Technology Assessment

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The clinical effectiveness and cost-effectiveness of interferon-beta and glatiramer acetate in the management of relapsing/remitting and secondary-progressive multiple sclerosis

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Contribution of authors

Paul Tappenden, Jim Chilcott and Christopher McCabe developed the ScHARR MS Cost-effectiveness Model in conjunction with the Cost Effectiveness of MS Therapies Working Group. Emma Simpson and Paul Tappenden undertook the review of clinical effectiveness. Paul Tappenden, Jim Chilcott and Christopher McCabe developed the cost-effectiveness model for use by the Centers for Medicare and Medicaid. Richard Nixon, Jason Madan, Paul Tappenden and Jim Chilcott undertook the Bayesian synthesis of RCT evidence using WinBUGS.

Disclaimer

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Conflicts of interest

Since the 2001 NICE Appraisal, authors of this report have provided advice concerning modeling the cost-effectiveness of treatments for MS to Biogen IDEC and Novartis. None of the treatments involved are within the scope of the AHRQ analysis. Advice is currently being given to the US Multiple Sclerosis Society.

Abbreviations

ABN	Association of British Neurologists
ADL	Activities of Daily Living
C1MSSG	Copolymer-1 Multiple Sclerosis Study Group
CCTR	Cochrane Controlled Trials Register
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness Acceptability Curve
CMS	Centers for Medicare and Medicaid Services
CNS	Central Nervous System
COS	Community of Science
CSF	Cerebrospinal fluid
DSS	Disability Status Scale
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQol 5D
EVIDENCE	EVidence of Interferon Dose-response: European North American Comparative Efficacy
FDA	Food and Drug Administration
GA	Glatiramer acetate
HRQoL	Health-Related Quality of Life
HUI3	Health Utilities Index (Mark 3)
IFNBMSSG	Interferon Beta Multiple Sclerosis Study Group
IFNβ	Interferon beta
IM	Intramuscular
INCOMIN	INdependent COMparison of INterferons
ITT	Intention to treat
MCMC	Markov Chain Monte Carlo
MMA	Medicare Modernization Act
MRC	Medical Research Council
MRDD	Medicare Replacement Drug Demonstration
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
MSCRG	Multiple Sclerosis Collaborative Research Group
NASPMS	North American Secondary Progressive Multiple Sclerosis
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Clinical Excellence
NRR	National Research Register
PPMS	Primary Progressive Multiple Sclerosis

PRISMS	Prevention of Relapses and Disability by Interferon β1a Subcutaneously in Multiple Sclerosis
PRMS	Primary Relapsing Multiple Sclerosis
QALY	Quality Adjusted Life Year
RCT	Randomized Controlled Trial
RRMS	Relapsing Remitting Multiple Sclerosis
RPMS	Relapsing Progressive Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis

Executive summary

Background

This report describes one of two studies undertaken to address a Congressional mandate to evaluate the cost-effectiveness of expanded drug coverage to Medicare under the Medicare Replacement Drug Demonstration. The demonstration aimed to improve beneficiary access to selected new oral anti-cancer drugs and other self-injected medications such as those used to treat multiple sclerosis (MS). Currently, treatment of MS using IFNβ-1a is covered under Medicare Part B when administered intra-muscularly by a physician. Until the new prescription drug benefit (Medicare Part D) began in 2006, subcutaneous injection of IFNβ-1a administered by the patient was not covered. The MRDD provided temporary national coverage to all self-administered treatments during the 16 months before Medicare Part D was implemented. Patient cost-sharing under the MRDD was structured to resemble Part D. The second study examines the cost-effectiveness of anti-TNF inhibitors for treating rheumatoid arthritis.

The main question addressed by this review is *"What is the clinical effectiveness and cost-effectiveness of interferon beta (IFNβ) and glatiramer acetate (GA) in the management of relapsing/remitting multiple sclerosis and secondary-progressive multiple sclerosis to the Medicare program in the United States?"*

Clinical effectiveness methods

The relevant patient population for inclusion within the review of clinical effectiveness was:

- adults with RRMS, eligible for treatment with IFNβ or GA; *or*
- adults with SPMS, eligible for treatment with IFNβ.

Five interventions were included in the review:

- GA 20mg (Copaxone/Copolymer-1), daily subcutaneous injection;
- IFNβ-1a 22μg (Rebif), subcutaneous injection 3 times a week;
- IFNβ-1a 44μg (Rebif), subcutaneous injection 3 times a week;
- IFNβ-1a 6MIU (Avonex), intramuscular injection once per week;
- IFNβ-1b 8MIU (Betaseron), subcutaneous injection every other day.

The relevant comparator for the assessment was placebo, or another disease-modifying therapy where head-to-head studies were available. The following co-interventions were defined for inclusion within the review: best supportive care, including symptom control, physiotherapy, psychiatric and social support, disability aids, concomitant medication (not immunomodulatory therapy) for relapses or treatment-related adverse events.

Chapter 4 presents the results of the systematic review of clinical effectiveness. Effectiveness parameters used in the subsequent cost-effectiveness analysis (i.e. relative relapse rates and relative hazard ratios for MS progression) are also reported within this chapter of the report.

Chapter 5 presents the methods used to evaluate the cost-effectiveness of IFNβ and GA in the management of MS. All major structural assumptions and sources of evidence used within the model are described within this chapter.

Chapter 6 reports the results of the cost-effectiveness analysis. The base case analysis reports estimates of the marginal cost-effectiveness of each therapy compared to best supportive care based exclusively upon the placebo-controlled evidence. Simple sensitivity analyses are presented to demonstrate the impact of discontinuing treatment upon progression to EDSS 7.0, alternative model time horizons, assumptions concerning the relationship between MS disability and the costs of care, and alternative values for other model parameters on the central estimates of cost-effectiveness. A further sensitivity analysis is presented using modified treatment effectiveness estimates informed by the head-to-head trials of disease-modifying therapies. All health economic analyses are reported from the perspective of the US health care payer. Finally, this chapter reports the results of the probabilistic sensitivity analysis, as represented by marginal Cost Effectiveness Acceptability Curves (See “Key Definitions”).

Chapter 7 discusses the results of the assessment of clinical effectiveness and cost-effectiveness and highlights implications for clinical practice in the US. Limitations concerning the current state of clinical and cost evidence are highlighted and their implications on the cost-effectiveness of the disease-modifying therapies are discussed. Areas in which further research is indicated are also discussed.

Chapter 8 presents the conclusions on the clinical effectiveness and cost-effectiveness of the disease-modifying therapies in the management of MS.

The mixed treatment comparison assumes that the number of relapses for patients within one arm of each trial is independently Poisson distributed. Under this assumption, it follows that the observed mean number of relapses in a trial arm estimates the expected mean number of relapses, and the observed mean number of relapses divided by the sample size in an arm estimates the variance of the mean number of relapses. Suppose we wish to estimate the relative relapse rate for IFNβ-1a 6MIU versus placebo from a trial. The log mean relapse rate is a more suitable scale to work on, as this will be approximately normally distributed. The observed log mean relapse rate in each arm will be normally distributed with means q_a and q_p and variances estimated by the inverse of the product of the sample sizes and the mean relapse rates themselves, call these w_a and w_p. As the two trial arms are independent, the difference in log mean relapse rate (the log of the relative relapse rate), will be normally distributed with the mean $q_{ap} = q_a - q_p$ and variance estimated by $w_a + w_p$.

A similar exercise was repeated for each of the trials included in the review, and the five observed comparisons are given five normal distributions, the mean of each being the population log relative relapse rate for the comparison made within the trial. We are interested in estimating q_{ap}, q_{bp} and q_{rp}. Two of the comparisons (IFNβ-1b 8MIU versus IFNβ-1a 6MIU, and IFNβ-1a 44μg versus IFNβ-1a 6MIU) give estimates of q_{ba} and q_{ra}. These can be used to provide estimates of the comparisons we are interested in, as $q_{ba} = q_{bp} - q_{ap}$ and $q_{ra} = q_{rp} - q_{ap}$. MCMC methods[16] were used to obtain estimates of the parameters $\exp(q_{ap}), \exp(q_{bp})$ and $\exp(q_{rp})$, the population relative relapse rates. The methods used to perform this data synthesis are described in further detail by Lu and Ades.[17] The WinBUGs relapse model was a fixed effect indirect comparison meta-analysis and did not allow for between-trial heterogeneities due to the limited data reported in the trial publications.

The WinBUGS relapse model syntax and data are detailed in Appendix 3.

Table 4 Design and characteristics of included studies

Trial	Study design	Intervention 1	Intervention 2	Type of MS	Number randomized	Setting	Primary outcome
European-Canadian (2001)[14]	Randomized placebo-controlled trial, double-blind	GA 20mg (Copaxone)	Placebo	RRMS	239 (GA 119 placebo 120)	Europe, Canada (29 centers)	MRI measures (relapse rate included as a tertiary outcome)
C1MSSG (1995, 1998)[19;20]	Randomized placebo-controlled trial, double-blind	GA 20mg (Copaxone)	Placebo	RRMS	251 (GA 125 placebo 126)	USA (11 centers)	Mean number of relapses
PRISMS (1998)[23]	Randomized placebo-controlled trial, double-blind	IFNβ-1a 22µg (Rebif)	IFNβ-1a 44µg (Rebif)	RRMS	560 (22µg 189 44µg 184 placebo 187)	Europe, Canada, Australia (22 centers)	Relapse rate
MSCRG (1996)[21]	Randomized placebo-controlled trial, double-blind	IFNβ-1a 6MIU (Avonex)	Placebo	RRMS	301 (IFNβ-1a 158 placebo 143)	USA (4 centers)	Time to sustained disease progression
IFNBMSSG (1993, 1995)[15;22]	Randomized placebo-controlled trial, double-blind	IFNβ-1b 8MIU (Betaseron)	Off-label dose IFNβ-1b 1.6MIU Placebo	RRMS	372 (IFNβ-1b 124 placebo 123 off-label dose 125)	USA, Canada (11 centers)	Relapse rate, and proportion of patients relapse-free
European Study Group (1998, 2001)[24;25]	Randomized placebo-controlled trial, double-blind	IFNβ-1b 8MIU (Betaseron)	Placebo	SPMS	718 (IFNβ-1b 360 placebo 358)	Europe (32 centers)	Time to sustained disease progression
NASPMS (1999)[26]	Randomized placebo-controlled trial, double-blind	IFNβ-1b 8MIU (Betaseron)	Off-label dose IFNβ-1b 5MIU per m squared, body surface area Placebo	SPMS	939 (IFNβ-1b 317 placebo 308 off-label dose 314)	USA, Canada (35 centers)	Time to sustained disease progression
INCOMIN (2002)[27]	Randomized head-to-head trial, unblinded, no placebo	IFNβ-1b 8MIU (Betaseron)	IFNβ-1a 6MIU (Avonex)	RRMS	188 (IFNβ-1b 96 IFNβ-1a 92)	Italy (15 centers)	Proportion of patients relapse-free (and MRI measures)
EVIDENCE (2002)[28]	Randomized head-to-head trial, unblinded, no placebo	IFNβ-1a 44µg (Rebif)	IFNβ-1a 6MIU (Avonex)	RRMS	677 (44µg 339 6MIU 338)	Europe, Canada, USA (56 centers)	Proportion of patients relapse-free

Table key

C1MSSG	Copolymer-1 Multiple Sclerosis Study Group
PRISMS	Prevention of Relapses and Disability by Interferon β1a Subcutaneously in Multiple Sclerosis
MSCRG	Multiple Sclerosis Collaborative Research Group
IFNBMSSG	Interferon Beta Multiple Sclerosis Study Group
NASPMS	North American Secondary Progressive Multiple Sclerosis
INCOMIN	INdependent COMparison of INterferons
EVIDENCE	EVidence of Interferon Dose-response: European North American Comparative Efficacy
IFNβ	Interferon beta
GA	Glatiramer acetate