



Cost-Effectiveness Analysis of Peginterferon Beta-1a in the Treatment of Relapsing-Remitting Multiple Sclerosis in Italy: Results of an Updated Analysis

Diego Centonze¹, Sergio Iannazzo², Laura Santoni³, Cecilia Saleri³, Elisa Puma³, Luigi Giuliani², Pier Luigi Canonico⁴

¹ IRCCS Neuromed, Pozzilli (IS), Italy & Laboratory of Synaptic Immunopathology, Tor Vergata University, Rome, Italy

² SIHS srl, Health Economics Consulting, Turin, Italy

³ Biogen Italia, Milan, Italy

⁴ Department of Pharmaceutical Sciences, University of Piemonte Orientale "Amedeo Avogadro", Novara, Italy

Keywords

Cost-Effectiveness; Peginterferon Beta-1a; Multiple Sclerosis

BACKGROUND

Multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system, is causing a progressive disability that impacts patients' quality of life and societal costs [1]. MS takes several forms, with new symptoms either occurring in isolated attacks (relapsing form) or building up over time (progressive form) [2]. Between attacks, symptoms may disappear completely; however, permanent neurological problems often remain, especially as the disease advances [2]. In 85% of patients with MS the onset form is relapsing-remitting MS (RRMS) [3]. While MS is currently considered incurable, treatment has advanced significantly over the past several decades. Disease modifying therapies (DMTs) can reduce the frequency of clinical relapses and delay disability progression [4]. As is the case in many different therapeutic areas, clinical progress in treating the disease has accompanied a rise in costs to purchase biologic products. In this light, economic evaluations are key elements for healthcare decision-making.

In 2016 we published in this journal a cost-effectiveness analysis that compared subcutaneous peginterferon beta-1a 125 µg every 2 weeks (Plegridy[®]) to the other injectable DMTs used in first-line therapy of RRMS from both the perspective of the Italian National Healthcare Service (NHS) and of the Italian Society [5]. The comparators considered in the analysis were: interferon (IFN) beta-1a 30 µg (Avonex[®]), IFN beta-1a 22 µg (Rebif[®] 22), IFN beta-1a 44 µg (Rebif[®] 44), glatiramer acetate (GA, Copaxone[®]) 20 mg, IFN beta-1b 250 µg (Betaferon[®] and Extavia[®]). The 2016 analysis showed that peginterferon beta-1a was an alternative dominant or cost-effective vs IFNs and GA for the treatment of RRMS in Italy from the NHS and societal perspectives. While the design of the model and the choice of clinical parameters remains well aligned with the most recent cost-effectiveness studies published in the literature [6], some economic inputs of that analysis appear now outdated. The objective of the current work is thus to provide an update of the original analysis [5].

Corresponding author
Prof. Diego Centonze
centonze@uniroma2.it

Received: 9 November 2018
Accepted: 19 November 2018
Published: 30 November 2018

UPDATE OF THE COST-EFFECTIVENESS ANALYSIS OF PEGINTERFERON BETA-1A IN ITALY

The 2016 analysis [5] was conducted using a Markov model (Figure 1), reviewed and accepted by – among other agencies – the National Institute for Health and Care Excellence (NICE) in the UK [7]. The model simulates mortality, disease progression between EDSS levels, relapse frequency and transition to secondary progressive multiple sclerosis (SPMS), estimating the survival (life years; LYs), the survival adjusted for quality of life (quality-adjusted life years; QALYs), the overall costs, and the incremental cost per QALY gained (incremental cost effectiveness ratio; ICER). Twenty-one health states are included in the model: 10 states in the RRMS form; 10 states in the SPMS form; 1 state for death.

The simulation starts with a hypothetical cohort distributed among the different EDSS levels of RRMS, according to the initial distribution and demographic characteristics of the patients in the ADVANCE study, which compared the safety and efficacy of peginterferon beta-1a 125 µg every 2 weeks with placebo [8,9]. At each (annual) simulation cycle the patients can progress/regress between the EDSS levels or remain in the same EDSS level, progress to the SPMS form, have a relapse according to the specific probability in each health state, or die. Patients cannot return from SPMS to RRMS, nor regress to lower EDSS levels in the SPMS form (such transitions are possible in RRMS). The treatments included in the model can exert their effect by either slowing down the disability progression (compared to the natural history of the disease) or by reducing the relapse incidence in the RRMS form. Treatment cannot affect the progression from RRMS to SPMS, the transition between EDSS levels in the SPMS form, or mortality. It is assumed that patients stop disease modifying therapy when reaching an EDSS level ≥ 7 in the RRMS form, or on transition to the SPMS form.

Efficacy data were derived from a published network meta-analysis [10]. Each treatment is associated with specific adverse events that occur at frequencies reported in clinical studies. Health state utilities were derived from a cross-sectional study of the burden of illness of patients with MS in Italy [11]. Unit costs were based on current Italian prices and tariffs, and the published literature. Costs and utilities were discounted at 3.5% [12]. The model considers a time horizon of 50 years. Full details have been published previously in 2016 [5].

While the design of the model and the choice of clinical parameters remains well aligned with the most recent cost-effectiveness studies published in the literature [6], some economic

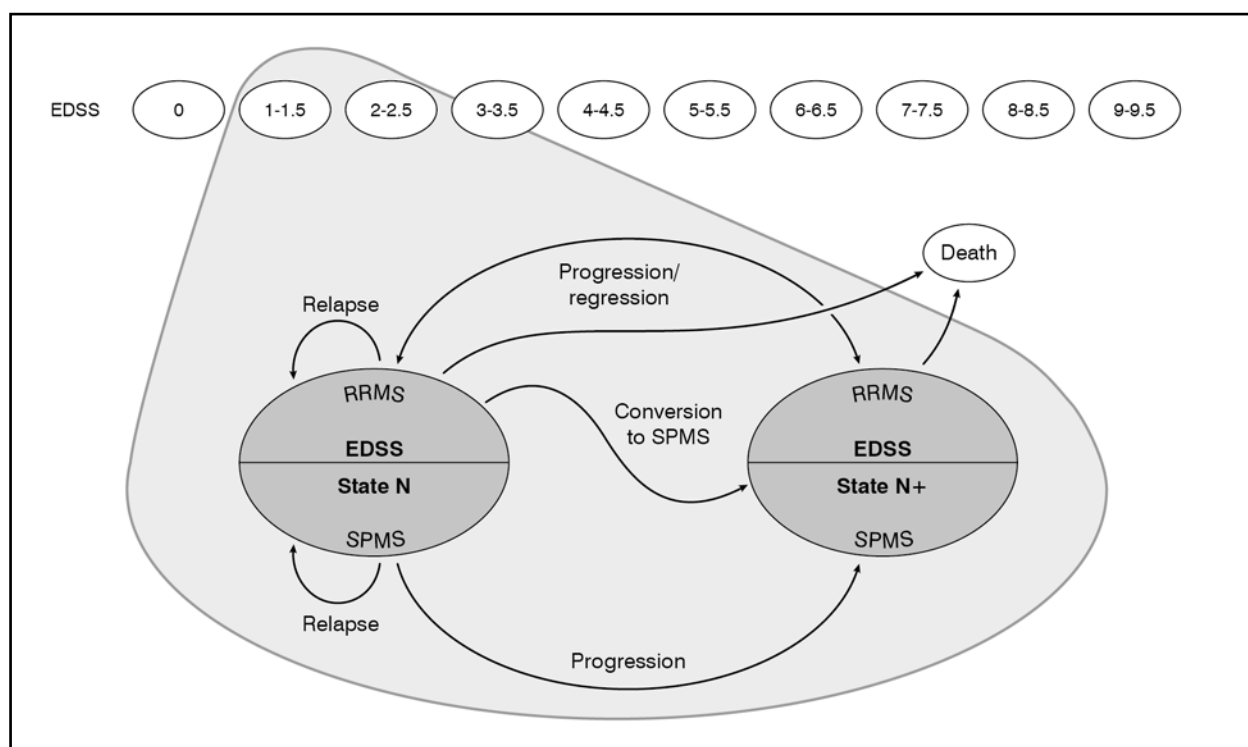


Figure 1. CEA model structure. Modified from [5]

EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; State N = current EDSS state

	Costs for the NHS (£/year)		Costs for the Society (£/year)	
	RRMS	SPMS	RRMS	SPMS
Routine management costs by EDSS score				
0	207	5,467	1,378	9,668
1-1.5	207	5,467	1,378	9,668
2-2.5	207	5,467	1,378	9,668
3-3.5	652	19,377	12,802	51,743
4-4.5	652	19,377	12,802	51,743
5-5.5	652	19,377	12,802	51,743
6-6.5	652	19,377	12,802	51,743
7-7.5	5,854	9,834	34,992	76,443
8-8.5	5,854	9,834	34,992	76,443
9-9.5	5,854	9,834	34,992	76,443
Management cost of relapse		1,574		2,681

Table I. Revised routine management costs and relapse costs. Elaborated from [15,16]

RRMS 0-6,5: only costs for co-medications. Not included the costs for DMTs and other disease management costs (e.g., monitoring, etc.) considered in other calculation sections of the model

EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

inputs of that analysis now appear outdated. Therefore, in the current analysis we reviewed all cost input data, with specific focus on the cost of drug purchase and the cost of relapse (Table I). The costs were updated to July 2018, by inflating them with consumer price index [13]. While ex-factory prices of most injectable DMTs were unchanged since 2016, we found a new Official Gazette for IFN beta-1a 22 µg and 44 µg [14]. Additionally, the source for direct medical and societal costs to manage a relapse, originally derived from Kobelt et al. [11], was changed to a more recent publication, namely the study from Battaglia et al. [15]. Furthermore, management costs for adverse events and routine costs by EDSS scores (Table I), based on Karampampa et al. [16], were revised based on current prices of generic products [17] and inflated to July 2018 [13]. Finally, the mortality tables of the general Italian population were aligned with the most recent evidence [18].

RESULTS OF THE UPDATED ANALYSIS

Peginterferon beta-1a was more effective than all first-line injectable DMTs included in the analysis, both in terms of survival (LYs, discounted) and of survival adjusted for quality of

	Peginterferon beta-1a 125 µg	IFN beta-1a 30 µg	IFN beta-1a 22 µg	IFN beta-1a 44 µg	IFN beta-1b 250 µg ¹	IFN beta-1a 250 µg ²	GA 20 mg
Outcomes							
LYs	20.09	19.86	19.88	19.96	19.83	19.83	19.83
QALYs	9.09	8.11	8.21	8.57	8.08	8.08	8.17
Incremental QALYs		0.98	0.88	0.52	1.02	1.02	0.92
Cost (£)							
Drugs + Monitoring	113,357	92,762	84,526	110,807	92,359	86,163	83,026
Relapses	5,896	6,261	6,091	5,884	5,910	5,910	5,706
Adverse events	102	154	107	151	110	110	94
Routine management	115,191	124,595	124,073	120,661	125,763	125,763	125,916
Total costs	234,548	223,770	214,798	237,502	224,143	217,947	214,742
Incremental costs		10,778	19,750	-2,955	10,404	16,601	19,805
ICER (£/QALY)		10,962	22,449	Dominant	10,226	16,317	21,451

Table II. CEA of peginterferon beta-1a vs first-line injectable DMTs in Italy from the NHS perspective

¹ Betaferon

² Extavia

	Peginterferon beta-1a 125 µg	IFN beta-1a 30 µg	IFN beta-1a 22 µg	IFN beta-1a 44 µg	IFN beta-1b 250 µg ¹	IFN beta-1a 250 µg ²	GA 20mg
Outcomes							
LYs	20.09	19.86	19.88	19.96	19.83	19.83	19.83
QALYs	9.09	8.11	8.21	8.57	8.08	8.08	8.17
Incremental QALYs		0.98	0.88	0.52	1.02	1.02	0.92
Cost (€)							
Drugs + Monitoring	113,357	92,762	84,526	110,807	92,359	86,163	83,026
Relapses	10,041	10,662	10,373	10,020	10,065	10,065	9,718
Adverse events	102	154	107	151	110	110	94
Routine management	664,715	735,002	730,957	704,933	744,146	744,146	745,346
Total costs	788,216	838,579	825,964	825,911	846,681	840,485	838,183
Incremental costs		-50,363	-37,748	-37,695	-58,465	-52,269	-49,967
ICER (€/QALY)		Dominant	Dominant	Dominant	Dominant	Dominant	Dominant

Table III. CEA of peginterferon beta-1a vs first-line injectable DMTs in Italy from the societal perspective

¹ Betaferon

² Extavia

life (QALYs, discounted) (Table II). Incremental QALYs gained ranged from 0.52 (peginterferon beta 1-a vs IFN beta-1a 44 µg) to 1.02 (peginterferon beta 1-a vs IFN beta-1b 250 µg).

The analysis from the perspective of the Italian NHS showed that the (discounted) total direct medical cost of a patient treated with peginterferon beta-1a was slightly higher than that of other DMTs, except for IFN beta-1a 44 µg (Table II). In the first cases, the higher drug cost was only partially offset by possible reductions in other cost categories.

Peginterferon beta-1a was dominant vs IFN beta-1a 44 µg because it was more effective and with lower costs and cost-effective versus the other first line injectable DMTs showing the following ICERs: € 10,962/QALY for IFN beta-1a 30 µg, € 22,449/QALY for IFN beta-1a 22 µg, € 10,226/QALY for IFN beta-1b 250 µg (Betaferon®), € 16,317/QALY for IFN beta-1b 250 µg (Extavia®), and € 21,451/QALY for GA 20 mg. In all cases, the ICER was below the commonly considered willingness-to-pay threshold for acceptability (€ 30,000-50,000/QALY) (Table II).

When the analysis was performed in the perspective of the Italian Society, the total cost of a patient treated with peginterferon beta-1a was lower than those of all the comparators included in the analysis (Table III).

Peginterferon beta-1a was dominant vs all injectable first-line DMTs included in the analysis (IFN beta-1a, IFNβ-1b, GA); that is, it is more effective, in terms both of survival (LYs) and of survival adjusted for quality of life (QALYs), and with a lower total societal cost (Table III).

Sensitivity analyses (deterministic and probabilistic) confirmed that, from both NHS and societal perspectives, the base case results are robust to variations in input parameters, in line with the 2016 analysis [5].

CONCLUSION

The model that was used to perform the cost-effectiveness analysis of peginterferon beta-1a published in 2016 was updated in economic data (all cost now determined at July 2018) and in reference statistical data (i.e., tables of mortality of the general Italian population). No changes were made to the structure and design of the model, or to the clinical parameters used as inputs. The results of the updated analysis confirm and strengthen those published in 2016, showing that peginterferon beta-1a is a valid alternative in the treatment of RRMS as compared to other available injectable first-line DMTs included in the model from the perspective of both the Italian NHS and the Italian society.

Funding

This manuscript was financially supported by Biogen Italia (Milan, Italy).

Conflicts of Interests

DC is an Advisory Board member of Bayer Schering, Biogen, Merck-Serono, Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen, Genzyme, GW Pharmaceuticals, Merck Serono, Novartis, Sanofi-Aventis, Teva. He is also principal investigator in clinical trials for Bayer Schering, Biogen, Novartis, Merck Serono, Sanofi-Aventis, Teva.

SI is a consultant that received fees by Biogen Italia for conducting the update of the analysis and for other projects.

LS, CS, EP are employees of Biogen Italia.

LG received fee by Biogen Italia for other projects.

PLC has received research grants, contributions and fees by the following pharmaceutical companies: Abbvie, Almirall, Amgen, A.C.R.A.F. – Angelini, Astellas, Astra Zeneca, Bayer, Biogen, Celgene, Eli Lilly, Grunenthal, Lundbeck, LeoPharma, Merck Serono, MSD, Menarini, Novartis Pharma, Otsuka, Roche, Sanofi, Takeda, Zambon, Jazz Pharmaceuticals, Amicus, Teva, Servier, UCB, Boehringer Ingelheim.

REFERENCES

1. Kobelt G, Pugliatti M. Cost of multiple sclerosis in Europe. *Eur J Neurol* 2005; 12 Suppl 1: 63-7; <https://doi.org/10.1111/j.1468-1331.2005.01193.x>
2. Milo R, Kahana E. Multiple sclerosis: geoeconomics, genetics and the environment. *Autoimmun Rev* 2010; 9: A387-94; <https://doi.org/10.1016/j.autrev.2009.11.010>
3. Multiple Sclerosis International Federation. Atlas of MS 2013. Available at <http://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf> (last accessed September 2018)
4. Noyes K, Weinstock-Guttman B. Impact of diagnosis and early treatment on the course of multiple sclerosis. *Am J Manag Care* 2013; 19(17 Suppl): s321-31
5. Iannazzo S, Santoni L, Saleri C, et al. Cost-effectiveness analysis of peginterferon beta-1a in Italian relapsing remitting multiple sclerosis management. *Farmeconomia. Health economics and therapeutic pathways* 2016; 17(Suppl 2): 13-36; <http://dx.doi.org/10.7175/fe.v17i2S.1230>
6. Iannazzo S, Iliza AC, Perrault L. Disease-modifying therapies for multiple sclerosis: a systematic literature review of cost-effectiveness studies. *Pharmacoeconomics* 2018; 36: 189-204; <https://doi.org/10.1007/s40273-017-0577-2>
7. Peninsula Technology Assessment Group (PenTAG). The effectiveness and cost-effectiveness of natalizumab for multiple sclerosis: an evidence review of the submission from Biogen. Evidence Review Group Report commissioned by NHS R&D HTA Programme on behalf of: NICE, 2007. Available at <https://www.nice.org.uk/guidance/ta127> (last accessed September 2018)
8. Calabresi PA, Deykin A, Arnold DL, et al. Analysis of 2-year clinical efficacy and safety of Peginterferon Beta-1a in patients with relapsing-remitting multiple sclerosis: data from the pivotal phase 3 ADVANCE study. American Academy of Neurology, 66th Annual Meeting. Philadelphia, 26 April-3 May 2014
9. Calabresi PA, Kieseier BC, Arnold DL, et al.; ADVANCE Study Investigators. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, doubleblind study. *Lancet Neurol* 2014; 13: 657-65; [https://doi.org/10.1016/S1474-4422\(14\)70068-7](https://doi.org/10.1016/S1474-4422(14)70068-7)
10. Tolley K, Hutchinson M, You X, et al. A network meta-analysis of efficacy and evaluation of safety of subcutaneous pegylated interferon beta-1a versus other Injectable therapies for the treatment of relapsing-remitting multiple sclerosis. *PLoS One* 2015; 1-21; <https://doi.org/10.1371/journal.pone.0127960>
11. Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life of multiple sclerosis in Italy. *Eur J Health Econ* 2006; 7 Suppl 2: S45-54; <http://dx.doi.org/10.1007/s10198-006-0385-7>
12. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Available at <http://www.nice.org.uk/article/pmg9/chapter/foreword> (last accessed September 2018)
13. ISTAT. Consumer price index inflation to July 2018. Available at <http://rivaluta.istat.it> (last accessed September 2018)

14. Agenzia Italiana del Farmaco – AIFA. DETERMINA 31 maggio 2018. Rinegoziazione del medicinale per uso umano «Rebif», ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 866/2018). Italian Official Journal (Gazzetta Ufficiale) n. 145, June 25th, 2018
15. Battaglia M, Kobelt G, Ponzio M, et al.; European Multiple Sclerosis Platform. New insights into the burden and costs of multiple sclerosis in Europe: Results for Italy. *Mult Scler* 2017; 23(2_suppl):104-116
16. Karampampa K, Gustavsson A, Miltenburger C, et al. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from Italy. *Mult Scler* 2012; 18(2 Suppl): 29-34; <https://doi.org/10.1177/1352458512441566c>
17. AIFA. Reference list for generic products (Lista di trasparenza). Update 09/08/2018. Available at <http://www.aifa.gov.it/content/liste-di-trasparenza-aggiornamento-del-09082018> (last accessed September 2018)
18. ISTAT. Mortality tables of the Italian general population. Year 2016. Available at <http://demo.istat.it> (last accessed September 2018)