Clinical effectiveness and cost-effectiveness of beta-interferon and glatiramer acetate for treating multiple sclerosis: systematic review and economic evaluation

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Scientific summary

Effectiveness of β-IFN and GA for treating MS

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Scientific summary

Background

Multiple sclerosis (MS) is a neurodegenerative disorder characterised by inflammation and demyelination of neurons in the brain and spinal cord. It is a leading cause of disability in working-age adults and affects over 100,000 people in the UK. The commonest form of MS is relapsing–remitting MS or RRMS. A single demyelinating event thought to precede MS is known as clinically isolated syndrome (CIS) and RRMS can progress to secondary progressive MS (SPMS). Although there is currently no cure for MS, there are a number of disease-modifying therapies (DMTs) available to help reduce the frequency of relapses and the rate of disease progression. Beta-interferons (IFN-β) and glatiramer acetate (GA) are two such drugs. At the time of publication of the most recent National Institute for Health and Care Excellence (NICE) technology appraisal (TA) of these drugs in 2002 (TA32), there was insufficient evidence of their clinical and cost-effectiveness. A risk-sharing scheme (RSS) was put in place, allowing patients to access the drugs and the NHS to adjust prices based on cost-effectiveness data, as well as to monitor long-term outcomes. This current study aimed to appraise the clinical effectiveness and cost-effectiveness of IFN-β and GA for MS, integrating published evidence with data from the RSS, and also to assess their role in CIS.

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Decision problem

Our first objective was to systematically review the evidence for the clinical effectiveness of IFN-β-1a, pegylated IFN-β-1a, IFN-β-1b and GA in people with relapsing MS (including people with RRMS and people with SPMS with active disease, evidenced by relapses) and CIS (i.e. a single demyelinating event, who are considered at high risk of developing subsequent MS) compared with best supportive care (BSC) without DMTs, and with each other. The following outcomes were investigated:

- relapse rate
- transition to clinically definite MS (in the case of CIS)
- severity of relapse
- disability [e.g. Expanded Disability Status Scale (EDSS)]
- symptoms of MS such as fatigue, cognition and visual disturbance
- freedom from disease activity
- discontinuation as a result of neutralising antibodies
- mortality
- adverse effects of treatment
- health-related quality of life (HRQoL).

The second objective was to systematically review existing economic evaluations, including use of the existing RSS model; develop a de novo economic model for CIS; assess the cost-effectiveness of the treatments (IFN-β-1a, pegylated IFN-β-1a, IFN-β-1b and GA) for CIS and RRMS against the stated comparators, expressed in incremental costs per quality-adjusted life-year (QALY), using a time horizon that was sufficiently long to reflect any differences in costs or outcomes between the technologies being compared and taking a NHS and Personal Social Services (PSS) perspective; and update model parameters and inputs to reflect available evidence from the literature, current costs, the NICE reference case, current practice and new data from the RSS.

Methods

Clinical effectiveness and cost-effectiveness reviews

Searches were undertaken in January and February 2016. Several relevant systematic reviews were identified for some populations and study types, allowing some searches to be limited by publication date to 2012 onwards. For those populations and study types for which no suitable systematic reviews were identified, database searches were undertaken from inception. The databases searched were The Cochrane Library, the Cochrane MS Group Specialised Register; MEDLINE; EMBASE and the Science Citation Index. For the cost-effectiveness review, the NHS Economic Evaluation Database (NHS EED), Research Papers in Economics (RePEc) and the Cost-effectiveness Analysis (CEA) Registry were searched. Online trial registers were also searched as well as company, patient and carer, professional and research group websites. The following designs were included: randomised controlled trials (RCTs), systematic reviews, meta-analyses and cost-effectiveness studies. The population of interest was people diagnosed with RRMS, SPMS or CIS and the intervention was one of the designated drugs used within its marketing authorisation (and including the recommended dose regimen). Searches of reference lists and information provided by the manufacturers of the interventions were carried out for additional eligible studies. Two reviewers independently screened and assessed identified titles and abstracts for inclusion, with recourse to a third reviewer in case of disagreement. Systematic reviews used to locate primary studies were appraised using the Assessing the Methodological Qualities of Systematic Reviews (AMSTAR) checklist, primary clinical effectiveness studies were appraised using the Cochrane risk of bias assessment tool and health economic studies were appraised using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) and Philips checklists. Narrative synthesis was undertaken. When possible, random-effects meta-analyses and network meta-analyses (NMAs) were performed for each outcome using Stata® 14 (StataCorp LP, College Station, TX, USA).

Cost-effectiveness methods

The RSS model is an economic analysis that was conducted to assess the cost-effectiveness of the combined treatment effect of DMTs included in the RSS compared with BSC for people with RRMS. It is a Markov model based on the British Columbia Multiple Sclerosis (BCMS) cohort for natural history compared with cohorts of patients taking the intervention drugs. Drug prices were agreed with the Department of Health as part of the RSS. We based our cost-effectiveness analysis on the RSS model, including data from the 10-year follow-up when available. For CIS we built a de novo economic model to assess the cost-effectiveness of the identified drugs. We used outcome values derived from our systematic reviews of the published literature, RSS pooled cost-effectiveness data, data submitted by the companies, expert opinion and NHS reference costs to input into the models to understand the relative costs and effectiveness of the different interventions and to explore the different assumptions made.

We used our modified RSS model (we assumed that standardised mortality was 1.0 and excluded carers' disutility) with clinical effectiveness inputs derived from the year 10 RSS analyses as the base case for RRMS, with additional evidence on time to progression used in the CIS base case. We estimated mean total costs and mean total QALYs for each intervention compared with BSC and with each other and adopted a NHS and PSS perspective with a 50-year time horizon. Costs were in 2014/15 prices and a discount rate of 3.5% was used. Outcomes are reported as incremental cost-effectiveness ratios (ICERs) expressed in terms of cost per QALY gained. The models were run deterministically. We undertook sensitivity analyses and explored uncertainty to investigate key drivers. For RRMS we undertook probabilistic analyses with 1000 bootstrapped iterations.

Results

Clinical effectiveness results

We identified 6420 publications, of which 63 publications relating to 35 primary studies were included in the review. In total, 86% (30/35) of the studies were at high risk of bias from either complete or partial

participant unblinding and studies also suffered from relatively short follow-up times; 29% (10/35) of the studies were also found to be at high risk of bias from missing data, based on large numbers of missing data, a difference in rates of loss to follow-up between arms or lack of reporting of imputation methods. In 17% (6/35) of studies outcomes were not reported as stated and these studies were designated as being at high risk of bias from selective reporting. Finally, all studies funded by drug manufacturers were designated as being at high risk of bias. Five studies investigated DMTs for CIS, three trials investigated SPMS and 27 compared different DMTs with each other or with placebo for RRMS using a variety of outcomes.

For CIS, all studies found a benefit of DMTs over placebo for time to progression to MS. Rankings from the NMA suggested that 44 µg of subcutaneous (SC) IFN-β-1a three times weekly was ranked best, followed by 250 µg of SC IFN-β-1b every other day, 30 µg of intramuscular IFN-β-1a once a week and 20 mg of SC GA once daily.

For RRMS there was very little difference between the different drugs in terms of reducing moderate or severe relapse rates. Random-effects NMA gave a pooled rate ratio (RR) of 0.65 [95% confidence interval (CI) 0.56 to 0.76] for annualised relapse rate (ARR) for all intervention drugs compared with placebo and a hazard ratio (HR) of 0.70 (95% CI 0.55 to 0.87) for time to disability progression confirmed at 3 months. Rankings suggested that the drug that had the highest probability of being the best at reducing the ARR was 20 mg of SC GA once daily, followed by 125 µg of SC pegylated IFN-β-1a every 2 weeks. For time to disability progression confirmed at 3 months, 44 µg of SC IFN-β-1a three times weekly had the highest probability of being the most effective.

For SPMS, the three trials demonstrated a benefit of beta-IFNs over placebo for ARR, with RRs ranging from 0.69 (95% CI 0.56 to 0.85) to 0.71 (95% CI 0.63 to 0.79). NMA suggested that 250 µg of SC IFN-β-1b every other day was superior to the equally ranked 44 µg of SC IFN-β-1a three times weekly and 22 µg of SC IFN-β-1a three times weekly.

Cost-effectiveness results

Our searches for systematic reviews identified 1566 records, of which nine were economic evaluation studies. Searches for economic evaluations in CIS revealed 614 records, of which nine were selected. Searches for primary cost-effectiveness, HRQoL, costs and resource use studies for DMTs in RRMS yielded 2451 studies, of which eight matched the inclusion criteria. The cost-effectiveness systematic review findings suggested that models were sensitive to time horizons. Most demonstrated an acceptable ICER for different formulations of IFN-β compared with BSC at standard levels of willingness to pay in a number of different countries. For RRMS, however, the findings were often not generalisable and studies were sensitive to time horizons used and starting distributions of disability.

In the RSS model submission, a mean RR of 0.72 (95% CI 0.6118 to 0.8309) for ARR and a HR of 0.7913 (95% CI 0.7705 to 0.8122) for disability progression (equivalent to our time to disability progression confirmed at 3 months value) were reported for patients taking DMTs compared with placebo based on year 10 analyses. Our base case, using a modified RSS model, resulted in mean incremental costs of DMTs compared with BSC of approximately £31,900 and incremental QALYs of 0.943, resulting in an ICER of approximately £33,800 per QALY. Probabilistic sensitivity analysis resulted in similar values, with an ICER of approximately £34,000 per QALY. Using the results from our NMA, DMTs were approximately £23,300 more costly than BSC using our clinical effectiveness results, while conferring 1.822 more QALYs, equating to an ICER of approximately £12,800 per QALY. Using the RSS base-case model and with individual HRs, we found that 125 µg of pegylated (peg) IFN-β-1a (Plegridy®; Biogen Idec Ltd, Cambridge, MA, USA) was the most cost-effective option, with an incremental cost of £17,800 and incremental QALYs of 2.559, giving an ICER of £7000 compared with BSC. We explored varying key model input parameters, finding that changes in the HR for disability progression had the greatest impact on the cost-effectiveness results. A decrease in treatment effect (increase in HR by 10%) resulted in an ICER of approximately £74,500 per QALY gained.

For CIS we found that, compared with BSC, the optimal strategy was treatment with 20 mg of GA (Copaxone®; Teva Pharmaceutical Industries, Petah Tikva, Israel) followed by DMTs for progression to RRMS. This was associated with an incremental cost of £98,400 and incremental QALYs of 5.95, giving an ICER of £16,500 per QALY. Sensitivity analyses showed that the model was most sensitive to change in the utility of the CIS health state. However, a 10% increase still gave an ICER for 20 mg of GA of £14,500 compared with BSC, well within the normal expected levels of willingness to pay.

Discussion and conclusion

We undertook systematic reviews, appraised the RSS model and designed a de novo model for CIS to assess the clinical effectiveness and cost-effectiveness of DMTs in MS. From our systematic reviews we found that DMTs are effective when used for both RRMS and CIS. In our NMA, GA was the most effective treatment at reducing the ARR. For RRMS we found that, overall, DMTs are not cost-effective at the current level of willingness to pay of £30,000 per QALY. The individual drug with the lowest ICER compared with BSC (£7000) was 125 µg of pegIFN-β-1a. We found that, for CIS, if DMTs are subsequently used for RRMS, the most cost-effective option was GA.

Strengths and limitations

The strengths of this study include the rigorous and comprehensive systematic reviews and the large number of NMAs alongside the careful assessment of manufacturers' submissions and the RSS model. We built a de novo decision tree model to assess cost-effectiveness in CIS and for each investigation undertook a number of sensitivity analyses. Limitations include the limitations of the underlying studies, with the heterogeneity of definitions, for example for progression, and subgroups, and the limitations of sparse networks, which restricted our ability to synthesise our findings fully. More importantly, we consider that the RCT evidence is problematic in that 30 out of 35 studies were at high risk of bias and this, along with the short-follow up times, may not allow for adequate assessment of the effects of DMTs. It is for these reasons that we elected to use a modified RSS model with appropriate adjustments as our base case for the assessment of the cost-effectiveness of the DMTs, even though it is based on an observational design with a non-contemporaneous control cohort. In addition, in the cost-effectiveness review we were unable to identify reliable estimates of utilities for CIS, although we were able to take account of this in sensitivity analyses. The economic model represents the care pathway to the best of our knowledge, but practice and management may vary.

Implications for health care

We did not include formulations outside the recommended usage in the UK. Also, we should recognise that our study was specifically designed to exclude the clinical effectiveness and cost-effectiveness of newer MS treatments such as newer monoclonal antibodies [alemtuzumab (Lemtrada®; Sanofi Genzyme, Cambridge, MA, USA) and daclizumab (Zinbryta®; Biogen Idec Ltd, Cambridge, MA, USA)]. This review should be considered in conjunction with newer NICE and other guidance on the clinical effectiveness and cost-effectiveness of these agents.

Research priorities

One key flaw in the assembled clinical effectiveness evidence was the lack of long-term follow-up. We consider that the distinctiveness of the different stages of MS is open to question. Additionally, valuation of health benefits continues to be a vexing area for MS and this was an issue identified in the original guidance resulting from TA32. Additional priorities include:

- How and under what circumstances MS progresses through different types (CIS, RRMS, SPMS) and how these transitions relate to changing imaging technologies and changes in clinical practice.
- Further research that does not concentrate on the lower end of the EDSS scale may be of value for populations with MS, as survival and advances in support and aids for those with disabilities improve.

- The RSS was designed to collect longer-term observational data in this area; however, a large-scale, longitudinal randomised trial comparing active first-line agents would contribute meaningfully towards resolving uncertainty about the remaining relative benefits of different IFN-β or GA formulations.
- We consider that a systematic review and meta-synthesis of qualitative studies relating to the lived experience of MS, with particular attention to the dominant clinical features, for example relapse and disability progression, would be of value. This would provide a basis for an understanding of relevant health states and benefits that more closely matches the preferences and experiences of people living with the target condition.

Study registration

This study is registered as PROSPERO CRD42016043278.

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This report

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