 45 with Rebif 44 µg three times weekly)	MS patients with RRMS or SPMS Avonex vs Rebif 22 µg vs Rebif 44 µg vs Betaferon Age mean (SD): 38.6 (9.7) Percent women: 64% Duration of disease (mean, SD): 10.98 (6) Median EDSS score: 2 (range 0-6.0) Patients with Betaferon were older and had higher BL EDSS scores and longer duration of disease.

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Rio, 2007 **Spain**	Probabilities of remaining progression free were 0.71, 0.49, 0.33 after 12, 24, 36 mos of treatment. For patients followed at least 2 and 3 yrs, the percentage of patients with confirmed progression were 75.5% and 79.5%. There were significant differences between patients with 2 or more relapses before INF β onset and those without; HR 1.97 (95% CI, 1.27 to 3.07; *P*=0.002) There were no difference between patients with or without relapses before treatment in terms of age, sex, duration of disease, EDSS at entry, and relapses on treatment. Regression analysis showed that the activity of the disease before treatment was the factor identifying patients at risk of disability increase.	6 patients lost to FU 52 patients (36%) stopped treatment: 16% because of lack of efficacy, 10% own will, 2% due to flu-like symptoms, 0.7% due to GI bleeding, 0.7% patient due to cerebral hemorrhage. 4 patients died (3 had sepsis and 1 had pulmonary hemorrhage) 3 patients discontinued due to AEs. Specific AEs were not reported (data not shown).		NR
Sbardella, 2009	<u>Clinical response categorized into groups</u> Group A: patients experiencing at least one relapse after first 6 months of therapy without confirmed disease progression Group B: patients experiencing sustained disability progression or without superimposed relapses Group C: patients with a stable disease (no relapse or disability progression) Presence of NAb according to clinical response categorized by groups [Group A (n=47) vs B (n=47)vs C (n=47)]: 17% vs 17% vs 2.1% NAB-positive vs NAB negative in group A and B: 17% vs 83% NAB negative <u>Presence of positive versus negative NAB by treatment groups, *P*=0.96:</u> Avonex: 8.9% vs 5.9% Betaferon: 25% vs 29.4% Rebif 22 µg: 33.8% vs 35.3% Rebif 44 µg: 32.3% vs 29.4%	NR		Not clearly reported. Stated that Merck provided assistance with preparation of the manuscript.

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Sorensen, 2007 **Denmark**	Retrospective cohort	N=468 (170 with Betaseron 8 MIU qod, 80 with Rebif 22 µg once weekly, 140 with Rebif 22 µg three times weekly, 19 with Rebif 44 µg three times weekly, and 59 with Avonex 30 µg once weekly)	Selected all patients who had been treated for at least 24 mos with the same IFN β preparation throughout the entire observation period lasting until December 2002. The authors compared the results of this observational study with those from randomized trials of IFN β. Mean FU: 42.8 mos Percent women: ~66.7% Patient characteristics in NAb negative population vs in eventually NAb positive population: Median age (yrs): 38 vs 39 Mean EDSS: 2.85 vs 2.70 Mean disease duration (yrs): 7.02 vs 6.41 Mean number of relapses 24 mos prior to treatment: 3.02 vs 2.86
Tremlett, 2008 **Canada**	Retrospective database	N=888 reports (131 with Avenox, 496 with Betaseron/Betaferon, 174 with Copaxone, 85 with Rebif, and 2 with Betaseron+Copaxone) n=885 sole suspected immunomodulatory drugs n=3 suspected as being involved in a drug interaction n=9 had taken 'interferon' and were excluded as there was insufficient information	Examined all adverse drug reactions reporting of MS immunomodulatory drugs to Health Canada from 1965 to March 2006. Percent women: 73.9% Mean age: 44.9 There were significant age differences (P<0.0005) between patients prescribed a single immunomodulatory drug. Betaseron group were the oldest (47.01 yrs), followed by Rebif (44.0 yrs), Avonex (42.9 yrs), and Copaxone (41.1 yrs). Patients were recorded as taking a mean of 2.3 (SD 3.3) concomitant medications at the time of adverse drug reaction.

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Sorensen, 2007 **Denmark**	No comparison arm other than results from other randomized trials of IFN β. Number of NAb-positive patients increased gradually from 6 to 24 mos, where 50% tested positive. At 6 mos neutralizing activity was detected in 18.9% of patients who remained NAb-negative, and 89.6% of those who became NAb-positive. At 12 mos, neutralizing activity was detected in 36.4% of patient who remained NAb-negative, and 97.2% in those who became NAb-positive. NAb-positive patients had higher relapse rates than NAb-negative patients from 6 to 48 mos of treatment.	NR		Funders of the Danish MS Research Center is from the Danish MS Society, the Warwara Larsen foundation, and the Danish Medical Research Council. The MS treatment register is funded by the Copenhagen Hosp Council and by the Assoc of Danish counties.
Tremlett, 2008 **Canada**	See harms	35.9% of patients recovered from adverse drug reaction without sequelae 3.5% of patients (n=30) did not fully recover from adverse drug reaction 55.1% either did not recover from adverse drug reaction or outcome was unknown at last FU adverse drug reactions were described using 3388 separate terms, averaging 3.8 terms per report. Each term was treated separately and coded into a major category. 16.8% of all reports for GA vs. 6.6% for INF β were for dermatology/skin reactions and also for pulmonary/upper respiratory tract symptoms (11.9% vs. 5.6%) 22.1% of patients using INF β vs. 15.4% of GA-treated patients reported neurological symptoms, hepatobiliary/pancreatic symptoms (5.5% vs. 0.83%). For INF βs, the 5 top WHO-adverse drug reaction terms used were: MS aggravated (4.2% of terms)> fever (2.3%)> ISR (0.18%)> fatigue (1.5%)> nausea (40%). For INF βs breathing difficulty (2.9%)> chest tightness (2.8%)> ISR (2.2%)> ISP (2.2%)> itching (2.1%).		MS Society of Canada

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Trojano, 2009 **Italy**	Prospective cohort	N=2570	IFN β treated RRMS patients Sex: 796 (31%) male Mean age at IFN β assignment (SD): 33.5 (9.2) years Mean age at disease onset (SD): 27.1 (8.6) yrs Mean EDSS at IFN β assignment (SD): 2.2 (1.0) Mean disease duration (SD): 6.4 (5.7) years Number of bouts 1 year prior to IFN β assignment (SD): 1.3 (0.9) Followed for up to 7 years with median FU time of 3.4 years

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Trojano, 2009 **Italy**	Multivariate Cox Regression Analysis: Lower incidence to first relapse in males (HR, 0.88; *P*=0.0097), in older patients (HR, 0.98; *P*<0.0001), in patients with a longer disease duration (HR, 0.98; *P*<0.0001). Higher incidence in those with higher EDSS score (HR, 1.18; *P*<0.0001) and number of bouts (HR, 1.21; *P*<0.0001). For incidence of 1-point EDSS progression Sex (male vs females): HR, 1.14; *P*=0.0897 Age at onset: HR, 1.02; *P*<0.0001 Disease duration: HR, 1.03; *P*<0.0001 EDSS at IFN β assignment: HR, 1.00; *P*=0.9839 Number of relapses 1 year prior to IFN β assignment: HR, 1.00; *P*=0.9755 The propensity score matched multivariate Cox Regression showed significant (HR, 0.87; *P*=0.0164) higher risk for the first relapse in females and the trend for a higher risk for 1 point EDSS progression in male group (HR, 1.17; *P*=0.0882). The Recursive Partitioning and Amalgamation method showed that male sex conferred a reduction in risk for first relapse (HR, 0.86; *P*=0.0226) in the subgroup with a low pre-treatment number of bouts, and higher risk for 1 point EDSS progression (HR, 1.33; *P*<0.05) in the subgroup with a delayed treatment, but a still young age (<32 years) at the start of treatment.	NR		NR

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Study design	Sample size	Population characteristics
Weber-Schoendorfer Germany	Prospective case-control (database)	n=69 IFN β n=31 GA n=64 MS controls n=1557 non-MS controls	The Teratology Information Service (TIS), Berlin offers risk assessment to physicians of all specialties and pregnant women. This service is accessed from all over Germany. Exposed pregnancies are documented through the risk inquiry. Most requests for information in regard to exposure to IFN β of GA came from physicians whose patients inadvertently became pregnant while on DMTs. Data were collected between 1996 and 2007. Patients were prospectively enrolled using structured questionnaires. Patient characteristics, GA vs IFN β vs MS controls vs non-MS controls: Median age (yrs): 31 vs 30 vs 32 vs 31 No smoking (%): 79.3 vs 81.2 vs 83.9 vs 90 Smoking >5 cigarettes/day (%): 17.2 vs 13 vs 9.6 vs 5.9 No alcohol (%): 96.6 vs 98.6 vs 98.4 vs 97.5 Median gestational age at first TIS contact (weeks): 8 vs 8 vs 8 vs 8 Previous children with birth defects (≥1) (%): 3.3 vs 2.9 vs 3.3 vs 1.4 Percent with no previous miscarriages: 96.8 vs 78.3 vs 85.3 vs 84.2

Evidence Table 16. Data abstraction of observational studies

Author, year Country	Efficacy/effectiveness outcomes	Harms	Comments	Funder
Weber-Schoendorfer **Germany**	See harms	All exposed mothers were treated for MS at least during the first trimester. In most pregnancies, DMTs were interrupted when the pregnancy was recognized. Median duration of DMT exposure during pregnancy (wks): GA: 6.9 (50% had taken medication beyond week 6 and 25% beyond week 7) IFN β: 8.8 (50% had taken medication beyond week 6 and 25% beyond week 9) Percent administration of glucocorticoids to treat relapse: GA: 9.7 IFN β: 11.6 MS control: 31 vs. IFN, *P*=0.01 vs. GA, *P*=0.03 Percent administration of immunoglobulins GA: 0 IFN β: 1.5 MS controls: 14 Miscarriage rate (%) GA: 3.9 IFN β: 11.7 IFN β-1b: 27.8 vs. IFN β-1a, *P*=0.02; vs. non-MS controls, *P*=0.03 IFN β-1a: 4.8 MS controls: 9.8 Non-MS controls: 9.1 2 major birth defects in GA cohort. Club feet in a term infant (week 40) of a 26-yr old who was exposed until week 6. A complex heart defect was diagnosed by ultrasound in 34 year old who injected GA until week 13. This patient had suffered from a relapse and received IV steroids for 3 days during first trimester.		German Bundesinstitut fur Arzneimittel und Medizinprodukte

Evidence Table 17. Quality assessment of trials

	Internal validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
RRMS - IFN						
Schwid, 2007 EVIDENCE trial	Yes	Unclear	Yes	Yes	Yes	No
Etemadifar, 2007	Yes	Unclear	Unclear	Yes	Yes	No
RRMS - GA						
Mikol, 2008 REGARD trial	Yes	Yes	Yes	Yes	Yes	No
RRMS - Natalizumab						
Havrdova, 2009 AFFIRM	Yes	Yes	Yes	Yes	Yes	Yes
O'Connor, 2004 RRMS+SPMS	Unclear	Yes	Yes - except for time since previous relapse	Yes	Yes	Yes
Investigators, 2008 CAMMS223 trial	Yes	Unclear	Yes	Yes	Yes for effectiveness	No
PPMS - Glatiramer acetate						
Wolinsky, 2007	Unclear	Unclear	Yes	Yes	Yes	Yes

Evidence Table 17. Quality assessment of trials

Author, Year Country	Patient masked?	Intention-to-treat analysis	Maintenance of comparable groups	Protocol violation: level acceptable?	Acceptable level of attrition?	Attrition similar between groups?	Quality rating
RRMS - IFN							
Schwid, 2007 EVIDENCE trial	No	Yes	Unclear	Yes	Unclear	Yes	Fair
Etemadifar, 2007	No	Yes	Unclear	Yes	Yes	unclear	Fair
RRMS - GA							
Mikol, 2008 REGARD trial	No	Yes	Unclear	Yes	Yes	Yes	Fair
RRMS - Natalizumab							
Havrdova, 2009 AFFIRM	Yes	Yes	Unclear	Yes	Yes	Yes	Good
O'Connor, 2004 RRMS+SPMS	Yes	Yes	Yes	Yes	Yes	Yes	Fair-Good - randomization process unclear otherwise good
Investigators, 2008 CAMMS223 trial	No	Yes	Yes	Yes	No - 40% of IFN group discontinued drug and 79% of AL did not receive 3rd dose	No - 40% IFN, 79% AL	Fair - able to evaluate up to FDA withdrawal date and compare to end of study data
PPMS - Glatiramer acetate							
Wolinsky, 2007	Unclear	Yes	Yes	Yes	Yes	Yes	Fair

Evidence Table 17. Quality assessment of trials

	Internal validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
RRMS+SPMS - NATALIZUMAB						
O'Connor, 2004	Unclear	Unclear	Yes - except for time since previous relapse	Yes	Yes	Yes
RRMS+SPMS - MITOXANTRONE						
Zipoli, 2008	No	No	No - MITO group had greater % of RRMS and CPA had greater % of SPMS, *P*<0.001	Yes	No	No
CIS+RRMS - IFNβ-1b vs GA						
Cadavid, 2009 BECOME trial	Unclear - "stratified by clinical site and presence of enhancement on MRI"	Unclear	Yes	Yes	Yes	No
CIS						
Comi, 2009 Europe, Argentina, Australia, New Zealand	Method not described	Method not described	Yes	Yes	Yes	Yes
Pakdaman, 2007 Iran	Method not described	Method not described		Yes	Unclear, described as DB	Unclear, described as DB

Evidence Table 17. Quality assessment of trials

Author, Year Country	Patient masked?	Intention-to-treat analysis	Maintenance of comparable groups	Protocol violation: level acceptable?	Acceptable level of attrition?	Attrition similar between groups?	Quality rating
RRMS+SPMS - NATALIZUMAB							
O'Connor, 2004	Yes	Yes	Yes	Yes	Yes	Yes	Fair - due to unclear randomization process and allocation concealment
RRMS+SPMS - MITOXANTRONE							
Zipoli, 2008	No	No - 162 enrolled, 153 analyzed	No - different at BL	NR	Yes	Yes	Poor/Fair - open, non-randomized, BL dissimilarity between groups
CIS+RRMS - IFNβ-1b vs GA							
Cadavid, 2009 BECOME trial	No	Yes	Unclear	Yes	Unclear	Yes	Fair - unclear randomization or allocation concealment
CIS							
Comi, 2009 Europe, Argentina, Australia, New Zealand	Yes	Yes	Unclear	Yes	Yes	No - more in treatment group; 39/243 (16%) GA vs 23/238 (9.6%) placebo	Fair
Pakdaman, 2007 Iran	Unclear, described as DB	No	Unclear	Yes	Yes	Unclear, numbers NR per group	Fair

Evidence Table 18. Quality assessment of observational studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Aarskog 2009 Norway	Yes. Consecutive sera from patients treated between 2005 and 2007	No missing data reported.	Yes	Yes
Baum 2007 Europe	Patients were recruited from 76 centers in 13 countries	No. Note: there were more patients treated with Betaferon than Rebif.	Yes	Yes, VAS used and patients were telephoned weekly
Boz 2007 Canada	Yes. Canadian clinic cohort treated with a single IFN β for more than 3 years. Annual visits required by health system for continued prescriptions.	Loss to FU not reported per se. Fewer data years 6 to 10.	Yes	Yes
Castelli-Haley 2010 USA	Yes. Data for this study were obtained from the i3 Lab Rx Database in 2007. Analysis included two distinct cohorts of MS patients with continuous insurance coverage from 6 months before to 24 months after medication start from July 2001 to June 2006.	NA Retrospective study	Yes	Yes
Cocco 2008 Italy	Patients were selected from 20 MS specialty units. All women with MS who had 3 cycles of MITO before 45 years of age with at least 3 months of FU after MITO discontinuation were included between June 2005 and 2006.	NA Retrospective study	Yes	Yes, a standardized questionnaire was used

Evidence Table 18. Quality assessment of observational studies

Author Year Country	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Aarskog 2009 Norway	Unclear if specimens blinded to treatment.	NA Descriptive study, no analysis	NA	Fair
Baum 2007 Europe	Yes, trained study nurses called patients weekly for FU.	Patients who used lower dose of study drug at least once, or in whom VAS assessment were not interpretable were excluded from analyses.	Possibly. Observation period was 4 to 5 weeks for evaluation of ISP and ISR.	Fair
Boz 2007 Canada	Yes	Yes	Yes	Good
Castelli-Haley 2010 USA	Yes	Yes	Yes	Good
Cocco 2008 Italy	Yes	Yes but not all confounders were assessed.	AE had to have lasted >6 months.	Fair

Evidence Table 18. Quality assessment of observational studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Debouverie 2007 France	No. Patients who had discontinued GA for any reason or whose disease had converted to a secondary progressive course were excluded. Note: neurologists had to submit applications to French Agency for Safety of Healthcare Products (AFSSAPS). Patients approved by AFSSAPS could be prescribed GA.	18% in initial treatment phase were lost to FU and 21% were lost to FU in the long-term extension phase	Tolerability was evaluated by spontaneous AE reporting. No explicit criteria were specified in the protocol for definition of relapse (potential for variance in classification). Progression of disability was defined using EDSS score.	Yes
Durelli 2008 Italy	Analysis limited to patients who were treated with IFN β-1b for a full 2-year period	Yes. NAB+ testing on 73% of patients.	Yes	Yes
Farrell 2008 England	Patients receiving care at the National Hospital for Neurology and Neurosurgery at Queen Square in London who received IFN β since 1996 who had serum samples stored were coded into an electronic database. (Not all patients had serum samples stored.)	~94% of originally identified patients were included. There was 23% loss of data for persistence.	Yes	Yes
Jordy 2008 companion to another study conducted in Brazil	Unclear. 390 patients were selected and then divided into 3 groups.	NA Prospective and retrospective study	Yes	No, not described.
Koch-Henriksen 2009 Denmark	Patients were selected from a Danish National MS Treatment Register	No	Yes	Yes

Evidence Table 18. Quality assessment of observational studies

Author Year Country	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Debouverie 2007 France	Unknown.	Intergroup comparisons were performed but analyses of potential confounders were not assessed. (Also, there was no comparator arm.)	Initial treatment phase: 4 to 58 months Long-term extension phase: 2 yrs and 9 months Total combined FU in both phases: 3.5 to 8 yrs	Poor
Durelli 2008 Italy	Yes	Yes	No, 2 years (not adequate for relationship of NABs to clinical outcome).	Fair
Farrell 2008 England	Yes for labs. Not clearly specified for chart review.	No	Yes	Poor
Jordy 2008 companion to another study conducted in Brazil	Unknown.	Unclear	Yes	Fair-Poor
Koch-Henriksen 2009 Denmark	Yes	No	Yes	Fair-Poor

Evidence Table 18. Quality assessment of observational studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Le Page 2008 France	No. First 100 consecutive patients with RRMS who were treated with MITO as induction therapy monthly for 6 months were included.	No. 97% (97/100) were used for effectiveness and harms.	Yes	Yes
Lugaresi 2008 Italy	Patients were selected from 19 neurological centers. Unclear how these patients were selected/recruited.	NA Single-arm, prospective cohort study which was 1 year in duration.	Yes	Patient questionnaires were completed monthly under supervision of trained nurses. Treating neurologists also completed second questionnaire.
Malucchi 2008 Italy	Unclear. Attempted to reduce bias by selecting only patients who were treated for 12 months or longer, but no information on sampling frame.	No missing data reported.	Yes	Yes
Mancardi 2008 Italy	Patients were selected from medical centers that had experience in MS patient treatment and immunosuppressive therapies, had an MRI scanner available, and expertise in PCR. Centers were to add new patients to the database.	NA Retrospective database study	No. Specific AEs were not prespecified and/or defined.	No, not described. Unclear how AEs were identified or organized in the database.

Evidence Table 18. Quality assessment of observational studies

Author Year Country	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Le Page 2008 France	Yes except there were discrepancies with how MRIs were done.	Yes but not all confounders were assessed.	Yes	Fair-Poor
Lugaresi 2008 Italy	It is unknown whether trained nurses coached patients through questionnaire independently or if they used a common script for uniformity to obtain information from patients.	None performed. Authors combined results from 66% of patients who were naïve to treatment and 34% who switched from other immunomodulatory drugs due to lack of efficacy.	1 year (not adequate FU for serious AEs)	Poor
Malucchi 2008 Italy	Unclear if specimens blinded to treatment.	No	No, 12 months (+/- 3 months of treatment); inadequate to show relationship of NAb status to clinical outcomes.	Poor
Mancardi 2008 Italy	Unknown.	None performed. 90% of patients included in database had RRMS whose condition did not respond to treatment with IFN or GA. 10% of patients in database had rapidly evolving severe RRMS who were naïve to immunomodifying medications.	NR	Poor

Evidence Table 18. Quality assessment of observational studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Miller 2008	Open-label compassionate-use trial, and only patients who received GA or placebo in DB, randomized pilot study in 1978 were eligible. At the time, there were no immunomodulatory drugs. in a double-blind, randomized pilot study initiated in 1978 [7] could also participat	Yes. 60.8% discontinued	Yes	Yes
Oturai 2009 Denmark	No. Patients were selected from 2 centers that offered treatment from the whole country. Authors included the first 234 consecutive RRMS patients.	Authors included patients who attended the planned visit at 3 months after start of therapy. Authors did not report if all patients from initial inclusion met this criteria.	Yes	Yes
Portaccio 2008 Italy	Patients were identified from database of the Department of Neurology at the Univ. of Florence and were prospectively followed. Unable to determine how patients were enrolled into the database. Data were evaluated from January 1996 to September 2005.	No. 2.2% were lost to FU	Yes	Yes
Rio 2007 Spain	Patients with SPMS who were started on therapy at the study center from 1998 to 2005 were included.	No. 4.1% were lost to FU	Yes	Yes

Evidence Table 18. Quality assessment of observational studies

Author Year Country	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Miller 2008	To promote consistency across study sites, attending neurologists were given guidelines to achieve concordance in ambulation index, EDSS, and relapses.	Yes	Yes, up to 22 years	Fair
Oturai 2009 Denmark	Unknown.	Patients were divided into 3 subgroups. No statistical analyses of potential confounders were assessed in these groups.	Median 11.3 months (not long enough for serious AEs like progressive multifocal leukoencephalopathy)	Fair-Poor
Portaccio 2008 Italy	Yes	Yes	Range 2 to 6 yrs	Fair
Rio 2007 Spain	Yes, all neurologists participating were trained in EDSS assessment.	Yes	88.4% were followed for at least 12 months 61% were followed for at least 3 yrs	Fair

Evidence Table 18. Quality assessment of observational studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Sbardella 2009 Italy	Unclear if all eligible patients included.	Unclear.	Yes	Yes
Sorensen 2007 Denmark	Patients were selected from a Danish National MS Treatment Register	No	Yes	Yes
Tremlett 2008 Canada	All adverse drug reaction reporting of MS immunomodulating drugs reported to Health Canada were included.	No. 1% of patients (9/888) were excluded due to insufficient information.	Yes	Yes
Trojano 2009 Italy	Yes. A cohort of 2570 IFN β-treated RRMS was prospectively followed for up to 7 years in 15 Italian MS Centers.	NR	Yes	Yes
Weber-Schoendorfer 2009 Germany	Patients were identified through the Teratology Information Service of Berlin. Most requests for information in regard to exposure to IFN β or GA came from physicians whose patients inadvertently became pregnant while on disease-modifying therapies. Data were collected between 1996 to 2007 and patients were prospectively enrolled using questionnaires.	Unclear. Possibly there were no loss to FU.	Yes	Yes, a standardized questionnaire was used.

Evidence Table 18. Quality assessment of observational studies

Author Year Country	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Sbardella 2009 Italy	Unclear if specimens blinded to treatment.	No	No, therapy duration ranged from 1 to 10 years, but no separate analysis by length of therapy.	Poor
Sorensen 2007 Denmark	Yes	No	Yes	Fair-Poor
Tremlett 2008 Canada	Reporting of adverse drug reactions is voluntary except for serious adverse drug reactions which is mandatory for manufacturers.	Yes	Range 13 days to 5 yrs	Fair
Trojano 2009 Italy	Yes	Yes	Yes, up to 7 years	Good
Weber-Schoendorfer 2009 Germany	Yes	Yes but not all confounders were assessed.	Yes	Fair-Poor