

Single Technology Appraisals

A supplement to *Health Technology Assessment Journal*

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Omalizumab for severe persistent allergic asthma

Eltrombopag for chronic idiopathic (immune) thrombocytopenic purpura

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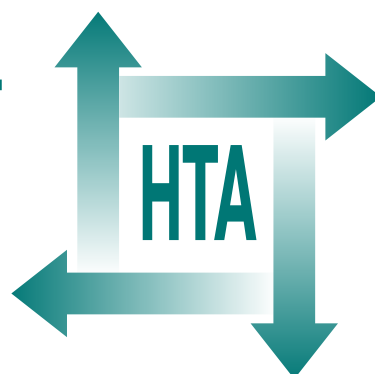
Liraglutide for type 2 diabetes

Golimumab for psoriatic arthritis



May 2011

Health Technology Assessment
NIHR HTA programme
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Health Technology Assessment

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The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy makers. TARs bring together evidence on the value of specific technologies.

This supplement to the Journal series contains a collection of summaries based on Evidence Review Group reports (ERGs), produced as part of NICE's Single Technology Appraisal (STA) process. The reports are mainly based on data submissions from manufacturers and do not undergo the standard peer-review process.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

Criteria for inclusion in the HTA Journal series and Supplements

Reports are published in the journal series and supplements if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the supplement was commissioned and funded by the HTA programme on behalf of NICE. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report. The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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Supplement introduction

Welcome to the sixth Supplement to the *Health Technology Assessment* journal series. The series is now over 10 years old and has published more than 500 titles, covering a wide range of health technologies in a diverse set of applications. In general, the series publishes each technology assessment as a separate issue within each annual volume.

The Supplements depart from that format by containing a series of shorter articles. These are all products from a 'call-off contract', which the HTA programme holds with a range of academic centres around the UK, at the universities of Aberdeen, Birmingham, Exeter, Liverpool, Sheffield, Southampton and York. These centres are retained to provide a highly responsive resource, which meets the needs of national policy makers, notably the National Institute for Health and Clinical Excellence (NICE).

Until recently, these HTA Technology Assessment Review (TAR) centres provided academic input to policy making through independent analyses of the impact and value of health technologies. As many readers will be aware, the perception that the advice NICE provides to the NHS could be made more timely has led to the development of the 'Single Technology Appraisal' process. In this approach, manufacturers of technologies, which are, in general, pharmaceuticals close to the time of launch, submit a dossier of evidence aiming to demonstrate effectiveness and cost-effectiveness. The independent academic input to NICE's process, which continues to be supported by the TAR centres around the UK under contract to the HTA programme, is to scrutinise, critique and explore this dossier of evidence.

The papers included in this Supplement report on this HTA programme-funded work, and we hope that the summaries of the work carried out to inform the development of NICE guidance for these technologies will be of interest and value to readers.

The papers included here contain reports of the position that the NICE guidance had reached at the time of submission to *Health Technology Assessment* for inclusion in this supplement. As we collect a series of papers together for an issue, the process of developing NICE guidance may have moved on further for some topics than others. Further details on the current position regarding each of the NICE Appraisals are available on the NICE website (www.nice.org.uk) and we welcome comments on the summaries via the HTA website (www.hta.ac.uk/correspond/).

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Bevacizumab in combination with a taxane for the first-line treatment of HER2-negative metastatic breast cancer

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

This paper presents a summary of the evidence review group (ERG) report into the use of bevacizumab (Avastin[®], Roche) in combination with a taxane for the treatment of untreated metastatic breast cancer (mBC). The main clinical effectiveness data were derived from a single, open-label randomised controlled trial (RCT) (E2100) that evaluated the addition of bevacizumab to weekly (q.w.) paclitaxel in patients with human epidermal growth factor receptor 2-negative mBC who had not previously received chemotherapy for advanced disease. This

trial reported statistically significant increases in median progression-free survival (PFS) for the addition of bevacizumab (5.8–11.3 months). Median overall survival was not significantly different between the two groups; whether this is a true null finding or due to crossover between treatment arms cannot be established, as relevant data were not collected. The manufacturer reported that the addition of bevacizumab to paclitaxel q.w. therapy was associated with a significant improvement in quality of life, as measured by FACT-B (functional assessment of cancer therapy for breast cancer) scores. However, the ERG noted that these results were based on extreme imputed values, the removal of which led to non-significant differences in quality of life. The manufacturer conducted an indirect comparison. However, owing to methodological limitations and concerns about the validity and exchangeability of the included trials, the ERG did not consider the findings to be reliable. One additional relevant RCT [AVADO (Avastin and Docetaxel); BO17708] evaluating the addition of bevacizumab to docetaxel was excluded from the manufacturer's submission. This was summarised by the ERG. In terms of response rate and PFS, AVADO reported a markedly smaller benefit of adding bevacizumab to docetaxel than that reported for adding bevacizumab to q.w. paclitaxel in E2100. AVADO also reported no statistically significant effect of combination therapy versus docetaxel in terms of overall survival. The manufacturer developed a de novo economic model that considered patients with the same baseline characteristics as women in the E2100 trial. The model assessed BEV + PAC – bevacizumab 10 mg/kg every 2 weeks in combination with paclitaxel 90 mg/m² weekly for 3 weeks followed by 1 week of rest; PAC q.w. – paclitaxel (monotherapy) 90 mg/m² weekly for 3 weeks followed by 1 week of rest; DOC – docetaxel (monotherapy) 75 mg/m² on day 1 every 21 days (considered current UK NHS clinical practice in the submission); and GEM + PAC – gemcitabine 1250 mg/m² on days 1 and 8 plus paclitaxel 175 mg/m² on day 1 every 21 days. Pairwise comparisons were made between BEV + PAC and PAC (using the E2100 trial), BEV + PAC and DOC, and BEV + PAC and GEM + PAC. Based on NHS list prices, the manufacturer's model estimated incremental cost-effectiveness ratios (ICERs) for BEV + PAC of £117,803, £115,059 and £105,777 per QALY gained, relative to PAC, DOC and GEM + PAC regimens, respectively. If the NHS Purchasing and Supply Agency prices for PAC with a 10-g cap on the cost per patient of BEV were used instead, the ICERs for BEV + PAC were estimated at £77,314, £57,753 and £60,101 per QALY, respectively. The submission suggested that the regimen of BEV + DOC is not cost-effective because it is considered less effective and more costly than BEV + PAC. Analysis by the ERG suggested that alternative assumptions can increase the ICERs further and, based on current prices, no plausible changes to the model assumptions will bring the ICERs for BEV + PAC lower.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS which is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor (in this instance, Roche). Typically, it is used for new pharmaceutical products that are close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Bevacizumab in combination with a taxane for the first-line treatment of human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer*.

Description of the underlying health problem

Breast cancer is the most common cancer in the UK, with almost 45,700 women diagnosed with the disease in 2007.¹ The incidence rates of female breast cancer in the UK have increased by 5% in the last 10 years,¹ and around 260 men are also diagnosed each year.^{2,3} In 2008, there were 12,116 deaths from breast cancer in the UK; 12,047 (99%) of these were women and 69 (1%) were men.⁴ It is estimated that 16–20% of women diagnosed with breast cancer have advanced disease with metastases, and around 50% of those diagnosed with early (or localised) breast cancer will eventually develop metastatic cancer.⁵

Current UK treatment depends on patients' previous therapy, human epidermal growth factor receptor 2 (HER2) status and oestrogen receptor status. First-line therapy for metastatic breast cancer (mBC) is usually an anthracycline-based regimen; when an anthracycline is not considered appropriate, NICE clinical guideline 81 recommends docetaxel monotherapy as the first-line therapy.⁶ Vinorelbine or capecitabine monotherapy is recommended for subsequent treatment.⁶

Scope of the evidence review group report

The decision problem specified by NICE was the use of bevacizumab (Avastin[®], Roche), in combination with a taxane, for the treatment of untreated metastatic HER2-negative breast cancer in patients for whom anthracyclines are not appropriate. Bevacizumab is licensed for the first-line treatment of HER2-negative mBC. The decision problem specified that bevacizumab in combination with paclitaxel should be compared with bevacizumab in combination with docetaxel; other comparators specified were docetaxel monotherapy, paclitaxel monotherapy and paclitaxel in combination with gemcitabine.

The outcome measures considered were overall survival (OS), progression-free survival (PFS), response rates, adverse events, health-related quality of life and incremental cost per quality-adjusted life-year (QALY) gained.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's submission (MS) to NICE as part of the STA process.

The ERG appraised the literature searches and carried out a search for ongoing trials. The systematic review methodology was appraised and, owing to the limited quality assessment of included trials in the MS, the ERG performed additional quality assessment. The manufacturer's economic evaluation was appraised using a validated checklist⁷ and a descriptive critical review, and the decision model was validated by running the model and conducting sensitivity analyses. The ERG also constructed a de novo decision model in EXCEL (Microsoft Corporation, Redwood, WA, USA) to explore sensitivity analyses and scenarios that were not fully addressed by the manufacturer's model.

Results

Summary of submitted clinical evidence

The clinical effectiveness data were primarily derived from a single, open-label randomised controlled trial (RCT) (E2100^{8–16}) that evaluated the addition of bevacizumab to weekly (q.w.) paclitaxel in patients with HER2-negative mBC who had not previously received chemotherapy

for advanced disease. The trial reported statistically significant increases in median PFS from 5.8 to 11.3 months [hazard ratio (HR) 0.54, 95% confidence interval (CI) 0.44 to 0.67] for bevacizumab plus paclitaxel versus paclitaxel alone (Table 1). Median OS was not significantly different between the two groups (26.5 vs 24.8 months; HR 0.87, 95% CI 0.72 to 1.05). A post hoc analysis indicated that OS at 1 year was significantly higher with paclitaxel plus bevacizumab than with paclitaxel alone (81.4% vs 74.0%, $p=0.017$). The addition of bevacizumab to paclitaxel therapy was associated with a significant improvement in quality of life as measured by the FACT-B (functional assessment of cancer therapy for breast cancer) trial outcome index (TOI-B) score at week 33 ($p=0.0042$) and by the FACT-B total score (TOT-B) at week 17 ($p=0.0475$) and week 33 ($p=0.0046$) compared with paclitaxel alone.

The manufacturer conducted an indirect comparison based on the method described by Bucher *et al.*²⁷ This reported that bevacizumab plus q.w. paclitaxel was associated with a significant improvement in PFS when compared with 3-weekly (q3w) docetaxel (HR 0.56, 95% CI 0.39 to 0.78) and with gemcitabine plus q3w paclitaxel (HR 0.46, 95% CI 0.34 to 0.64). No significant difference was found for PFS between q.w. paclitaxel and q3w docetaxel (HR 1.15, 95% CI 0.89 to 1.48) or between q.w. paclitaxel and gemcitabine plus q3w paclitaxel (HR 0.96, 95% CI 0.76 to 1.21).

TABLE 1 Key characteristics and efficacy data from direct comparison bevacizumab RCTs (E2100 and AVADO)

	E2100 ⁹⁻¹⁶		AVADO ¹⁷⁻²⁶		
Participants	HER2-negative mBC not previously treated with chemotherapy ($n=722$)		HER2-negative previously untreated locally recurrent or mBC ($n=736$)		
Intervention	Bevacizumab 10 mg/kg + paclitaxel 90 mg/m ² , q.w.		Bevacizumab 7.5 mg/kg + docetaxel 100 mg/m ² , q3w Bevacizumab 15 mg/kg + docetaxel 100 mg/m ² , q3w		
Comparator	Paclitaxel 90 mg/m ² , q.w.		Placebo + docetaxel: docetaxel 100 mg/m ² , q3w		
Length of follow-up for the analysis	Patients were enrolled between December 2001 and May 2004 <i>PFS and objective response</i> Data collected prior to 9 February 2005 <i>OS</i> Data collected prior to 21 October 2006		Patients were enrolled between March 2006 and April 2007 <i>PFS</i> Primary analysis: median follow-up 10.2 months Updated analysis: conducted at time of final OS analysis (additional 18 months of follow-up) <i>OS</i> Median follow-up 25 months		
				Bevacizumab 7.5 mg/kg + docetaxel ($n=248$)	Bevacizumab 15 mg/kg + docetaxel ($n=247$)
	Paclitaxel ($n=354$)	Bevacizumab + paclitaxel ($n=368$)	Docetaxel + placebo ($n=241$)		
Median PFS (months)	5.8	11.3	8.0 8.2 ^a	8.7 9.0 ^a	8.8 10.1 ^a
PFS: HR (95% CI)	–	0.48 (0.39 to 0.61)	– – ^a	0.79 (0.63 to 0.98) 0.86 (0.72 to 1.04) ^a	0.72 (0.57 to 0.90) 0.77 (0.64 to 0.93) ^a
Response rate (%)	22.2	49.8	44.4 46.4 ^a	55.2 55.2 ^a	63.1 64.1 ^a
OS: HR (95% CI)	–	0.87 (0.72 to 1.05)	–	1.05 (0.81 to 1.36)	1.03 (0.79 to 1.33)

AVADO, Avastin and Docetaxel (BO17708); CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; q.w., weekly; q3w, 3-weekly.

a Updated analysis applies for the AVADO trial only.

On the basis of the E2100 study and a large uncontrolled study [ATHENA (Avastin Therapy for Advanced Breast Cancer); MO19391],²⁸⁻³⁴ the manufacturer concluded that bevacizumab is not associated with the commonly recognised side effects of cytotoxic anticancer therapies and that the most common adverse events associated with bevacizumab therapy are hypertension and proteinuria.

Summary of submitted cost-effectiveness evidence

The submission identified six cost-effectiveness analyses but stated that they were not relevant as they were all conducted outside the UK. The manufacturer, therefore, justified the development of a de novo economic model that considered patients with the same baseline characteristics as seen in women in the E2100 trial.⁸⁻¹⁶ The model assessed:

- BEV + PAC bevacizumab 10 mg/kg (every 2 weeks) in combination with paclitaxel 90 mg/m² (weekly for 3 weeks followed by 1 week of rest)
- PAC q.w. paclitaxel (monotherapy) 90 mg/m² weekly for 3 weeks followed by 1 week of rest
- DOC docetaxel (monotherapy) 75 mg/m² on day 1 every 21 days (considered current UK NHS clinical practice in the submission)
- GEM + PAC gemcitabine 1250 mg/m² on days 1 and 8 plus paclitaxel 175 mg/m² on day 1 every 21 days.

Pairwise comparisons were made between BEV + PAC and PAC (using the E2100 trial⁸⁻¹⁶), BEV + PAC and DOC, and BEV + PAC and GEM + PAC.

The model was a Markov model with three states (progression free, progressed and dead) and used a 10-year time horizon. Parametric survival functions were used to model the rate of metastatic disease progression based on data from the E2100 trial.⁸⁻¹⁶ Based on the results of the indirect comparison of treatment effects, it was assumed that the rate of disease progression was the same after PAC q.w. as after DOC and after GEM + PAC. It was assumed that the hazard of death after progression was constant over time and the same across all treatments, meaning that any difference in PFS between treatments is mirrored in terms of OS. The costs and disutility associated with treatment-related adverse events were included, based on the incidence of events in the E2100 trial.⁸⁻¹⁶ Utility estimates were derived from a non-systematic literature review of studies of patients with breast cancer. A number of cost categories were considered: drug acquisition, drug administration, duration of treatment, supportive care, adverse event and end of life. Two alternative base-case analyses were presented for the acquisition costs of the drugs: product list prices (*British National Formulary*³⁵) and PASA (Purchasing and Supply Agency, NHS) prices for paclitaxel along with a capping scheme for the cost to the NHS of bevacizumab.

Based on NHS list prices, the manufacturer's model estimated incremental cost-effectiveness ratios (ICERs) for BEV + PAC of £117,803, £115,059 and £105,777 per QALY gained, relative to PAC, DOC and GEM + PAC regimens, respectively. If PASA prices for PAC with a 10-g cap on the cost per patient of BEV are used instead, the ICERs for BEV + PAC are estimated at £77,314, £57,753 and £60,101 per QALY, respectively. The manufacturer stated that the regimen of BEV + DOC would not be cost-effective compared with BEV + PAC because it is considered less effective and more costly than BEV + PAC, but did not conduct an economic evaluation to compare these regimens. *Table 2* shows the results of the manufacturer's model for BEV + PAC versus PAC q.w.

Commentary on the robustness of submitted evidence

Strengths

The manufacturer's systematic review of the literature used appropriate search methods. The E2100⁸⁻¹⁶ RCT was conducted in a relevant population and steps were taken to mitigate against

TABLE 2 Results of the main cost-effectiveness analyses undertaken by the manufacturer and the ERG

Scenario	Analyst	Intervention and comparator	Source of cost data	Source of effectiveness data	Incremental cost (£)	Incremental QALY	ICER (£)
1	MS	BEV + PAC vs PAC q.w.	List prices	E2100 PFS	30,469	0.259	117,803
2	MS	BEV + PAC vs PAC q.w.	PASA prices with cap on BEV	E2100 PFS	19,997	0.259	77,314
3	ERG	BEV + PAC vs PAC q.w.	PASA prices and no cap	E2100 PFS	28,573	0.259	110,475
4	ERG	BEV + DOC vs DOC q3w	List prices	AVADO PFS	34,712	0.136	254,530
5	ERG	BEV + PAC vs PAC q.w.	List prices	E2100 OS	29,675	0.114	259,267

AVADO, Avastin and Docetaxel (B017708); BEV, bevacizumab; DOC, docetaxel; ERG, evidence review group analysis; ICER, incremental cost-effectiveness ratio; MS, manufacturer's submission; OS, overall survival – QALYs based on extrapolation from estimates of OS; PAC, paclitaxel; PASA, NHS Purchasing and Supply Agency (including discounts); PFS, progression-free survival – QALYs based on extrapolation from estimates of PFS; QALY, quality-adjusted life-year; q.w., weekly; q3w, 3-weekly.

methodological limitations (e.g. intention-to-treat analyses of independently reviewed outcomes were undertaken). The safety evaluation included the most comprehensive and robust study available to assess this outcome.

The MS largely conforms to the NICE reference case for cost-effectiveness analysis and was reasonably clearly presented.

Weaknesses

The manufacturer's search identified a second RCT (the AVADO trial^{17–26}) that evaluates the addition of bevacizumab to q3w docetaxel. The manufacturer excluded this trial because they considered the docetaxel dose unrepresentative of UK clinical practice, but this conflicted with clinical advice given to the ERG.

The manufacturer identified an existing economic evaluation but stated that as it was populated with Swiss unit costs the results were not relevant to the NHS.³⁶ However, the effectiveness estimate used in this study was based on PFS and OS in the E2100 trial^{8–16} and therefore has some relevance to this appraisal. This analysis found that the ICER for BEV + PAC versus PAC q.w. was €189,000 per QALY.

Limitations in the collection and analysis of data in E2100^{8–16} affect the reliability of the trial's findings. Data were not collected on the treatment regimens received by patients after disease progression; therefore, the influence of postprogression treatment on OS in this trial is unknown. Also, the significant improvements in quality of life reported in E2100^{8–16} were based on analyses using extreme imputed data for missing values; without these imputed data, differences between groups are statistically insignificant. These data were not further used in the cost-effectiveness model.

The ERG identified several methodological limitations relating to the indirect comparison. One inclusion criterion (< 60% of patients receiving second-line chemotherapy for mBC) may have been formulated to allow the inclusion of a specific trial. The AVADO trial^{17–26} was excluded from the indirect comparison on the basis of docetaxel dose, but another trial that used the

same dose was included.³⁷ One included trial³⁸ had compromised internal validity owing to an imbalance in the proportion of patients receiving second-line treatment between the q.w. (16%) and q3w (41%) paclitaxel arms. There was also a lack of similarity in terms of the proportion of patients receiving second-line treatment between included trials (e.g. 55% in Jones *et al.*,³⁷ 0% in E2100⁸⁻¹⁶ and Albain *et al.*³⁹), highlighting the issue of exchangeability between treatment effects and different patient samples. Given these methodological limitations identified, the ERG did not consider the findings of the indirect comparison to be reliable.

The manufacturer's cost-effectiveness model did not consider all relevant comparators. Specifically, bevacizumab in combination with either docetaxel or q3w paclitaxel were not formally considered despite the latter being used in clinical practice in the UK. The manufacturer assumed that the rate of death after progression is constant over time and the same for all initial treatments, with the implication that differences in mean PFS between treatments are maintained in the mean OS estimates. However, the E2100 RCT did not find any statistically significant differences in OS, despite finding a statistically significant difference in PFS. The manufacturer stated that this might be because patients received different treatments after progression in each arm, including bevacizumab after failure of paclitaxel monotherapy. However, this may be a strong assumption and alternative model structures were not considered by the manufacturer. The manufacturer's model predicted a greater difference in OS for BEV + PAC versus PAC than in the result of the E2100 trial.⁸⁻¹⁶

The base-case model assumed that the regimens PAC, DOC and GEM + PAC are equally effective; no alternative scenarios were presented.

Despite the use of a disease-specific health-related quality of life instrument in the E2100 trial⁸⁻¹⁶ (the FACT-B), no mapping algorithm was used to link this to a preference-based (utility) instrument, such as the European Quality of Life-5 Dimensions (EQ-5D). Instead, external utility estimates were used based on a literature search, which was not systematic. No attempt was made to collate or synthesise the alternative estimates, and the selection of utilities for the model appeared arbitrary.

In an alternative base case, the analysis assumed that the cost of bevacizumab would be capped at 10 g per patient. The ERG understands that the price cap assumed for bevacizumab has not been agreed with the Department of Health and should not, therefore, have been assumed in the model. The patent for docetaxel expired in November 2010, but the manufacturer did not explore the implications of a likely reduction in its acquisition cost. The analysis also ignored the possibility of dose reductions. The extent to which dose reductions occur may differ between alternative treatments, and the ERG expects this to affect the results. The manufacturer undertook no subgroup analysis. The model results were presented as a series of pairwise ICERs comparing BEV + PAC individually with the alternative regimens. This is inappropriate and a full incremental analysis should have been undertaken.

Areas of uncertainty

Efficacy outcomes for bevacizumab plus q.w. paclitaxel versus q.w. paclitaxel alone were based on an interim analysis of the E2100 trial.⁸⁻¹⁶ PFS and response data were collected up to February 2005 and OS data were collected up to October 2006. Analysis of more complete follow-up data would be valuable, although the manufacturer stated that no such analyses are available.

The reason for the lack of OS benefit for combination therapy observed in the E2100 trial⁸⁻¹⁶ cannot be established, as data on postprogression treatment were not collected.

Methodological limitations in the indirect comparison mean that the relative efficacy of bevacizumab plus q.w. paclitaxel versus comparators other than paclitaxel alone, outlined in the decision model, remains highly uncertain.

The methodological weaknesses in the model described above give rise to a number of uncertainties; the ERG undertook a series of analyses to explore their implications.

The use of the PASA discount (without the cap on the costs of BEV) made little difference to the incremental costs of BEV + PAC versus PAC, compared with using NHS list prices (see *Table 2*).

The ERG evaluated BEV+DOC versus DOC alone based on the results of the AVADO RCT.¹⁷⁻²⁶ This found that the ICER was more than £250,000 per QALY (see *Table 2*).

The ERG constructed an alternative model that was calibrated to the E2100⁸⁻¹⁶ results for OS. The ICER of BEV + PAC versus PAC q.w. was > £250,000 per QALY in the revised model (see *Table 2*). This result should be considered a 'worst-case' scenario regarding the cost-effectiveness of BEV + PAC versus PAC q.w. because it is assumed that there is no difference in OS. The manufacturer's model might be considered a 'best-case' scenario as it assumes that the difference in PFS from the E2100 trial would be fully reflected in an equivalent difference in OS in clinical practice.

Conclusions

Despite some methodological limitations, the E2100 trial⁸⁻¹⁶ provides direct evidence to suggest that the addition of bevacizumab to q.w. paclitaxel increases PFS and objective response in the first-line treatment of mBC. This trial fails to show a significant benefit in terms of OS. The ERG noted that the manufacturer inappropriately excluded the large relevant AVADO trial in which the docetaxel dosing regime was generally reflective of UK current practice. The ERG extracted the limited available published data from this trial,¹⁷⁻²⁶ which reported a markedly smaller benefit in terms of PFS and response rate of adding bevacizumab to docetaxel than was reported for adding bevacizumab to q.w. paclitaxel in E2100⁸⁻¹⁶ (see *Table 1*). The AVADO trial also reported a non-significant benefit in combination therapy versus docetaxel monotherapy in terms of OS.¹⁷⁻²⁶

Given the considerable limitations in the evidence selected and methods used for the indirect comparison, the manufacturer's reporting of a statistically significant benefit of bevacizumab plus q.w. paclitaxel over the currently recommended first-line treatment of docetaxel monotherapy cannot be considered reliable.

The cost-effectiveness analysis presented by the manufacturer included judgements and assumptions that are subject to uncertainty. The manufacturer's most optimistic analyses suggested an ICER for BEV + PAC versus PAC q.w. of £77,000 per QALY gained using PASA prices for PAC and a 10-g cap on BEV, and £118,000 using NHS list prices. Further analysis by the ERG suggested that more pessimistic assumptions about the relative impact of bevacizumab on OS can increase the ICERs yet further, and, based on current prices, no plausible changes to the model assumptions will bring the ICER for BEV + PAC versus PAC q.w. within the threshold currently considered cost-effective by NICE.

Summary of NICE guidance issued as a result of the STA

The guidance document issued by NICE in February 2011 states that bevacizumab in combination with a taxane is not recommended for first-line treatment of metastatic breast cancer. Following consultation on the appraisal consultation document, the manufacturer provided additional subgroup data; the ERG provided commentary and validity checks on the additional evidence submitted by the manufacturer, as requested by NICE.

During the course of this appraisal, the European Medicines Agency (EMA) conducted a review of the use of bevacizumab in combination with taxanes for the treatment of mBC. Following that review, the EMA's Committee for Medicinal Products for Human Use recommended that bevacizumab, when used to treat mBC, should be used only in combination with the taxane, paclitaxel.

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Omalizumab for the treatment of severe persistent allergic asthma in children aged 6–11 years

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

This paper presents a summary of the evidence review group report into the clinical effectiveness and cost-effectiveness of omalizumab for the treatment of severe persistent asthma in children aged 6–11 years, based upon the evidence submission from Novartis Pharmaceutical UK Ltd to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The manufacturer's submission was generally considered to be of good quality. The submission was based primarily on a preplanned subgroup IA-05

EUP (European Union Population) from the IA-05 trial, with outcomes including the number of clinically significant (CS) and clinically significant severe (CSS) exacerbations. Omalizumab therapy was associated with a statistically significant reduction in the rate of CS exacerbations, but the reduction in the rate of CSS exacerbations was not statistically significant. The benefit in terms of CS exacerbations was achieved mainly in patients with more than three exacerbations per year at baseline. The manufacturer found no previous published cost-effectiveness studies of omalizumab in children aged 6–11 years, so their de novo economic evaluation formed the basis of the submitted economic evidence. The economic model was considered appropriate for the decision problem. The results from the model indicated that omalizumab in addition to standard therapy compared with standard therapy alone did not appear cost-effective in either the overall population or a subgroup of patients hospitalised in the year prior to enrolment, with incremental cost-effectiveness ratios of £91,169 and £65,911 per quality-adjusted life-year, respectively. These findings were found to be robust across a wide range of alternative assumptions through one-way sensitivity analyses. The guidance issued by NICE states that omalizumab is not recommended for the treatment of severe persistent allergic asthma in children aged 6–11 years.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS, which is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.^{1,2} Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG) – an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Omalizumab for the treatment of severe persistent asthma in children aged 6 to 11 years*.³

Description of the underlying health problem

Asthma affects approximately 1.1 million children in the UK,⁴ and within this group there is a small, but very significant, number of children with severe symptoms in whom asthma control remains poor despite best available therapy. The manufacturer's submission estimated there to be 307 children in the UK with severe persistent allergic asthma who remain uncontrolled despite best available therapy, and who would meet the criteria for treatment with omalizumab, a recombinant humanised anti-immunoglobulin E (IgE) monoclonal antibody that inhibits the activity of IgE – a key mediator of allergic reactions. These children may receive frequent or maintenance doses of oral corticosteroids (OCSs) together with other controller medications. Children are at risk of serious OCS-related side effects, including growth retardation, osteoporotic fractures, diabetes and cardiovascular events.⁵ Clinical guidelines specify that the treatment aim is to control asthma using the lowest possible OCS dose and, if possible, stop OCS treatment completely.⁶

Scope of the evidence review group report

The scope for the appraisal specified by NICE was the clinical effectiveness and cost-effectiveness of omalizumab, within its licensed indication, for the treatment of severe persistent allergic asthma in children aged 6–11 years. Omalizumab is licensed as an add-on to existing therapy in patients aged 6–11 years with severe, persistent allergic IgE-mediated asthma whose condition remains uncontrolled despite treatment with high-dose inhaled corticosteroids (ICSs) and long-acting beta-agonist (LABA). This treatment has been appraised previously by NICE for its use in adults.⁷

The ERG report presents an assessment of the manufacturer's (Novartis Pharmaceutical UK Ltd) submission to NICE on the use of omalizumab in addition to standard therapy compared with standard therapy alone. The manufacturer's submission generally reflected the NICE scope; however, it positions omalizumab as treatment for the most severely affected children who require OCSs [at step 5 of the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines⁶], i.e. children with more severe asthma than specified in the NICE scope (steps 4 and 5 of the BTS/SIGN guidelines).

The manufacturer's submission presented evidence for the efficacy of omalizumab based primarily on a preplanned subgroup of children from a single, multinational randomised controlled trial (RCT): the IA-05 trial.⁸ The subgroup (European Union Population: IA-05 EUP) comprised those children who received appropriate concomitant medication (high-dose ICS and LABA). (It should be noted that these children were not all in the European Union (EU) but instead received medications in accordance with EU practice.)

The submission also presented the results of a *de novo* economic evaluation of the use of omalizumab in addition to standard therapy versus standard therapy alone in the IA-05 EUP patients and in a subgroup of patients who had been hospitalised in the year prior to enrolment. A depiction of the decision-analytic model used in the economic evaluation is shown in *Figure 1*. The model estimated costs and quality-adjusted life-years (QALYs) from the perspective of the NHS and Personal Social Services, which is consistent with NICE guidelines.¹

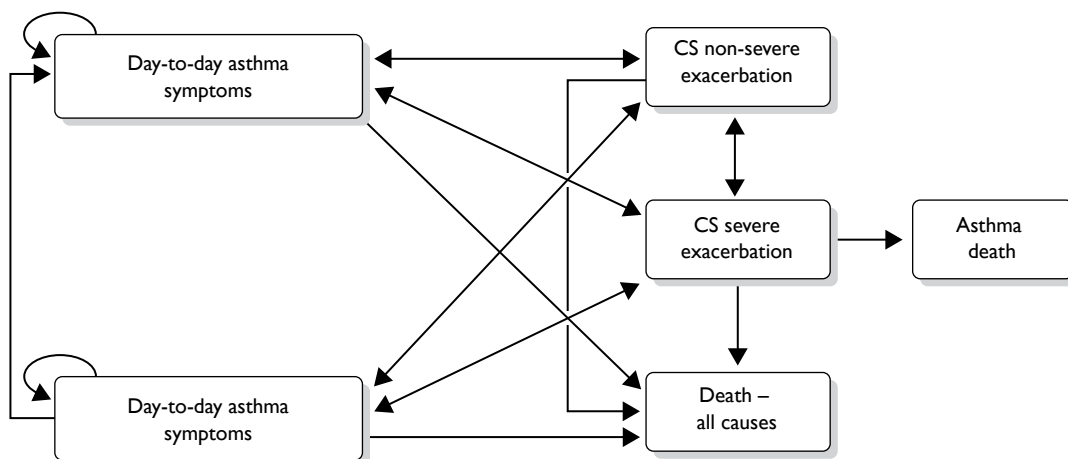


FIGURE 1 Markov model. CS, clinically significant.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's submission to NICE as part of the STA process. In addition, the ERG modified the manufacturer's decision-analytic model to examine the impact of altering some of the key assumptions and parameter values.

Results

Summary of submitted clinical evidence

The submission was based primarily on the preplanned subgroup IA-05 EUP from the IA-05 trial, which comprised those children who received appropriate concomitant medication (high-dose ICS and LABA). The primary analysis of efficacy was conducted on a 'modified' intention-to-treat population, which excluded participants from trial centres found to be in breach of good clinical practice. Outcomes included the number of clinically significant (CS) exacerbations (defined as those requiring a doubling of the baseline ICS dose and/or treatment with rescue systemic corticosteroids for ≥ 3 days – likely to be managed at home) and clinically significant severe (CSS) exacerbations [defined as requiring treatment with systemic corticosteroids and where the patients had peak expiratory flow or forced expiratory volume of $< 60\%$ of their personal best – likely to require hospitalisation]. The ERG noted that the doubling of ICS would not constitute a CS exacerbation in UK clinical practice, and so the numbers classified as CS in the trial may be greater than in clinical practice.

Omalizumab treatment was associated with a statistically significant reduction in the rate of CS exacerbations, but the reduction in the rate of CSS exacerbations did not reach statistical significance (although it should be noted that the trial was not powered to find a difference in CSS exacerbations). The evidence suggests relatively large reductions in the rate of exacerbations with omalizumab compared with placebo, but the absolute reduction in the number of exacerbations is small. However, even small reductions in the number of CS exacerbations can be an important positive outcome for children with severe asthma symptoms. The benefit in terms of CS exacerbations was achieved mainly in children with three or more exacerbations per year at baseline (Table 1).

TABLE 1 Analysis for CS exacerbations stratified on baseline exacerbation rate

	Sample size		Initial 24-week fixed-steroid period		52-week treatment period	
	Om.	Pl.	Om.	Pl.	Om.	Pl.
Full EUP mITT population	159	76	0.42	0.63	0.73	1.44
			0.662 ^a (95% CI 0.441 to 0.995), $p=0.047$		0.504 ^a (95% CI 0.350 to 0.725), $p<0.001$	
Two or more exacerbations at baseline	63	31	0.45	0.29	0.71	0.67
			1.562 ^a (95% CI 0.662 to 3.684), $p=0.309$		1.061 ^a (95% CI 0.594 to 1.895), $p=0.842$	
Three or more exacerbations at baseline	96	45	0.37	0.78	0.69	1.78
			0.481 ^a (95% CI 0.305 to 0.758), $p=0.002$		0.388 ^a (95% CI 0.254 to 0.592), $p<0.001$	

CI, confidence interval; EUP, European Union Population; mITT, 'modified' intention-to-treat; Om., omalizumab; Pl., placebo.
a Ratio of exacerbation rate.

Symptom-free days and nights, primary outcomes required in the NICE scope, were not assessed in the included trial. Mean-change-in-symptom scores were presented as surrogate measures and showed no statistically significant difference between omalizumab and placebo. There were no statistically significant differences in the health-related quality of life (QoL) between omalizumab and placebo, assessed using the standardised Paediatric Quality of Life Questionnaire.

Omalizumab use has been demonstrated to have only numerically small and clinically/statistically insignificant reductions in ICS use. There is no good evidence of a reduction in OCS being achieved with the use of omalizumab.

The adverse effect profile of omalizumab looks favourable but, as with any new drug, particularly one used in children, the long-term adverse effects are uncertain.

Summary of submitted cost-effectiveness evidence

No previously published cost-effectiveness studies of omalizumab in children aged 6–11 years with severe persistent allergic asthma were identified by the manufacturer. Therefore, the manufacturer's de novo economic evaluation forms the basis of the submitted economic evidence. Omalizumab in addition to standard therapy was compared with standard therapy alone in children with severe persistent allergic asthma, and in a subgroup of patients from the IA-05 EUP study who had been hospitalised in the year before enrolment. The data used to populate the model were largely drawn from the IA-05 EUP study. As no deaths were observed in the study, evidence on asthma-related mortality was drawn from Watson *et al.*⁹ Health-related QoL scores were also not available from the trial so have been drawn from other sources.^{10–12} The key effectiveness and mortality data used in the model are presented in *Table 2*.

The economic evaluation was based on a Markov model. The results from the model indicated that omalizumab did not appear to be cost-effective in either the overall population or the subgroup of previously hospitalised patients. The incremental cost-effectiveness ratio (ICER) of

TABLE 2 Values for key parameters on treatment effectiveness and asthma-related death used in the model

Treatment effectiveness			
Parameter	Omalizumab ^a	Standard therapy alone	Source
Exacerbation rate per patient for initial 24-week period	1.363	1.939	IA-05 EUP study
Percentage of exacerbations for initial 24-week period that were severe	23.0	23.5	
Proportion of omalizumab patients who respond at 16 weeks (%)	74.2	N/A	
Exacerbation rate post 24 weeks	0.519 per year per patient	2.028 per year per patient	
Percentage of exacerbations post 24 weeks that were severe	27.3	22.9	
Asthma-related death by age group			
Age group (years)	Rate of death per CSS (%)		Source
0–11	0.097		Watson <i>et al.</i> ⁹
12–16	0.319		
17–44	0.383		
45+	2.478		

CSS, clinically significant severe; EUP, European Union Population; N/A, not applicable.

a Those parameters post 24 weeks refer to omalizumab responders only.

£91,169 per QALY (or £65,911 per QALY in the subgroup) is well above the normally accepted NICE threshold of £20,000–30,000 per QALY.¹ These results are presented in *Table 3*. These findings were found to be robust across a wide range of alternative assumptions through one-way sensitivity analyses.

The main driver of cost-effectiveness is the reduction in asthma-related mortality associated with the reduced number and frequency of CSS exacerbations. A shorter treatment duration also had a marked effect on cost-effectiveness, increasing the ICER notably (reducing treatment duration from 10 years in the base case to 2 years increased the ICER to £684,665 per QALY).

Commentary on the robustness of submitted evidence

Strengths

The review of clinical effectiveness was considered by the ERG to be thorough. Despite only one RCT⁸ being eligible for the review, the quality of the included RCT was considered good. The authors made attempts to supplement the data from this trial using other relevant sources and by undertaking a non-systematic survey of UK specialist paediatric respiratory centres.

In general, the ERG considered the economic submission to be of good quality, meeting the requirements of the NICE reference case. The structure of the Markov model was considered appropriate for the decision problem, and many of the key uncertainties were explored through one-way sensitivity analyses.

Weaknesses

The appraisal was based on a small subgroup of children from a single study, many of whom appeared not to be receiving optimal treatment owing to the high rate of exacerbations per year at baseline. The average number of children recruited to each of the 87 trial centres in seven countries was seven for the whole population, and three for the EUP subgroup. This has implications for quality and consistency of application of the trial protocol. There were breaches in good clinical practice at three centres, resulting in recruitment being stopped and children from two centres being excluded from the analysis of efficacy. However, given the rarity of the condition, the need to recruit over such large numbers of trial centres seems unavoidable.

The ERG identified a number of potential weaknesses relating to the economic submission. These included (1) the use of response to omalizumab assessed at 52 weeks rather than 16 weeks as specified in the licence and clinical guidelines; (2) the assumption that exacerbation rates observed in the IA-05 EUP study will remain constant over a child's lifetime; (3) the non-systematic approach to identifying evidence for the mortality rates associated with exacerbations;

TABLE 3 Cost-effectiveness results for base case and hospitalisation subgroup

Per patient	Total costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Base case					
Standard therapy	39,151	16.0793			
Standard therapy + omalizumab	94,774	16.6894	55,623	0.6101	91,169
Hospitalisation subgroup					
Standard therapy	41,333	14.36			
Standard therapy + omalizumab	82,222	14.98	40,890	0.62	65,911

QALY, quality-adjusted life-year.

(4) uncertainty around costs was omitted from the probabilistic sensitivity analysis; (5) exacerbation costs were not differentiated according to severity; and (6) treatment with omalizumab is assumed to last for 10 years (the clinical adviser to the ERG felt that, in practice, treatment duration could be closer to 1 or 2 years).

The ERG has not been able to explore the robustness of the model results to all of these weaknesses/uncertainties. However, the ERG did explore the main drivers of the cost-effectiveness results and found that the mortality rate associated with CSS exacerbations would have to be significantly higher (> 3% instead of 0.097% as in the model base case) for the ICER to reduce to around £30,000 per QALY.

Areas of uncertainty

From a clinical perspective, the main areas of uncertainty are (1) whether there is any benefit of omalizumab on CSS exacerbations (that would require hospitalisation in clinical practice) or emergency visits; (2) the relative efficacy and safety of omalizumab compared with OCS in children at step 5 of the BTS/SIGN guidelines; and (3) the longer-term safety of omalizumab in a paediatric population.

The cost-effectiveness of omalizumab remains subject to a number of areas of uncertainty in terms of informing current NHS practice. These uncertainties include (1) whether the response to treatment measured at 52 weeks is a reasonable proxy to response at 16 weeks; (2) after 16 weeks, exacerbation rates in the model were determined by comparing the rates observed in omalizumab responders with those in the standard therapy group (the appropriateness of this comparison is questionable as it excludes non-responders entirely); (3) the manufacturer's assumption that exacerbation rates remain constant over time does not account for patients undergoing adolescence, which can have an impact on the severity of their asthma; (4) the manufacturer's use of a single observational study for mortality⁹ without conducting a systematic search to identify mortality rates; (5) the failure to differentiate CS and CSS exacerbations in terms of cost; (5) the estimates for health-related QoL utilised in the model come from studies in adults^{7,12} and make use of a mapping algorithm;¹¹ and (6) a potentially relevant subgroup of patients with three or more exacerbations per year was not considered in the cost-effectiveness analysis.

Conclusions

The benefit of omalizumab in children with severe persistent asthma appears to be limited to a reduction in CS exacerbations, with no clear evidence of improvement in day-to-day symptoms. The definition used by the manufacturer for CS exacerbation (worsening of asthma symptoms requiring doubling of the baseline ICS dose and/or treatment with systemic corticosteroids for ≥ 3 days), means that most of these exacerbations would not require hospital admission. No statistically significant benefit of omalizumab on CSS exacerbations (that would require hospitalisation in clinical practice) or in emergency visits or hospitalisations has been demonstrated.

The benefit of omalizumab appears to be in children experiencing frequent (three or more) exacerbations per year at baseline. An apparent increase in the benefit of omalizumab in terms of a reduction in CS exacerbations over time appears to be primarily due to an increase in the exacerbation rate in the placebo group, most likely due to below-optimal treatment and a gradual deterioration in asthma control of children receiving placebo.

The available evidence indicates that omalizumab may be an efficacious alternative to OCS in children with more severe asthma who are not being optimally treated with OCS. Research into the management of the most severely affected children with asthma is warranted, directly comparing the efficacy of these two agents and investigating the OCS-sparing potential of omalizumab.

The main driver of cost-effectiveness is the reduction in asthma-related mortality that is associated with the reduced number and frequency of CSS exacerbations. However, as the absolute reduction in the number of exacerbations is low, and the level of asthma-related mortality in children is also low, the absolute gain in QALYs associated with the use of omalizumab therapy is also low, whereas the additional cost of treatment is high. Although the evidence for the rate of mortality due to CSS exacerbations was not identified in a systematic way, the true rate is unlikely to differ substantially from the values explored in the cost-effectiveness model. The cost per QALY gained with omalizumab was estimated to be far higher than £30,000 in both the overall population of children with severe asthma and in the more severe subgroup of children hospitalised in the previous year owing to asthma exacerbations. The cost per QALY gained with omalizumab remained >£30,000 even under the most favourable scenario analyses, suggesting that the health gains offered by omalizumab in a paediatric population with severe asthma are not sufficient to justify the additional cost of treatment.

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Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in October 2010 states:

Omalizumab is not recommended for the treatment of severe persistent allergic asthma in children aged 6–11 years.

Children currently receiving omalizumab for the treatment of severe persistent allergic asthma should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinician and the child and/or the child's parents or carers.

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Eltrombopag for the treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP)

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of eltrombopag for the treatment of adults with chronic idiopathic (immune) thrombocytopenic purpura (ITP), based on a review of the manufacturer's submission (MS) to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. ITP is an autoimmune disorder by which antibodies are formed against platelets with annual incidence rates in the UK/USA ranging from 1.13 to 6.62 cases per 100,000 adults. Eltrombopag increases the production of platelets at a rate that outpaces their destruction by the immune system, and has a UK marketing authorisation both for the treatment of adult ITP in splenectomised patients who are refractory to other treatments and as a second-line treatment for adult non-splenectomised patients for whom surgery is contraindicated. Both splenectomised and non-splenectomised patient groups were considered in the analysis. Two economic models were presented, one for a watch-and-rescue treatment scenario and the second for the long-term treatment of patients with more severe ITP. The submission's evidence was sourced from the relatively high-quality RAISE [RAndomized placebo-controlled Idiopathic thrombocytopenic purpura (ITP) Study with Eltrombopag] randomised controlled trial. The study indicated a statistically significant difference in favour of eltrombopag compared with placebo in the odds of achieving the primary outcome of a platelet count of between 50 and $400 \times 10^9/l$ during the 6-month treatment period (odds ratio 8.2, 99% confidence interval 3.6 to 18.7). In the eltrombopag group, 50/83 (60%) non-splenectomised patients and 18/49 (37%) splenectomised patients achieved this outcome. Median duration of response for all patients was 10.9 weeks (splenectomised patients 6 weeks and non-splenectomised patients 13.4 weeks). Patients treated with eltrombopag required less rescue medication and had lower odds of bleeding events than placebo-treated subjects in both patient groups. In the watch-and-rescue economic model, the ERG found that substantial reductions in the cost of eltrombopag are needed for the incremental cost-effectiveness ratio (ICER) to fall below £30,000. Further analyses found that the ICER varied from £33,561 to £103,500 per quality-adjusted life-year (QALY) (splenectomised) and from £39,657 to £150,245 per QALY (non-splenectomised). Other than bleeding, no adverse events were modelled. In relation to the long-term treatment model, the ERG found that using non-randomised non-comparative data may result in biased estimates of unknown magnitude and direction. None of the treatment sequences resulted in an ICER approaching the recommended threshold of £30,000. The base-case results, using a 2-year time horizon and prescribing eltrombopag as second-line treatment post rituximab, were found to be favourable towards eltrombopag. In conclusion, based on the MS and additional ERG work, eltrombopag appears to be a safe treatment for ITP (although long-term follow-up studies are awaited) and has short-term efficacy. However, there is no robust evidence on long-term efficacy or cost-effectiveness of eltrombopag, and there is a lack of robust direct evidence on the effectiveness and cost-effectiveness of eltrombopag compared with other relevant comparators. NICE did not recommend eltrombopag for the treatment of chronic ITP within its marketing authorisation for splenectomised or non-splenectomised patients.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor. Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled *Eltrombopag for the treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP)*.

Description of the underlying health problem

Idiopathic (immune) thrombocytopenic purpura (ITP) is a condition in which autoantibodies are formed against platelets, leading to increased clearance from the circulation. When the rate of destruction exceeds production, the platelet count will fall, which may lead to a reduced ability for blood to clot. ITP may present as bleeding and/or bruising or be asymptomatic and picked up on blood counts taken for other reasons. The incidence rates quoted for adult ITP in the UK/USA range from 1.13¹ to 6.62² cases per 100,000 adults per year. Traditionally, the only licensed medical treatments for ITP were steroids, intravenous immunoglobulin (IVIg) and anti-D immunoglobulin, although anti-D immunoglobulin has now been withdrawn as a treatment for ITP from the European market by the manufacturer owing to safety concerns. Other treatments include splenectomy (a surgical treatment), cyclophosphamide, vinca alkaloids, danazol, azathioprine, ciclosporin, rituximab, mycophenolate mofetil, dapsone, alemtuzumab, autologous stem cell transplantation, interferon and combination chemotherapy. Recently, thrombopoietin analogues (romiplostim and eltrombopag), which increase platelet production, have been licensed for treatment of ITP.

Eltrombopag is designed to increase the production of platelets at a rate that outpaces their destruction by the immune system. On 3 August 2007, orphan designation (EU/3/07/467) was granted by the European Commission to GlaxoSmithKline Research & Development Ltd, London, UK, for eltrombopag olamine for the treatment of adult ITP. Eltrombopag is indicated for the treatment of adult ITP when at least one other prior treatment has failed.

Scope of the evidence review group report

The manufacturer's submission (MS) assessed the clinical effectiveness and cost-effectiveness of eltrombopag for the treatment of chronic ITP in adult patients who had, prior to treatment, a baseline platelet count of $< 30 \times 10^9/l$. They were considered to have responded to treatment when the platelet count reached $50 \times 10^9/l$. Two patient populations were considered: splenectomised patients who were refractory to other treatments and non-splenectomised patients who had inadequate response to first-line treatment and for whom splenectomy was contraindicated.

The data used to assess the safety and efficacy of eltrombopag came from three randomised controlled trials (RCTs): TRA100773A,³ TRA100773B⁴ and TRA102537 RAISE [Randomized placebo-controlled Idiopathic thrombocytopenic purpura (ITP) Study with Eltrombopag].⁵

The manufacturer submitted two separate economic evaluations. The first considered the addition of eltrombopag to a 'watch-and-rescue' strategy and compared this with a watch-and-rescue strategy with the use of placebo. The second considered the use of eltrombopag as part of a treatment sequence provided for those patients needing longer-term continuous care who had tried, and failed, to respond to a number of treatment options. These patients were heavily pretreated and represented a smaller number of patients with more severe ITP.

Both models were constructed using Microsoft EXCEL (Microsoft Corporation, Redwood, WA, USA), and for both models two patient populations were modelled (splenectomised and non-splenectomised). The watch-and-rescue model mirrored the trial-based comparison of eltrombopag with placebo using data from the RAISE trial.⁵ The longer-term care model was a cohort-type model ($n = 25$) in which a Markov model was used to compare strategies in which eltrombopag was used as part of a sequence of treatments. The analysis also compared treatment sequences with eltrombopag versus the same sequences without eltrombopag. The principal source of the clinical effectiveness data for eltrombopag used to inform this model was the RAISE trial.⁵ Pooled data from the RAISE⁵ and EXTEND (Eltrombopag Extended Dosing study) trials were also used. The EXTEND trial is an extension study (case series) that is due to be completed in June 2012.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the MS to NICE as part of the STA process.⁶

Following submission of the manufacturer's report, the ERG:

- requested clarification from the manufacturer on a number of issues, mainly regarding clinical effectiveness and cost-effectiveness aspects together with requests for more detailed information to be provided in other areas
- assessed the clinical effectiveness section of the MS for its methodological quality and accuracy
- undertook independent searches for eltrombopag and the clinical effectiveness of the comparators
- performed additional sensitivity analyses on the manufacturer's indirect comparison between eltrombopag and romiplostim
- performed an array of additional sensitivity analyses on each of the economic models with a particular focus on multivariate sensitivity analysis.

Results

Summary of submitted clinical evidence

Evidence in relation to the efficacy of eltrombopag came principally from the RAISE study (Table 1).⁵ This was a 6-month phase III RCT, with 197 participants randomised 2:1 to eltrombopag plus standard care or placebo plus standard care. Of the 197 participants, 71 (36%) had undergone a splenectomy. Additional supporting evidence came from two 6-week RCTs comparing eltrombopag with placebo. TRA100773A³ was a phase II dose-finding study involving 118 participants, and TRA100773B⁴ was a phase III RCT involving 114 participants.

Efficacy

In the RAISE study,⁵ there was a statistically significant difference in favour of eltrombopag compared with placebo in the odds of achieving the primary outcome of a platelet count of between 50 and $400 \times 10^9/l$ during the 6-month treatment period [odds ratio (OR) 8.2, 99% confidence interval (CI) 3.6 to 18.7]. In the eltrombopag group, 50/83 (60%) of non-splenectomised patients and 18/49 (37%) of splenectomised patients achieved this outcome. The median cumulative weeks of response were 10.9 for eltrombopag (splenectomised patients 6 weeks, non-splenectomised patients 13.4 weeks) compared with none for placebo. Patients treated with eltrombopag were less likely to require rescue treatment than those treated with placebo [25/135 (19%) vs 25/62 (40%)]. The OR between eltrombopag and placebo was

TABLE 1 Summary of the results from the RAISE study⁵

Outcome measure	All participants	Splenectomised	Non-splenectomised
Odds of achieving a platelet count of between 50 and 400 × 10 ⁹ /l over the 6-month treatment period	OR 8.2 (99% CI 3.6 to 18.7)	Elt 37%, Pla 15%	Elt 60%, Pla 18%
Durable response – median cumulative weeks of response	Elt 10.9, Pla 0	Elt 6, Pla 0	Elt 13.4, Pla 0
Need for rescue medication during the intervention	Elt 25/135 (18%), Pla 25/62 (40%), <i>p</i> < 0.001	Elt 11/50 (22.0%), Pla 10/21 (47.6%) – OR 0.33 (95% CI 0.11 to 1.02)	Elt 14/85 (16.5%), Pla 15/41 (36.6%) – OR 0.34 (95% CI 0.14 to 0.79)
Reduction in dose/frequency of concomitant ITP medications taken at baseline	Elt 18%, Pla 40%, <i>p</i> = 0.001	Elt 12/27 (44.4%), Pla 5/13 (38.5%) – OR 1.29 (95% CI 0.33 to 5.04)	Elt 25/36 (69.4%), Pla 5/18 (27.8%) – OR 5.87 (95% CI 1.67 to 20.59)
Odds of any bleeding (WHO grades 1–4)	Elt vs Pla 0.24 (76% lower), <i>p</i> < 0.001	Elt 41 (82%), Pla 18 (90%) – OR 0.87 (95% CI 0.12 to 6.07)	Elt 65 (76%), Pla 38 (95%) – OR 0.10 (95% CI 0.02 to 0.53)
Odds of clinically significant bleeding (WHO grades 2–4)	Elt vs Pla 0.35 (65% lower), <i>p</i> < 0.001	Elt 19 (38%), Pla 14 (70%) – OR 0.27 (95% CI 0.08 to 0.95)	Elt 25 (29%), Pla 18 (45%) – OR 0.31 (95% CI 0.11 to 0.83)

CI, confidence interval; Elt, eltrombopag; ITP, idiopathic (immune) thrombocytopenic purpura; OR, odds ratio; Pla, placebo; WHO, World Health Organization.

statistically significant for non-splenectomised (OR 0.34, 95% CI 0.14 to 0.79) but not for splenectomised (OR 0.33, 95% CI 0.11 to 1.02) patients (OR for overall group was not reported). Thirty-seven out of 63 (59%) patients treated with eltrombopag reduced or discontinued concomitant ITP medication compared with 10/31 (32%) of patients receiving placebo (*p*-value not reported). The OR was statistically significant for non-splenectomised (OR 5.87, 95% CI 1.67 to 20.59) but not splenectomised (OR 1.29, 95% CI 0.33 to 5.04) patients (OR for overall group was not reported).

In a meta-analysis of the TRA100773A, TRA100773B and RAISE⁵ studies for the outcome of a platelet count of 50–400 × 10⁹/l at day 43, eltrombopag was associated with statistically significantly greater odds of platelet response than placebo for all patients [OR (fixed) 8.39, 95% CI 4.77 to 14.75]. Splitting the data by splenectomy status, eltrombopag was associated with statistically significantly greater odds of platelet response than placebo for both non-splenectomised (OR 9.17, 95% CI 4.52 to 18.60) and splenectomised (OR 7.20, 95% CI 2.82 to 18.35) patients.

Safety

The odds of any bleeding [World Health Organization (WHO) grades 1–4] during 6-month eltrombopag treatment were 76% lower in the eltrombopag group than in the placebo group (*p* < 0.001). The OR was statistically significant for non-splenectomised (OR 0.10, 95% CI 0.02 to 0.53) but not for splenectomised (OR 0.87, 95% CI 0.12 to 6.07) patients. The odds of clinically significant bleeding (WHO grades 2–4) were 65% lower in the eltrombopag group (*p* < 0.001). The OR was statistically significant for both non-splenectomised (OR 0.31, 95% CI 0.11 to 0.83) and splenectomised (OR 0.27, 95% CI 0.08 to 0.95) patients. ORs were not reported for the overall group for either any or clinically significant bleeding.

During the 6-month treatment period, eltrombopag and placebo had similar risks for any adverse event (118/135, 87% vs 56/61, 92%), any serious adverse event (15/135, 11% vs 11/61, 18%), adverse events related to study medication (48/135, 36% vs 18/61, 30%) and adverse events leading to withdrawal (12/135, 9% vs 4/61, 7%). Types of adverse events appeared to be similar between the eltrombopag and placebo groups.

The risk of liver function disturbances was higher for eltrombopag (8% during 6-week treatment and 13% during 6-month treatment) than for placebo (3% during 6-week treatment and 8% during 6-month treatment). No cases of bone marrow fibrosis, phototoxicity, cardiotoxicity or renal toxicity occurred during the intervention.

Indirect comparison between eltrombopag and romiplostim

An indirect comparison was possible only between eltrombopag (RAISE study⁵) and romiplostim (two RCTs⁷), as no RCTs reporting any of the other treatments used placebo as a comparator.

There was a statistically significant difference in favour of romiplostim for overall response for all patients (OR 0.17, 95% CI 0.03 to 0.82). When the patients were split by splenectomy status, the point estimates of the OR favoured romiplostim but they were not statistically significant. For durable response, there was no statistically significant difference between eltrombopag and romiplostim, either for all patients (OR 0.26, 95% CI 0.03 to 2.62) or separately by splenectomy status. *Durable response* was defined as a weekly platelet count of $\geq 50 \times 10^9/l$ during ≥ 6 weeks of the last 8 weeks of treatment, excluding those who received rescue medication at any time during the study, whereas *overall response* was durable plus transient response (four or more weekly responses of $\geq 50 \times 10^9/l$ during the study without a platelet response from weeks 2 to 25).

In the manufacturer's analysis, all participants who did not complete treatment were classed as non-responders (worst scenario). The ERG undertook further analysis in which all such participants were classed as responders (best scenario). In this further analysis the results for overall response (all patients) remained statistically significant in favour of romiplostim (OR 0.26, 95% CI 0.07 to 0.97), while the point estimate for durable response (all patients) changed to favour eltrombopag rather than romiplostim, although the difference remained non-significant (OR 1.04, 95% CI 0.32 to 3.44).

Comparator treatments

No attempt was made to statistically or narratively synthesise data on the effectiveness of comparators. The manufacturer stated that best available evidence was used to generate values for the long-term economic model. However, alternative evidence could have been used for IVIG [American Society for Haematology (ASH) guideline⁸ and a Health Technology Assessment review⁹] and for anti-D immunoglobulin (ASH guideline⁸).

Summary of submitted cost-effectiveness evidence

The manufacturer submitted two economic evaluations and models analysing the cost-effectiveness of eltrombopag for the treatment of adult ITP.

Watch-and-rescue model

The watch-and-rescue model compares eltrombopag plus standard care with standard care. The model was based on the double-blind RAISE RCT,⁵ with uptake rates of the drug determined from an internal GlaxoSmithKline study.

The incremental cost per quality-adjusted life-year (QALY) for the base-case analyses for splenectomised and non-splenectomised patients was £78,253 and £90,471, respectively. Sensitivity analyses varying the risk of death, target platelet counts and use of concomitant medications did not reduce the incremental cost per QALY greatly. A probabilistic analysis showed that there was little or no chance of eltrombopag being cost-effective at a threshold of £30,000 per QALY. Substantial reductions in the price of eltrombopag would be required to obtain a cost per QALY of £30,000.

The ERG conducted additional sensitivity analyses around the source of cost data for managing bleeds, discount rate and the annual risk of bleeding. Only by combining these changes into an optimistic multivariate sensitivity analysis did the incremental cost per QALY begin to approach £30,000. Sensitivity analyses conducted by the manufacturer and by the ERG are presented in *Table 2*.

Long-term care model

This model referred to a smaller patient group with more severe ITP and aimed to assess the most cost-effective sequence of treatments [rituximab, romiplostim, IVIG, anti-D immunoglobulin (which was considered only for those in whom splenectomy was contraindicated) and eltrombopag] for the treatment of chronic adult ITP. Given the input parameters used, the model was very similar for the two patient groups.

The analyses conducted by the manufacturer assumed that patients would always be offered an active treatment and it was found that a treatment sequence of rituximab, eltrombopag, romiplostim and IVIG was the least costly but least effective of the non-dominated sequences. No other sequences had an incremental cost per QALY approaching £30,000. The manufacturer reported that treatment sequences including eltrombopag dominated the same sequences without eltrombopag when patients had received prior treatment with rituximab. The manufacturer's deterministic sensitivity analysis varied the response rate used in the model and the model time horizon. These did not greatly change the results.

The ERG's further univariate analyses (varying the discount rate, changing response rates of eltrombopag, allowing romiplostim to respond over a 12-week period and varying the assumption of a fatal bleeding event between 0% and 100%) did not greatly alter the results. Plausible combinations of changes could change which treatment sequence was least costly but least effective, but, again, no other sequence had an incremental cost-effectiveness ratio (ICER) approaching £30,000. The ERG also conducted a further exploratory sensitivity analysis by introducing a standard-care sequence in which patients received only rescue medication. This treatment sequence was the least effective but least costly sequence. No other treatment sequence was associated with an ICER <£50,000.

TABLE 2 Exploratory sensitivity analyses for splenectomised and non-splenectomised patients (watch-and-rescue model)

Scenario	Incremental cost per QALY (£)	
	Splenectomised	Non-splenectomised
1. Baseline results	77,496	90,471
2. Typo correction	78,253	90,471
3. Micro cost	83,284	91,175
4. All bleeding events	100,350	89,850
5. 0% discount rate	47,712	55,622
6. 6% discount rate	103,500	118,847
7. Annual risk of fatal bleed (Cohen, ¹⁰ lower bound)	131,841	150,245
8. Annual risk of fatal bleed (Cohen, ¹⁰ upper bound)	55,778	64,882
9. Combining scenarios 2, 3, 4, 6 and 7 (worst-case scenario)	231,195	193,293
10. Combining scenarios 5 and 8 (best-case scenario)	33,561	39,657

QALY, quality-adjusted life-year.

Commentary on robustness of submitted evidence

The overall quality of the RCTs used to support the watch-and-rescue model appears reasonable. However, within the model, benefits were allowed to accrue over a patient's lifetime, but costs for this period were assumed to occur over only the 26-week trial period, with no extrapolation to a longer time horizon. This is likely to introduce a bias in favour of eltrombopag in the analysis.

Only indirect evidence relating to relatively short follow-up was available for use in the long-term model, and the use of these data introduces a bias of unknown direction and magnitude. Owing to the lack of other suitable data, two different measures of utilities were used (the Short Form questionnaire-6 dimensions and the European Quality of Life-5 Dimensions). Furthermore, apart from bleeding, no other utility decrements (e.g. for other adverse events) were included in either of the economic models. Information on other parameters for both models can be questioned, but even when assumptions were varied the incremental costs per QALYs remained well above £30,000.

Conclusions

Overall, the key issues for a decision-maker to note are as follows.

Effectiveness

Key issues

- Eltrombopag appears to be a safe treatment for ITP, although long-term follow-up studies are awaited.
- Eltrombopag has short-term efficacy for the treatment of ITP.
- There is no robust evidence on long-term efficacy of eltrombopag.
- Eltrombopag appears to be less effective in achieving an overall response rate than romiplostim in a 6-month intervention period.
- There is no robust direct evidence on the effectiveness of eltrombopag compared with other relevant comparators.

Watch-and-rescue model

Key issues

- Substantial reductions in the cost of eltrombopag are needed before the incremental cost per QALY is < £30,000.
- If the chance of dying from a bleeding event increases towards the upper boundary considered by the manufacturer, and the price of eltrombopag is reduced, then it is plausible that the cost per QALY could be reduced to < £30,000.
- Other than bleeding, no adverse events were modelled. The bias this causes is unknown.

Long-term treatment model

Key issues

- Using non-randomised non-comparative data may result in biased estimates. The magnitude and direction of these biases is uncertain.
- The inclusion of standard care in the model allows one to begin to think about how cost-effective any of the treatment sequences are. No sequence results in an ICER approaching the recommended threshold of £30,000.
- Restricting the time horizon to 2 years results in a treatment sequence in which eltrombopag given after rituximab is most likely to be cost-effective. A 50-year time horizon favours a sequence involving romiplostim in treatment post rituximab.

- Many assumptions are used to estimate the target patient population and the numbers of patients who will require long-term treatments. It is unclear how applicable these are.

Furthermore, the representativeness of participants in the eltrombopag trials of the UK population of patients with chronic ITP is uncertain, as are the estimates of incidence and prevalence given in the MS.

Summary of NICE guidance issued as a result of the STA

The final appraisal determination was published by NICE in September 2010 and final guidance published in October 2010.¹¹ NICE did not recommend eltrombopag within its marketing authorisation for the treatment of chronic ITP in splenectomised adults whose condition is refractory to other treatments (e.g. corticosteroids, immunoglobulins) or as second-line treatment in non-splenectomised adults where surgery is contraindicated.

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Trastuzumab for the treatment of HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

This paper presents a summary of the evidence review group (ERG) report into trastuzumab for the treatment of human epidermal growth factor receptor 2 (HER2)-positive metastatic adenocarcinoma of the stomach (mGC) or gastro-oesophageal junction. HER2 positivity is defined by immunohistochemistry (IHC)3+ or IHC2+/fluorescence in situ hybridisation (FISH)+. The decision problem addressed was the testing of the whole mGC population with IHC and, for IHC2+ patients, also with FISH, followed by treatment of HER2-positive patients with trastuzumab combined with cisplatin and either capecitabine or 5-fluorouracil (5-FU) [HCX (trastuzumab, cisplatin, capecitabine)/fluorouracil (F)] compared with current standard NHS therapy. The manufacturer's submission contained direct evidence from the ToGA trial, a well-conducted, multinational, phase III randomised controlled trial (RCT) that compared HCX/F with cisplatin and a fluoropyrimidine alone [cisplatin, capecitabine (CX)/F]. HCX/F showed statistically significantly better overall survival in the European Medicines Agency-licensed population subgroup (74%) (hazard ratio 0.65, 95% confidence interval 0.51 to 0.83), corresponding to median survival of 16 months versus 11.8 months. No other evidence exists for the efficacy of any therapy in a known HER2-positive mGC population; other comparisons extrapolate from trials in mixed HER2 status populations. The ERG accepted the manufacturer's view that a meaningful network meta-analysis to establish a comparison for HCX/F compared with current standard NHS therapy [epirubicin, cisplatin, capecitabine (ECX)/epirubicin, oxaliplatin, capecitabine (EOX)/epirubicin, cisplatin, 5-FU (ECF)] was not possible, but was unconvinced by arguments advanced in the alternative narrative synthesis. These involved disregarding evidence from a meta-analysis and interpreting non-significant results of small RCTs comparing epirubicin-containing triplets with cisplatin, 5-FU (CF)/capecitabine (X) doublets as evidence of no difference between triplet and doublet regimens. The high CX/F dose in the ToGA trial was an additional basis for the contention of equivalence. An appropriate de novo economic evaluation, including an economic model that separately compared HCX or trastuzumab, cisplatin, 5-FU (HCF) with the triplet regimens ECX, EOX and ECF, based on a simple, three-state cohort model (progression-free, disease, progression and death), was submitted. Utility weights were applied to estimate quality-adjusted life-years (QALYs). Costs were assessed from an NHS perspective, and incorporated the acquisition and monitoring costs of the alternative regimens, HER2 testing, adverse events and other supportive care costs. An 8-year time horizon was used to represent a lifetime analysis. Results from the ToGA trial were combined with a series of assumptions on relative treatment effects and testing strategies. The manufacturer's results produced an incremental cost-effectiveness ratio (ICER) of £53,010 per QALY for HCX versus ECX. Although the manufacturer undertook a detailed set of sensitivity analyses, several alternative model assumptions were not evaluated. The ERG undertook a series of alternative base-case analyses. As a result of these analyses, EOX replaced ECX as the appropriate comparator, and the ICER for the comparison of HCX vs EOX increased to between £66,982 and £71,636 per QALY. The impact of implementation of alternative testing strategies remained unclear. There is also considerable uncertainty surrounding the true estimate of effectiveness for the comparison between triplet regimens containing epirubicin (ECX/ECF/EOX) and doublet CX/F regimens. Consequently, the view of the ERG was that there is insufficient evidence on the efficacy of HCX/F compared with current NHS standard therapy for an ICER to be determined with any degree of certainty.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of

people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor (in this instance, Roche). Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology.¹ In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Trastuzumab for the treatment of HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction*.²

Description of the underlying health problem

Gastric cancer is the 10th most commonly diagnosed cancer in the UK. Approximately 7000 cases are diagnosed each year in England and Wales³ and these account for around 4574 deaths.⁴ For the 80% of patients unsuitable for curative surgery, palliative chemotherapy is an option, and it is estimated that just over one-half (around 2900) of the patients with advanced or metastatic adenocarcinoma of the stomach* (mGC) receive such treatment, which modestly improves survival as well as relieving disease-related symptoms. In the UK, the standard treatments for patients who are considered sufficiently fit are triplet regimens comprising a fluoropyrimidine [capecitabine (X) or 5-fluorouracil (F)], a platinum agent [cisplatin (C) or oxaliplatin (O)] and an anthracycline [epirubicin (E)]. Capecitabine is considered at least comparable to 5-fluorouracil (5-FU), and oxaliplatin at least comparable to cisplatin.^{5,6} A proportion of patients with mGC have tumours that overexpress the human epidermal growth factor receptor 2 (HER2) receptor, meaning that they are potentially suitable for treatment with the monoclonal antibody trastuzumab (Herceptin[®], Roche). The tests used to determine HER2 positivity are immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH).

Scope of the evidence review group report

The decision problem addressed was the use of trastuzumab (H) in combination with cisplatin and either capecitabine or 5-FU (HCX/F) compared with current standard NHS therapy in patients with HER2-positive mGC or gastro-oesophageal junction cancer. HER2 positivity is defined as IHC3+ or IHC2+/FISH+. Such patients constituted 17.8% of the total screened population in the ToGA trial, which formed the basis of the manufacturer's submission (MS).^{7,8} The ERG considered that the decision problem comprised the testing of the whole mGC population with IHC, and for IHC2+ patients also with FISH, followed by treatment with trastuzumab in accordance with HER2 status, as specified by the licensed indication.

Methods

The ERG report comprised a critical review of the clinical effectiveness and cost-effectiveness of the technology based upon the MS to NICE as part of the STA process.

The ERG appraised the searches used to identify studies and the assessment tools used to critically appraise identified studies for both direct and indirect comparisons. The manufacturer's decision not to use a network meta-analysis in the assessment of clinical effectiveness was reviewed, and the narrative synthesis submitted in place of such an analysis was scrutinised.

* The stomach is understood to include the gastro-oesophageal junction.

The ERG appraised the assumptions adopted in the economic model and reviewed the sources of the model data and the programming of the model. Following a response by the manufacturer to clarifications requested by the ERG, which included a revised model, the ERG further revised the base-case cost-effectiveness estimates to account for inconsistencies identified in the model. The ERG then carried out a series of sensitivity analyses to evaluate alternative assumptions, and produced an alternative base-case cost-effectiveness estimate based on equally plausible assumptions.

Results

Summary of submitted clinical evidence

The MS focused on direct evidence from the ToGA trial.⁷ This was a phase III randomised controlled trial (RCT) that compared a doublet regimen of cisplatin plus a fluoropyrimidine [capecitabine or 5-FU (CX/F)] alone or in combination with trastuzumab (HCX/F) in patients with HER2-positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction. The choice of fluoropyrimidine was at the discretion of the investigator; 87% of patients in each arm received capecitabine and 13% received 5-FU. The primary outcome was overall survival (OS). A subgroup of 74% of patients from this trial with IHC2+/FISH+ or IHC3+ mGC constituted the European Medicines Agency (EMA)-licensed population.

The hazard ratio (HR) for OS in the EMA subgroup [74% of the full analysis set (FAS) population (all randomised patients who received study medication at least once)] was 0.65 (95% confidence interval 0.51 to 0.83), corresponding to median survival of 16 months for the HCX/F group versus 11.8 months for the CX/F group. Progression-free survival (PFS) and response rates also showed evidence of a benefit of HCX/F (*Table 1*).

As doublet therapy with CX/F at the high doses evaluated in the ToGA trial⁷ is not used in an NHS context, the MS attempted to construct a network meta-analysis for the comparison of HCX/F with ECX (epirubicin, cisplatin, capecitabine), ECF (epirubicin, cisplatin, 5-FU) and EOX (epirubicin, oxaliplatin, capecitabine). It was decided, correctly in the view of the ERG, that construction of a meaningful network using the available clinical evidence was not possible. Therefore, a narrative discussion was presented, including the rationale for assumptions key

TABLE 1 Summary of outcome data reported in the MS for the EMA subgroup (IHC2+/FISH+ or IHC3+; 74% of the FAS population) of the ToGA trial⁷

Outcome	HCX/F	CX/F	Statistical results (HCX/F vs CX/F)
OS (median), (months)	16.0	11.8	HR 0.65 (95% CI 0.51 to 0.83)
PFS (median), (months)	7.6	5.5	HR 0.64 (95% CI 0.51 to 0.79)
Response rate (%) ^a	47.3	34.5	OR 1.70 (95% CI 1.22 to 2.38)
QoL	Graphical presentation of EORTC data only; ERG unable to form conclusions as to differences between the groups		
Adverse events ^a	Statistically significantly more grade 1 and grade 2 adverse events (multiple categories) in HCX/F group Statistically significantly more asymptomatic LVEF reductions in HCX/F group did not translate into increased symptomatic cardiac events No statistically significant differences in grade 3 or 4 events		

CI, confidence interval; CX/F, cisplatin, capecitabine/5-fluorouracil; EORTC, European Organisation for Research and Treatment of Cancer; ERG, evidence review group; HCX/F, trastuzumab, cisplatin, capecitabine/5-fluorouracil; HR, hazard ratio; LVEF, left ventricular ejection fraction; OR, odds ratio; OS, overall survival; PFS, progression-free survival; QoL, quality of life.

a Data for full-analysis set population.

to the economic model (see *Commentary on the robustness of submitted evidence*). The studies discussed in this narrative are detailed in *Table 2*.

Summary of submitted cost-effectiveness evidence

The MS did not identify any published cost-effectiveness studies of trastuzumab in HER2-positive patients with mGC. Therefore, the manufacturer's de novo economic evaluation formed the basis of the submitted economic evidence.

The economic model included two separate trastuzumab regimens in combination with either cisplatin and capecitabine (HCX) or cisplatin and 5-FU (HCF). The trastuzumab regimens were compared with three other triplet regimens containing epirubicin in combination with either cisplatin and capecitabine (ECX), oxaliplatin and capecitabine (EOX) or cisplatin and 5-FU (ECF).

The manufacturer's cost-effectiveness analysis was based on a simple, three-state cohort model (progression free, disease progression and death). Quality of life was quantified by applying utility weights to the separate model states in order to estimate quality-adjusted life-years (QALYs). Costs were assessed from an NHS perspective and incorporated the acquisition and monitoring costs of the alternative regimens, HER2 testing, adverse events and other supportive care costs associated with the management of progression-free disease and progressive disease. An 8-year time horizon was used and was considered to represent a lifetime analysis. Both one-way sensitivity analyses and probabilistic sensitivity analyses (PSAs) were undertaken.

In the absence of direct evidence comparing all five regimens, the manufacturer combined the results from the ToGA trial,⁷ which provided PFS and OS curves for HCF/X regimens and CF/X

TABLE 2 Summary of the network of evidence considered by the manufacturer and/or the ERG for the comparison of HCX/F with triplet therapies used in current standard NHS practice

Study	n	Comparison	Estimate of OS: HR (95% CI)
RCTs			
ToGA ⁷	594	HCX/F vs CX/F in patients who are IHC3+ or IHC2+/FISH+ for HER2	0.65 (0.51 to 0.83)
REAL-2 ⁵	1002	(ECX + EOX) vs (ECF + EOF) (ECX + ECF) vs (EOF + EOX)	0.89 (0.77 to 1.02) 0.95 (0.82 to 1.09)
Kim 2001 ¹¹	121	ECF vs CF	0.83 (0.42 to 1.61)
Tobe 1992 ¹⁰	60	ECF vs CF	0.57 (0.27 to 1.20)
Ross 2002 ¹³	580	ECF vs MCF	0.79 (0.62 to 0.95) ^a
Yun 2010 ¹²	91	ECX vs CX	NR ^b
Meta-analyses			
Wagner 2010 ⁹	501	ECF vs CF Meta-analysis of Kim 2001, ¹¹ Tobe 1992, ¹⁰ Ross 2002 ¹³	0.77 (0.62 to 0.95)
Okines 2009 ⁶		(ECX or CX) vs (ECF or CF) IPD meta-analysis of REAL-2 ⁵ and ML17032 ¹⁴	0.87 (0.77 to 0.98)

CF, cisplatin, 5-fluorouracil; CI, confidence interval; CX, cisplatin, capecitabine; CX/F, cisplatin, capecitabine/5-fluorouracil; ECF, epirubicin, cisplatin, 5-fluorouracil; ECX, epirubicin, cisplatin, capecitabine; EOF, epirubicin, oxaliplatin, 5-fluorouracil; EOX, epirubicin, oxaliplatin, capecitabine; FISH, fluorescence in situ hybridisation; HCX/F, trastuzumab, cisplatin, capecitabine/5-fluorouracil; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; IPD, individual patient data; MCF, mitomycin, cisplatin, 5-fluorouracil; NR, not reported; OS, overall survival; RCT, randomised controlled trial.

a A total of 32.8% of patients had oesophageal cancer and were excluded from the Wagner *et al.*⁹ meta-analysis.

b Primary outcome was progression-free survival [HR 0.96 (95% CI 0.58 to 1.57)].

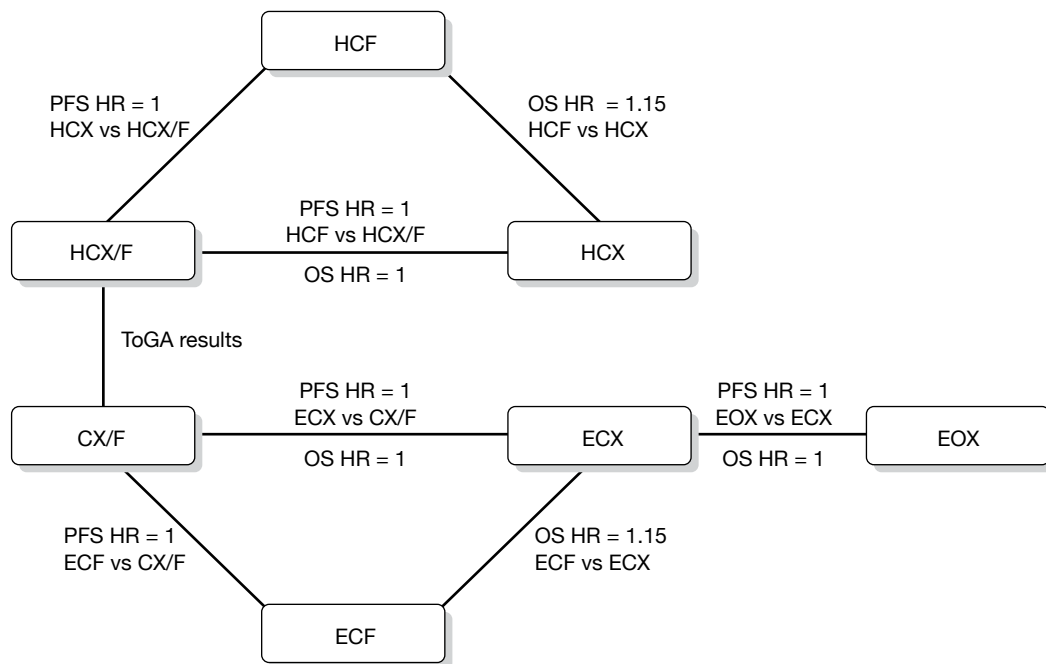


FIGURE 1 Network of assumptions used in the economic model presented in the manufacturer's submission.

regimens, with a series of assumptions. As mentioned above, it was not possible to perform a robust network meta-analysis. The network of assumptions and the hazard rates used in the manufacturer's economic model are illustrated in *Figure 1*.

Key clinical effectiveness assumptions in the manufacturer's model were:

1. CX/CF regimens with a higher dose of cisplatin had equal effectiveness to ECX/ECF regimens.
2. Capecitabine regimens had a survival benefit over 5-FU regimens.
3. Oxaliplatin regimens were equivalent to cisplatin regimens.

The manufacturer's results showed that HCX resulted in a mean gain of 0.25 QALYs compared with ECX/EOX, 0.31 QALYs compared with ECF and 0.07 QALYs compared with HCF. ECX was the next most effective regimen after HCX that was not dominated (i.e. less effective and more costly) by another regimen, and the incremental cost-effectiveness ratio (ICER) of HCX versus ECX was £53,010 per QALY.

Commentary on the robustness of submitted evidence

The ToGA trial⁷ was a well-conducted, open-label phase III trial that directly compared trastuzumab in its licensed therapeutic combination with CX/F and CX/F alone. CX/F is considered to be standard therapy in other non-UK settings. The ToGA trial⁷ was appropriately randomised, and protocol amendments and termination took place on the advice of an independent data monitoring committee. While the evidence directly relevant to the decision problem is based on a subgroup of the ToGA trial,⁷ this constituted a clear majority of the trial population and was defined as a result of advances in the understanding of HER2 testing, giving it credibility as a distinct population. The use of subgroup data as the basis for the submission was therefore not considered problematic. Outcome assessors were unblinded, but, as the primary outcome was OS, this was not of major concern.

The economic model structure was considered to be appropriate for the decision problem, and the general approach used by the manufacturer to estimate lifetime cost-effectiveness met the requirements of the NICE reference case approach. Both one-way sensitivity analyses and PSA were used to reflect uncertainty in the model inputs and assumptions, and these were informative in exploring the robustness of the results and identifying potential key drivers of cost-effectiveness.

Two principal weaknesses were identified in the clinical effectiveness sections of the MS. First, as the HER2-positive mGC population has not been identified within previous trials, the efficacy of standard triplet regimens (or indeed any therapy) in this particular group is unknown. The comparator used in the ToGA trial⁷ (CX/F) is not the standard UK treatment and, where used in frailer patients, is used at lower doses. Indirect evidence is therefore required to assess the efficacy of HCX/F compared with current standard UK treatment for fit patients (ECX, ECF or EOX). This requires the assumption that the HER2-positive population is equivalent to a mixed HER2 population, containing an unknown proportion of HER2-positive patients. It is known that the rate of HER2 positivity varies with histological subtype; whether the histology seen in the ToGA trial⁷ is representative of the UK population is not clear, as the ToGA trial⁷ was primarily conducted in non-European settings.

The ERG considered as correct the manufacturer's finding that it was not possible to create a network meta-analysis to compare HCX/F with triplet therapies using data from the general mGC population. However, the second major weakness of the MS was the approach of the narrative synthesis of relevant trials, in particular the argument that a meta-analysis of CF versus ECF regimens, which found an OS advantage for ECF,⁹ should be disregarded in favour of the results of individual small trials.¹⁰⁻¹² The ERG considered that the evidence of the meta-analysis, which was likely to be conservative to ECF and, by inference, to ECX, could not be disregarded (see *Table 2*). The alternative approach of the MS involved the argument that, as small RCTs did not show a statistically significant advantage of ECX/F over CX/F, this could be regarded as evidence of no advantage. An additional argument was that the higher dose of CX/F used in the ToGA trial⁷ provided additional efficacy over standard doses, giving comparable efficacy to epirubicin-based triplet regimens. The manufacturer therefore contended that the CX/F comparator in ToGA could be considered equivalent to ECX/F (and hence EOX on the basis of the evidence from the REAL-2 trial⁵). The ERG considered this argument to be unconvincing and non-conservative with respect to ECX/F. Further, they considered that there is a high level of uncertainty around the estimate of effect for the addition of epirubicin to CX/F regimens, and hence the estimate of effect for HCX/F versus triplet regimens.

From a cost-effectiveness perspective there were a number of additional weaknesses considered by the ERG. These stem largely from the lack of direct comparison of the different regimens incorporated in the economic analysis and the series of assumptions that were then necessary in order to estimate the incremental cost-effectiveness of the relevant regimens. Although the manufacturer undertook a detailed set of sensitivity analyses, several of the model assumptions were not incorporated.

The PSA did not include the uncertainty surrounding some of the estimates of effectiveness, yet the PSA still resulted in a wide range of estimates. Given this level of uncertainty and the number of assumptions required, scenario analyses could have been undertaken to demonstrate the combined effect of other plausible assumptions.

The ERG considered there to be equally plausible alternative estimates for the following significant assumptions used in the manufacturer's base-case analysis:

1. relative effectiveness estimates of particular comparators
2. utility values applied during PFS
3. frequency of cardiac monitoring with trastuzumab and epirubicin.

In addition to these assumptions, the ERG also considered that there was insufficient discussion of the logistical issues of undertaking HER2 testing in this population and whether the effectiveness results from the ToGA trial⁷ (where parallel testing using IHC and FISH tests was used) could be generalised without any loss in treatment effect due to potential delays that could arise for IHC2+ patients, based on the sequential testing approach included in the model.

The ERG undertook a series of alternative base-case analyses to address these perceived weaknesses. As a result of these analyses, EOX replaced ECX as the next most effective regimen, after HCX, that was not dominated, and the ICER for the comparison of HCX versus EOX increased to between £66,982 and £71,636 per QALY. The REAL-2 trial⁵ indicated that EOX may be more effective than other triplet regimens.⁵

Conclusions

There is considerable uncertainty surrounding the true estimate of effectiveness for the comparison between triplet regimens containing epirubicin (ECX/ECF/EOX) and doublet CX/F regimens. As a consequence of this, the estimate of effectiveness and hence the true ICER for HCX/F versus ECX/F and hence EOX is equally uncertain. Other areas of uncertainty include the generalisability of data to the HER2-positive subgroup; all trials other than ToGA⁷ were conducted in populations of mixed HER2 status. In the absence of a planned RCT of ECX/EOX versus HCX/F in HER2-positive patients, the ERG recommends that, if feasible, tissue samples from the REAL-2 trial⁵ be HER2 typed and correlated with outcome data. This would provide some indication of the efficacy of triplet therapies in the HER2-positive subpopulation. There is also some uncertainty as to the applicability of the ToGA trial,⁷ with its predominantly non-European population, to the UK mGC population.

Other areas of uncertainty involve the appropriate diagnostic testing strategy. The MS assumed that sequential testing would be performed. However, the effectiveness evidence related to parallel testing. The impact of delay in treatment arising from sequential testing has not been evaluated. The impact of the need for HER2 testing across the entire mGC population, 82% of whom will not be eligible for treatment with trastuzumab, is uncertain. In addition, the cost-effectiveness of the diagnostic testing used in the MS has not been demonstrated to be better than other ways of defining HER2 positivity and eligibility for trastuzumab.

Finally, the view of the ERG was that there was insufficient evidence as to the efficacy of HCX/F compared with current NHS standard therapy for an ICER to be determined with any degree of certainty.

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Gerry Richardson, Senior Research Fellow, Centre for Health Economics, University of York, UK.

Summary of NICE guidance issued as a result of the STA

NICE guidance states that trastuzumab, in combination with cisplatin and capecitabine or 5-FU, is recommended as a treatment option for people with HER2-positive mGC who have not received prior treatment for their metastatic disease and who have tumours that express high levels of HER2, defined as IHC3+. This guidance was issued subsequent to the submission, following consultation on the appraisal consultation document, of additional analyses relating to this more narrowly defined subgroup by the manufacturer, and the ERG's consideration of these data.

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Prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief. The ERG report is based on the manufacturer's submission (MS) to the National Institute for Health and Clinical Excellence as part of the single technology appraisal process. In the submission, quality-of-life data [Patient Assessment of Constipation Quality of Life (PAC-QOL) and Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaires] from trials of prucalopride were extrapolated to EQ-5D (European Quality of Life-5 Dimensions) data and used to inform effectiveness in an economic model. Response rates to prucalopride were derived from observed response rates in trials, defined as the proportion of patients achieving an average of three or more spontaneous complete bowel movements over the 4- or 12-week trial periods. Adult (18–64 years) and elderly (≥ 65 years) patients were considered separately in the model. Cost-effectiveness was determined from estimated improvements in EQ-5D and anticipated response rates, adjusted for baseline severity of chronic constipation. The ERG considered that the patients participating in these trials were not representative of those in the licensed indication. They were not all refractory to laxatives, and baseline EQ-5D scores showed a large spread in quality of life, with many patients experiencing little baseline dissatisfaction. The mapping of quality-of-life data from trials (PAC-QOL and PAC-SYM data) to EQ-5D was unclear and invalidated. The assumption of the long-term effectiveness and safety of prucalopride to 1 year was considered unjustified. There was no justification or sources given for coefficients used to predict effectiveness in the economic model, and no costs other than the cost of prucalopride were incorporated into the model. Owing to the many areas of uncertainty, particularly the effectiveness of prucalopride in the licensed patient group and its long-term effectiveness and safety, it was considered that the MS provided no evidence for whether prucalopride is effective or not in women with laxative-refractory chronic constipation. Further subgroup analysis of the actual patient group of interest may have better guided decision-making. However, long-term efficacy data, with validated estimates of quality of life incorporated in a well-founded model, would be important for an evidence-based judgement to be made.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.¹ Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief*.²

Description of the underlying health problem

Chronic constipation may be idiopathic or secondary to other causes, such as drug use or neuromuscular conditions. This submission relates to patients with idiopathic chronic constipation that is not secondary to other causes and is a long-term disease. Rates of chronic constipation are higher in women than in men. Clinical trials of chronic constipation include ~90% women compared with ~10% men,³⁻⁵ and this may be representative of the relative prevalence in men and women.

The majority of patients with chronic constipation are managed in primary care. Non-pharmacological measures, such as dietary modification and exercise, are recommended in the first instance, and, where these fail, pharmacological measures (a range of laxative treatments) can be prescribed. However, for a small proportion of these patients, laxative measures used over a long period of time fail to bring about bowel movements. These patients, with chronic constipation that is refractory to laxative treatments, are the population for whom prucalopride is licensed and the patient group for which guidance was to be made.

Estimates for the prevalence of chronic constipation vary and it is difficult to make a precise estimate of the size of this patient group. Furthermore, it is difficult to assess, from within this group, the number of laxative-refractory patients for whom prucalopride may be indicated. In the manufacturer's submission (MS), it was estimated that the total eligible adult patient group that might benefit from prucalopride in the UK is 363,000 (estimated from a 47 million UK adult population, assuming an average prevalence of chronic constipation of 7.7% and that 10% of patients are dissatisfied with, or refractory to, laxatives).

Scope of the evidence review group report

Prucalopride is licensed in women with chronic constipation who are refractory to laxative medications. The licence is for daily doses of 2 mg for adult patients (18–64 years) and 1 mg for elderly patients (≥65 years), and treatment costs are £2.13 and £1.38 per day, respectively.

In the submission, data from nine trials were used to inform the assessment of clinical effectiveness, and four of these trials, along with data from six additional trials, were used to inform the economic evaluation. In trials, response to treatment was measured in terms of the number of spontaneous complete bowel movements (SCBMs) and by using quality-of-life questionnaires. The main outcome measure was number of patients achieving a mean of three or more SCBMs over the first 4 and 12 weeks of trials. Patient Assessment of Constipation Quality of Life (PAC-QOL) and Patient Assessment of Constipation Symptoms (PAC-SYM) surveys, designed by manufacturers for use in the prucalopride trials, were used to obtain quality-of-life data and SF-36 questionnaires (Short Form questionnaire-36 items) were also used in some of the trials. Data from PAC-QOL and PAC-SYM questionnaires were mapped to give quality of life in terms of EQ-5D (European Quality of Life-5 Dimensions). Results from SF-36 questionnaires were used in the development of regression equations for the mapping of PAC-QOL and PAC-SYM data to EQ-5D.

For the economic model, quality of life gained by responders was estimated by one of eight different regression equations. Scenarios varied, depending on the definition of patient response (three or more SCBMs per week or an increase of one or more SCBM per week), whether patients had previously been on laxative treatment and whether constipation severity at baseline was considered. The cost of prucalopride was the only cost included in the model, and incremental cost-effectiveness ratios (ICERs) were presented separately for the adult and elderly populations.

The ERG report aimed to assess the extent to which the clinical effectiveness and cost-effectiveness parts of the MS covered the appropriate population, intervention, comparators and outcomes, and the extent to which information used in the economic model was valid and incorporated in an appropriate way.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology, based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

Searches for studies of clinical effectiveness and cost-effectiveness were conducted. The clinical effectiveness part of the MS was assessed in terms of its coverage of relevant trials/studies, its relevance to the proposed drug indication and the quality of the presented data. The cost-effectiveness part of the submission was assessed in terms of the applicability of included data, the transparency in which model parameters were selected and the validity of assumptions used in the model.

Using the manufacturer's economic model, the ERG performed additional analysis to investigate the effect of assuming that patients take prucalopride every day (instead of 220 days/year), incorporating an allowance for adverse events and reducing the estimated gain in quality of life.

Results

Summary of submitted clinical evidence

Results from nine trials were presented: three 'pivotal' trials,³⁻⁵ one trial in elderly patients,⁶ one re-treatment study,⁷ one trial in patients with opioid-induced chronic constipation⁸ and three long-term open-label studies.⁹⁻¹¹ Results for the three 'pivotal' trials³⁻⁵ (pooled by the ERG) and the trial in elderly patients⁶ are given in *Table 1*.

The open-label studies, conducted in patients from a mixture of different trials, showed that satisfaction with treatment in patients remaining in the study remained constant over the first year of treatment. However, 60% of patients had dropped out at 1 year (17% insufficient response, 8% adverse events). The re-treatment study showed that treatment with prucalopride in patients remaining in the study was just as effective. However, only data for 4 mg prucalopride were presented in the submission and only data from patients who did not drop out between study periods were used for the analysis. The trial in patients with opioid-induced chronic constipation was not relevant to this submission so was not assessed by the ERG.

Summary of submitted cost-effectiveness evidence

A cost-effectiveness model included costs for only prucalopride and no alternative treatment costs were incorporated. The quoted costs per responder were based on 292 days' treatment (80% 'compliance') and estimated at £622 per adult patient and £402 per elderly patient per year on treatment. The base-case model predicted quality-adjusted life-year gains per responder of 0.0369 [standard deviation (SD) 0.0450] and 0.0342 (SD 0.1495) for adult and elderly patients, respectively, giving ICERs of £16,800 and £11,700, respectively.

TABLE 1 Pooled results for pivotal trials^{a-5} and results for the trial in elderly patients⁶

	Prucalopride	Placebo
Proportion of patients with mean of three or more SCBMs/week: % (n/N)		
Pivotal trials ^a	23.8 (151/635)	11.4 (73/640)
Elderly ^b	39.5 (30/76)	20.0 (14/70)
Proportion of patients with average increase of one or more SCBMs/week: % (n/N)		
Pivotal trials	43.2 (264/612)	24.6 (155/630)
Elderly	61.1 (44/72)	33.8 (22/65)
Average number of SCBM/week: mean (mean change from baseline)		
Pivotal trials	1.9 (1.5)	1.2 (0.7)
Elderly	2.7 (1.9)	1.7 (0.6)
Overall PAC-SYM symptoms score: mean (mean change from baseline)		
Pivotal trials	1.33 (-0.69)	1.57 (-0.42)
Elderly	0.88 (-0.53)	1.22 (-0.23)
Overall PAC-QOL score: mean (mean change from baseline)		
Pivotal trials	1.33 (-0.77)	1.68 (-0.44)
Elderly	0.95 (-0.53)	1.26 (-0.20)
SF-36 score: mean (mean change from baseline)		
Pivotal trials	48.2 (2.5)	47.5 (1.9)
Elderly	Not measured	Not measured

PAC-QOL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms; SCBM, spontaneous complete bowel movement; SF-36, Short Form questionnaire-36 items.

a Pivotal trials: > 18 years old, 12-week data, 2 mg of prucalopride.

b Elderly patient trial: > 65 years old, 4-week data, 1 mg of prucalopride.

Commentary on the robustness of submitted evidence

The submitted evidence was not considered to be robust and many factors remained unclear even after requests for clarification. There was poor transparency around the submission and the modelling process. The main specific areas for concern were:

1. The trials on which data for this submission were based were not conducted in patients with chronic constipation that was refractory to laxatives. This was evidenced in a number of ways:
 - i. Around 17.0% of patients in pivotal trials had found their previous treatment adequate.
 - ii. Bisacodyl, a laxative, was used as a rescue medication in the trials and, on average, it induced one or more bowel movements per week in study participants.
 - iii. Baseline EQ-5D scores (higher score, less severe) for adult (18–65 years) and elderly (≥65 years) patient data (*Figure 1*) suggest that these were not homogeneous patient groups and that many patients were not representative of the severe cases for whom prucalopride is licensed.

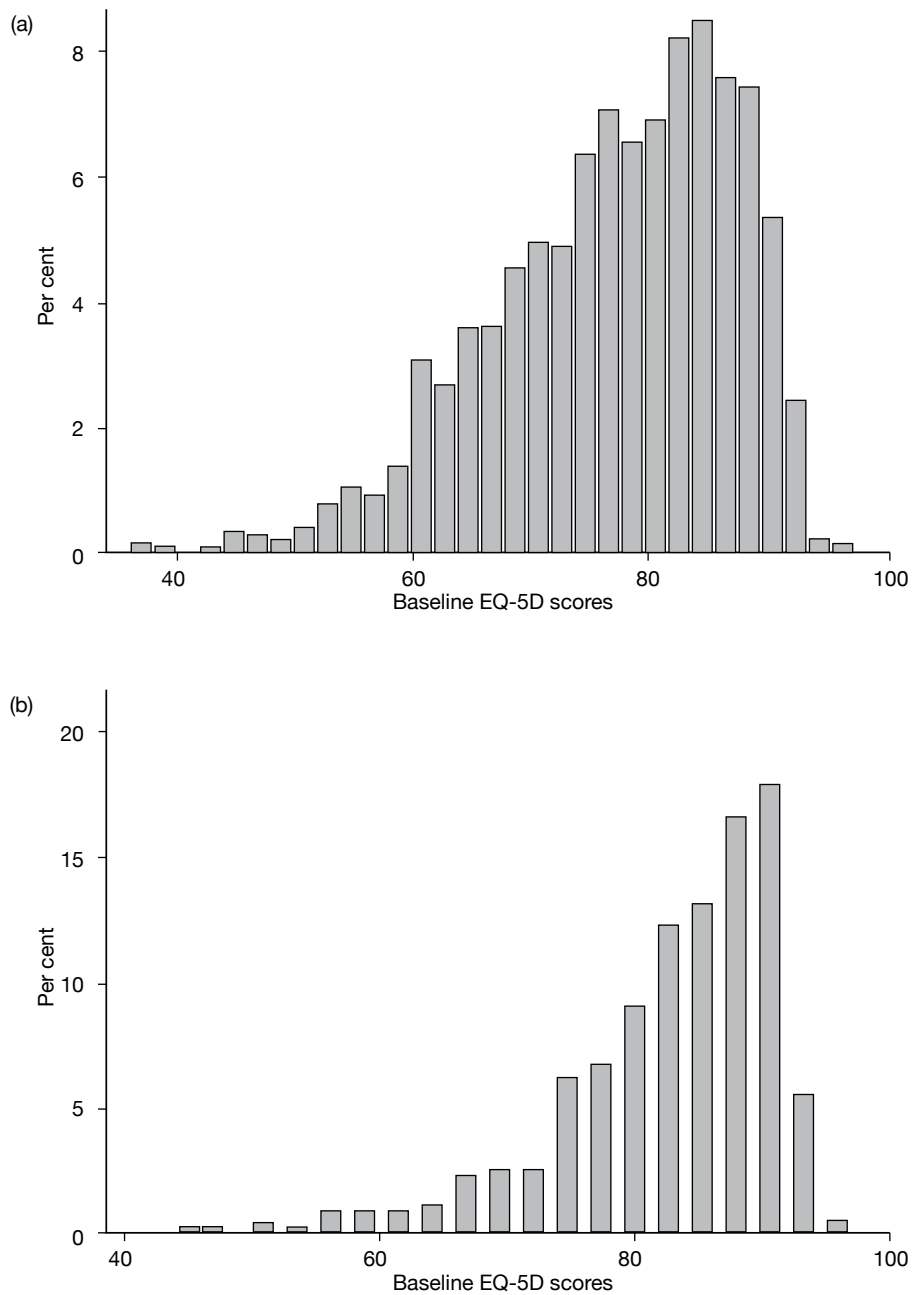


FIGURE 1 Baseline EQ-5D scores for (a) adult (18–64 years) and (b) elderly (≥ 65 years) patient data used in the economic model.

2. The extrapolation of data from PAC-QOL and PAC-SYM trial surveys to EQ-5Q data used in the economic model was unclear.
3. The model assumption that the relative advantage in quality of life in patients treated with prucalopride at the end of study follow-up (4 or 12 weeks) is maintained at 52 weeks is inappropriate owing to:
 - i. The high attrition in follow-up studies ($> 60\%$). Patients remaining in the trial were likely to have been those who were relatively more satisfied.
 - ii. Decreases in efficacy from the periods 1–4 weeks compared with 1–12 weeks in pivotal trials suggest that effectiveness was likely to decrease with time.

- iii. The lack of comparative data. If relative quality of life is to be compared, follow-up data in the placebo group would also be required.
 - iv. Patients in long-term follow-up trials included patients who were not refractory to laxatives, and patient groups were mixtures of adult/elderly patients and patients with opioid-induced constipation.
 - v. This assumption is not tested in the manufacturer's model. In order to test the effect of a reduction in quality-of-life gain over time, the ERG re-ran the model, considering a decrease in change in EQ-5D of 25%, 50% and 75% and the ICER was substantially increased.
4. There was no justification or explanation for the parameters used in the economic model. It was not possible to link the data that populated the model to the clinical trials. There was no way of discerning whether coefficients used in the model truly represented treatment effects.
 5. No costs, other than the cost of prucalopride, were incorporated into the economic model.
 6. In the model, the average use of prucalopride in responders has been assumed to be for 220 days per year but this assumption may not be justified. The ERG re-ran the model considering that all responders take treatment for the full year (365 days), and this made a substantial increase in the ICER.
 7. No specific allowance was made for withdrawal from treatment at any time after 4 weeks.
 8. Adverse events were not included in the model.

The population targeted in the scope of this technology appraisal is unlikely to be the same as that used to populate the economic model. Overall, it was felt that this submission provided no proper evidence on whether or not prucalopride is likely to be cost-effective compared with other treatment strategies in patients in the licensed indication.

Conclusions

Owing to the many areas of uncertainty, particularly the effectiveness of prucalopride in the licensed patient group and its long-term effectiveness and safety, it was considered that the MS provided no evidence for whether prucalopride is effective or not in women with laxative-refractory chronic constipation. Further subgroup analysis of the actual patient group of interest may have better guided decision-making. However, long-term efficacy data, with validated estimates of quality of life incorporated in a well-founded model, would be important for an evidence-based judgement to be made.

Summary of NICE guidance issued as a result of the STA

- 1.1 Prucalopride is recommended as an option for the treatment of chronic constipation only in women for whom treatment with at least two laxatives from different classes at the highest tolerated recommended doses for at least 6 months has failed to provide adequate relief and invasive treatment for constipation is being considered.
- 1.2 If treatment with prucalopride is not effective after 4 weeks, the patient should be re-examined and the benefit of continuing treatment reconsidered.
- 1.3 Prucalopride should only be prescribed by a clinician with experience of treating chronic constipation, who has supervised the woman's previous courses of laxative treatments specified in 1.

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Denosumab for the prevention of osteoporotic fractures in postmenopausal women

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

This paper presents a summary of the evidence review group (ERG) report into denosumab for the prevention of osteoporotic fractures in postmenopausal women. Denosumab has been shown in a large randomised trial to reduce the frequency of osteoporotic fractures when given subcutaneously at 6-monthly intervals. Compared with placebo, the relative risks of clinical vertebral and hip fractures were 0.32 and 0.60, respectively. Clinical vertebral fractures occurred

in 0.8% of women taking denosumab and 2.6% of control subjects. Hip fractures occurred in 1.2% of women on placebo and 0.7% on denosumab. The expected use is in women who cannot tolerate oral bisphosphonates. Other options in that situation include strontium ranelate and zoledronate, which, compared with placebo, also reduced the risk of clinical vertebral fractures [relative risk (RR) 0.65 and 0.23, respectively]. Zoledronate also significantly reduced the risk of hip fractures (RR 0.59). The ERG concluded that zoledronate was the main comparator. The relative cost-effectiveness of denosumab and zoledronate depends mainly on assumptions about costs of administration.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.¹ Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Denosumab for the prevention of osteoporotic fractures in postmenopausal women*.²

Description of the underlying health problem

Postmenopausal osteoporosis has been defined as '... a progressive, systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.'³

It is estimated that there are 180,000 osteoporosis-related symptomatic fractures each year in England and Wales.³ Of these, 70,000 are hip fractures that necessitate hospital admission and surgical treatment, and are associated with significant morbidity and mortality.³ In women over the age of 50 years, the lifetime risk of a hip fracture is one in five.³ A recent meta-analysis of all anti-osteoporosis drugs found that treatment reduces mortality.⁴

Scope of the evidence review group report

Bone is in a state of continuous breakdown and renewal. Breakdown is carried out by cells called osteoclasts and renewal by osteoblasts. The cytokine receptor activator of nuclear factor kappa-B (RANK)-ligand plays a pivotal role in mediating osteoclast activity. Denosumab is a human monoclonal antibody that inhibits RANK-ligand, thereby reducing osteoclast activity and hence bone breakdown.

Marketing authorisation for denosumab has been granted by the Committee for Medicinal Products for Human Use of the European Medicines Agency.⁵

The manufacturer's submission (MS) argued that denosumab was clinically effective and cost-effective in the prevention of osteoporotic fractures among postmenopausal women. The submission assumed that because of the low cost of oral bisphosphonates (OBPs), denosumab would be used in women who were unable to tolerate those drugs.

In a large trial against placebo [the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial⁶], denosumab was shown to reduce fracture risk. The MS included evidence from studies comparing denosumab with several comparator treatments with changes in bone mineral density (BMD) as the primary end point. However, given that fracture rates have been reported in trials of denosumab and comparator treatments, that evidence was preferred, and information relating to BMD was not considered by the ERG.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of denosumab presented in the MS to NICE.

Reviews of the clinical effectiveness of treatment for osteoporosis had been conducted⁷ to support the development of a NICE osteoporosis guideline.⁸ The manufacturer updated these by searching for studies published since these reviews. The ERG also conducted searches to identify if any relevant studies had been missed.

The control group in the FREEDOM trial⁶ was given placebo. The effectiveness of denosumab relative to other bone loss therapies was therefore estimated from an indirect comparison using trials of other drugs against placebo, using the adjusted indirect comparison method described by Bucher and colleagues.⁹ Although not ideal, this is the only approach that could be adopted in the absence of head-to-head trials.

The ERG explored the challenges associated with the adjusted indirect comparison method, and considered whether differences in the baseline characteristics of studies included in the indirect comparison (which could modify the relevant treatment effect) had been taken into account by the manufacturer.

The manufacturer used an economic model that took account of costs from short-term drug costs to long-term nursing home costs. The ERG evaluated the model against the 10-point checklist developed by Drummond and colleagues¹⁰ and the NICE reference case.¹¹ The ERG also sought opinion regarding assumptions made within the manufacturer's model, following which the model was re-run after making adjustments based on the views and information received.

The manufacturer had also conducted a systematic review of economic studies assessing the costs and/or cost-effectiveness of denosumab. The ERG undertook further searches to identify if any relevant studies had been missed.

Results

Summary of submitted clinical evidence

The main evidence submitted was the FREEDOM trial of denosumab against placebo,⁶ and an indirect comparison of denosumab against other drugs.

The FREEDOM trial⁶ was a large, good-quality trial involving women with postmenopausal osteoporosis. Denosumab given by subcutaneous injection at 6-monthly intervals for 3 years was effective in reducing fractures. The frequency of hip fractures was reduced by 40%, from 1.2% of women in the placebo group to 0.7% in the denosumab group. Clinical vertebral fractures were reduced by 69% from 2.6% in the placebo group to 0.8% in the denosumab group.

Safety data are available from 30 studies with 14,000 patients, of whom 11,000 are postmenopausal women. Based on these studies, denosumab appears safe. However, a US Food and Drug Administration summary of safety¹² noted that people receiving denosumab appeared to have a slightly increased risk of serious infections of the skin, ear, urinary tract and abdomen. They also noted a non-significant increase in cancer incidence, and theoretical concerns about denosumab suppressing dynamic bone formation leading to delayed fracture healing and atypical fracture.¹²

Persistence with osteoporosis treatment is known to be poor for many existing drugs, such as the OBPs.¹³⁻¹⁵ It is likely that the 6-monthly administration in a GP surgery or hospital clinic will encourage persistence with denosumab.

The MS stated that because of the availability of inexpensive generic OBPs '... denosumab is expected to be an appropriate option for diagnosed patients for whom oral BPs are unsuitable; reasons for unsuitability include inability to comply with the special instructions for administration, a contraindication or intolerance' (p. 15). The drugs used in the indirect comparison were therefore strontium, raloxifene, teriparatide, zoledronate and intravenous (i.v.) ibandronate.

The indirect comparison included a comparison of the relative risks (RRs) of fracture for each drug versus placebo, and an adjusted estimation of the RR of fracture for denosumab versus the other drugs. This demonstrated that denosumab, strontium ranelate and zoledronate provided statistically significant decreases in the risk of clinical vertebral fractures (RR 0.32, 0.65 and 0.23, respectively) compared with placebo, but raloxifene did not (RR 0.45, not significant). Denosumab and zoledronate reduced the risk of hip fractures compared with placebo (RR 0.61 and 0.59 respectively, both statistically significant) but strontium ranelate did not (RR 0.89, not significant). Data on the risk of wrist fractures relative to placebo were available for denosumab (RR 0.84) and strontium ranelate (RR 0.98), but in neither case was the difference statistically significant. No data on wrist fractures were available for zoledronate or raloxifene. The RRs obtained from the direct comparison of each drug with placebo were used to model cost-effectiveness.

Summary of submitted cost-effectiveness evidence

The manufacturer provided multiple comparisons of cost-effectiveness using a good-quality Markov model that took account of drug costs, administration and monitoring costs, costs associated with fractures, and long-term nursing home costs. Utility weights derived from a review of the literature were used to adjust time spent in fracture states, allowing quality-adjusted life-years (QALYs) to be estimated. The base-case analysis was conducted for 70-year-old women with a *T*-score of ≤ -2.5 and no prior fracture, and 70-year-old women with a *T*-score of ≤ -2.5 with a prior fragility fracture. Subgroup analyses based on *T*-score and independent clinical risk factors were also undertaken. The analysis complied with the NICE reference case.

The submission argued that denosumab:

- dominated strontium for both primary and secondary prevention, i.e. was both more effective and less costly
- was cost-effective compared with raloxifene, with costs per QALY of £9289 in primary prevention and around £2000 in secondary prevention
- could be cost-effective compared with no treatment in some subgroups of women without prior fracture, who might not be treated with a second drug if unable to tolerate OBPs, according to the current NICE guidance

- could be cost-effective versus no treatment in women with fragility fractures (£12,381 per QALY)
- dominated i.v. ibandronate
- was cost-effective compared with zoledronate with the incremental cost-effectiveness ratio (ICER) for zoledronate versus denosumab reported to be £70,000 per QALY in women with no prior fracture and £29,000 in women with a prior fracture.

However, a key assumption was that denosumab would be given in general practice at the average cost of two standard GP visits a year. This would make it less costly than zoledronate, which is given by i.v. infusion, in hospital clinics, once a year. Given the similar effectiveness of denosumab and zoledronate, the cost-effectiveness comparison depended largely on the relative costs. The ERG were of the opinion that GPs would be likely to regard administration of a new biological agent as not part of General Medical Services, and might expect it to be part of an enhanced service. The ERG also expected that denosumab would be initiated in secondary care, and that patients might also be followed up in secondary care.

Commentary on the robustness of submitted evidence

Strengths

The key trials considered were of good quality, had large numbers of recruits and were of adequate duration. The economic model was of high quality. The submission and appendices provided very detailed accounts of underlying assumptions and sensitivity analyses.

Weaknesses

The manufacturer submitted a very large amount of material, far exceeding the NICE guidance on length of submission. However, the ERG considered the evidence of effects of drugs on BMD to be not relevant, partly because of doubts about the value of BMD in assessing effects of most drugs in osteoporosis, but mainly because there were fracture data for all the drugs. Nor did the ERG consider the data on morphometric vertebral fractures to be useful, and it was noted that the manufacturer did not use such data in the modelling.

The MS argued that zoledronate and i.v. ibandronate should not be primary comparators because they were 'not standard care' and because they had not been appraised by NICE. However, despite not having been appraised by NICE, both have been licensed for some time and are in routine use in the UK.

In the ERG's opinion, the major weakness lay in the economic modelling of zoledronate versus denosumab. The ERG considered zoledronate to be a key comparator for denosumab, and the relative cost-effectiveness of these two drugs was sensitive to assumptions about relative costs of administering them.

If the cost of denosumab was increased, by assuming it would be delivered in secondary care, the ICER for denosumab compared with no treatment would rise to £36,185 per QALY in women with no prior fragility fracture, and to £15,720 per QALY in women with a prior fragility fracture. This change led to zoledronate dominating denosumab in women with and without a prior fragility fracture.

The ERG also re-ran the model, assuming equal efficacy of denosumab and zoledronate for the prevention of wrist fractures. This reduced the costs per QALY for zoledronate relative to denosumab by about £10,000 in primary prevention, and by about £5000 in secondary prevention.

The MS also examined the cost-effectiveness of denosumab in women who could not tolerate OBPs, but whose risk level meant that other drugs were not currently cost-effective, according to NICE Technology Appraisals (TAs) 160 and 161.^{3,16} The ERG considered these data and surmised that denosumab might be considered cost-effective in some of these women if the manufacturer's costing assumptions were to be accepted (assuming a cost-effectiveness threshold of £30,000 per QALY). This could provide a partial solution to the unsatisfactory situation in which clinicians could not offer an alternative treatment to women unable to tolerate OBPs until their clinical condition deteriorated.

Following advice from clinical experts, the NICE Appraisal Committee '...concluded that while treatment with denosumab may be started in secondary care, it would be subsequently delivered almost exclusively in primary care. The relatively small proportion of women with severe osteoporosis would continue to be followed-up in secondary care, in line with current UK clinical practice'.¹⁷

Conclusions

The clinical effectiveness of denosumab is not in doubt, and it appears safe. The key issue in the cost-effectiveness analysis is its cost relative to zoledronate. For women with no prior fragility fractures, its potential cost-effectiveness relative to no treatment in some groups is also highly relevant, as current NICE guidance³ recommends no treatment for many women in this group if they cannot tolerate OBPs.

Areas of uncertainty

The indirect comparison was necessary because of the lack of direct head-to-head trials. It appeared to be well done, but the ERG wondered if differences in baseline characteristics of the women in the trials (such as duration of follow-up, age, body mass index and proportion with previous fractures) would affect some comparisons.

Because of absence of data on the effect of zoledronate on wrist fractures, the Amgen modelling assumed that it would not reduce the incidence of those, whereas it was assumed that denosumab would, based on data from the FREEDOM trial.⁶ However, given the equivalence, or a non-significant slight superiority, of zoledronate to denosumab, the ERG considered it unlikely that zoledronate would have no effect on wrist fractures.

In the modelling, the reduction in breast cancer incidence from raloxifene treatment was not included. This was raised with the manufacturer, who stated that this was in line with the precedent set in NICE TAs 160³ and 161.¹⁷

In the indirect comparison, data from a trial of oral ibandronate were used, and assumed to apply to i.v. ibandronate. However, the DIVA (Dosing Intravenous Administration) trial¹⁸ of oral versus i.v. ibandronate showed that the i.v. form, given at 3-monthly intervals, was more effective, with fracture incidence of 4.8% in the i.v. groups versus 6.2% in the oral group. This difference was at 2 years' follow-up and was not statistically significant, but it could be used in a sensitivity analysis.

Two recent studies using data from British general practice have examined the risk of oesophageal cancer.^{19,20} The first, by Cardwell and colleagues,¹⁹ was a case-control study that started with OBP use, and compared oesophageal cancer rates in users versus age- and sex-matched control subjects who did not take OBPs. They found no increase in cancer risk

[RR 1.07, 95% confidence interval (CI) 0.77 to 1.49]. The second, by Green and colleagues,²⁰ started with cancer cases, and compared OBP use in cancer cases and non-cancer controls. Green and colleagues²⁰ concluded that the risk was increased in patients taking OBPs (RR 1.30, 95% CI 1.02 to 1.66). Therefore, the association between OBP use and oesophageal cancer is currently uncertain.

Summary of NICE guidance (from Final Appraisal Determination, as issued 15 September 2010)

1.1 Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures:

- who are unable to comply with the special instructions for the administration of OBPs, are intolerant of OBPs or for whom treatment with OBPs is contraindicated *and*
- who also have a combination of *T*-score, age and number of independent clinical risk factors for fracture (see section 1.3) as indicated in the following table.

T-scores (SD) at (or below) which denosumab is recommended when OBPs are unsuitable

Age (years)	No. of independent clinical risk factors for fracture		
	0	1	2
65–69	– ^a	–4.5	–4.0
70–74	–4.5	–4.0	–3.5
75 or older	–4.0	–4.0	–3.0

OBP, oral bisphosphonate; SD, standard deviation.

^a Treatment with denosumab is not recommended.

1.2 Denosumab is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for the administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.

1.3 For the purposes of this guidance, independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of four or more units per day, and rheumatoid arthritis.

1.4 People currently receiving denosumab for the primary or secondary prevention of osteoporotic fragility fractures who do not meet the criteria specified in recommendations 1.1 or 1.2 should have the option to continue treatment until they and their clinician consider it appropriate to stop.

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Ofatumumab for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a critique of the submission from GSK

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of ofatumumab for the treatment of refractory chronic lymphocytic leukaemia (CLL), based upon the manufacturer's submission (MS) to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The submitted clinical evidence included one study: a non-randomised, single-arm

study. Two other studies were identified but both were non-comparative and provided evidence for therapies other than ofatumumab. For this reason these studies were not discussed in full in the main body of the submission. In the Hx-CD20-406 study, the overall response rate was 58% (99% confidence interval 40% to 74%, $p < 0.001$). Complete resolution of constitutional symptoms and improved performance status occurred in 57% of patients. Median progression-free survival (PFS) and overall survival (OS) times were 5.7 and 13.7 months, respectively. The most common adverse events during treatment were infusion reactions and infections, which were primarily grade 1 or 2 events. The MS concluded that ofatumumab provides a new, effective and well-tolerated therapy for patients with CLL who are refractory to both fludarabine and alemtuzumab [double refractory (DR)]. The ERG undertook a critical appraisal of the submission. The ERG had a number of concerns regarding the manufacturer's estimates of effectiveness based on evidence from a single-arm, non-randomised study. An 'area-under-the-curve' or 'partitioned-survival' model was used to project expected clinical and economic outcomes for patients with DR CLL who were assumed to receive ofatumumab or best supportive care (BSC). The model had a three-state structure: 'alive pre-progression', 'alive post progression' and 'dead'. Overall, the modelling approach is reasonable given the limited evidence available for the drug in the patient population under review. However, a number of uncertainties were identified in the economic evaluation; for example, the BSC arm used data from patients in the Hx-CD20-406 study who did not respond to ofatumumab treatment – 'non-responders' – and the ofatumumab arm used data from all of those treated in the Hx-CD20-406 study. Further uncertainty arose regarding the choice of utilities, the omission of 17p and 11q chromosomal deletions as factors in the Cox proportional hazards models for PFS and OS, and the omission of the costs of drugs in progressive disease. It was felt that these factors biased cost-effectiveness in favour of ofatumumab. When revisions were made to the assumptions in the model based on the ERG's review of the published and submitted evidence, the revised base-case incremental cost-effectiveness ratio for ofatumumab increased to £81,500 per quality-adjusted life-year. The final appraisal determination was issued by NICE in September 2010 (www.nice.org.uk/nicemedia/live/12264/50758/50758.pdf).

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.¹ Typically, the process is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Ofatumumab for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a critique of the submission from GSK*.²

Description of the underlying health problem

Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells (lymphocytes). CLL causes abnormal lymphocytes to proliferate, which, in turn, causes anaemia and increased susceptibility to infection. CLL often remains undiagnosed either until it is well

advanced or until a chance test shows abnormally high levels of lymphocytes in the blood. It is a chronic and incurable disease. CLL is the most common form of leukaemia in the UK. In England, 1961 cases of CLL were diagnosed in 2004. In England and Wales, CLL caused 1019 deaths in 2007. It mainly affects older people, with 75% of diagnoses being made in people over the age of 60 years. Overall incidence is approximately three cases per 100,000 of the population per year. Twice as many men as women are affected. CLL is genetically heterogeneous, with median survival ranging from about 3 to 12 years depending on the genetic subtype and the stage at which the disease is diagnosed. Other prognostic factors include age at onset, spread of disease and response to treatment.²

In the UK, first-line medical management of CLL usually involves chemotherapy with fludarabine and cyclophosphamide, with or without the addition of rituximab, or, in some cases, chlorambucil is used. Refractory CLL is generally considered to be disease that has not responded adequately to treatment or that has relapsed within 6–12 months of an adequate response. Refractory CLL is associated with a poorer prognosis. People whose disease is refractory to first-line treatment with fludarabine combination therapies may be given alternative non-fludarabine therapies, such as cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) with or without rituximab, or may be given non-chemotherapy treatments, such as alemtuzumab or high-dose steroids. Some people with refractory disease will receive best supportive care (BSC). There is an ongoing appraisal of rituximab in combination with chemotherapy for relapsed or refractory CLL.²

Scope of the evidence review group report

The purpose of the ERG report was to comment on the validity of the manufacturer's submission (MS) on the technology of interest. The scope for this submission, and hence the scope for the ERG report, is shown in *Table 1*.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the MS to NICE as part of the STA process.

Specific steps undertaken by the ERG included:

- discussion of the nature of the problem with a clinical expert
- re-running searches indicated to have been performed to inform the MS
- extending searches
- formal critical appraisal of systematic review underpinning the MS, using the principles found in the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care^{2,3}
- checking and appraising the economic model submitted
- re-running the model to correct for potential problems as best as possible within the limited time available
- commenting on further analyses provided by the company immediately prior to the appraisal committee.

The work was carried out between 2 February 2010 and 1 April 2010.

Members of the ERG team attended and advised the meeting of the NICE appraisal committee at which this guidance was discussed on 5 May 2010.

TABLE 1 Submission scope²

Appraisal objective	To appraise the clinical effectiveness and cost-effectiveness of ofatumumab within its indication for the treatment of refractory CLL
Intervention(s)	Ofatumumab
Population(s)	Patients with refractory CLL whose disease has not responded adequately to: <ul style="list-style-type: none"> ■ fludarabine- and alemtuzumab-containing therapy ■ fludarabine-containing therapy and for whom alemtuzumab-containing therapy is inappropriate (owing to bulky disease)
Standard comparators	CHOP, with or without rituximab Rituximab in combination with chemotherapy (other than fludarabine-containing chemotherapy; subject to ongoing NICE appraisal) High-dose corticosteroids BSC
Outcomes	The outcome measures to be considered included: <ul style="list-style-type: none"> ■ PFS ■ Response rates ■ OS ■ AEs of treatment ■ Health-related quality of life
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY The time horizon should be long enough to reflect any differences in costs or outcomes between the technologies being compared Costs were considered from an NHS and Personal Social Services perspective
Other considerations	Guidance will be issued only in accordance with the marketing authorisation

AE, adverse effect; BSC, best supportive care; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CLL, chronic lymphocytic leukaemia; NICE, National Institute for Health and Clinical Excellence; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

Results

Summary of submitted clinical evidence

The submission from GlaxoSmithKline (GSK) included one study: a non-randomised, single-arm study (Hx-CD20-406) of ofatumumab. From a total of 138 patients, treatment effectiveness is taken from the 59 patients defined as 'double refractory' (DR; refractory to both fludarabine and alemtuzumab treatment). After week 28, disease status evaluation (physical examination, spleen and liver measurement, and blood samples) took place every 3 months until month 24.

Two other studies were identified, Tam *et al.*⁴ and Dunganwalla *et al.*,⁵ which were ruled out because they are non-comparative and provide evidence for therapies other than ofatumumab.

In the Hx-CD20-406 study the overall response rate (ORR) was 58% (99% confidence interval 40% to 74%, $p < 0.001$). Complete resolution of constitutional symptoms and improved performance status occurred in 57% of patients. Median progression-free survival (PFS) and overall survival (OS) times were 5.7 and 13.7 months, respectively.

The most common adverse events (AEs) during treatment were infusion reactions, which were primarily grade 1 or 2 events. The AE profile is consistent with that seen with other monoclonal antibody therapies.

Summary of submitted cost-effectiveness evidence

The manufacturer used a cohort-based 'area-under-the-curve' model to project expected clinical and economic outcomes for patients with DR CLL who received either ofatumumab or BSC. The model had three states: 'alive pre-progression', 'alive post progression' and 'dead'.

GlaxoSmithKline's base-case analysis produced an incremental cost-effectiveness ratio (ICER) of £38,241 per quality-adjusted life-year (QALY). When we updated GSK's model with what we thought were more appropriate assumptions of the utilities for PFS and progressive disease (PD), and included the 17p and 11q chromosomal deletions, the base-case ICER increased to at least £81,500 per QALY.

Commentary on the robustness of submitted evidence

Strengths

The review of effectiveness was generally systematic. The searches were appropriate and included all relevant studies.

The overall modelling approach is reasonable given the dearth of available clinical evidence for the drug in this population. There are no logical errors in the economic model.

Weaknesses

The most challenging aspect of the critique of the submitted evidence on clinical effectiveness is the impact of the chosen study design, which is essentially a case series in which all patients receive the drug of interest. However, the manufacturer uses this to produce comparative data by taking the responses of all of those in the study as the 'intervention' group, and using those patients who did not respond to ofatumumab in the single arm study as the 'control' group. This is an unusual approach to assessing effectiveness, which, although understandable given the target population and having some logical basis, still presents a major challenge of interpretation. There is clearly potential for additional bias relative to that which might be expected in a double-blind, randomised controlled trial comparing ofatumumab and BSC with BSC alone.

There was concern that the evidence was based on one non-randomised, single-arm study. Moreover, the outcome data reported are from a planned interim analysis (2008) with no recent data available. In this immature data set, median OS for the responder group had not yet been reached. Although the patient population is in line with the approved indication for ofatumumab, the patient population is small. This is because data from only the DR subgroup are presented in the submission ($n = 59$), of whom 14 are from the UK.

The AE profile is consistent with that seen with other monoclonal antibody therapies. However, using a single-arm study (Hx-CD20-406), there is no way of assessing the AE profile truly related to the intervention.

The outcomes considered were in line with the final scope; however, the impact on health-related quality of life was not measured.

In the economic evaluation, the BSC arm uses data from those patients in the Hx-CD20-406 study who did not respond to ofatumumab treatment – 'non-responders'. The ofatumumab arm of the model uses data from all of those treated in the Hx-CD20-406 study. It was felt that the following factors bias cost-effectiveness in favour of ofatumumab: GSK's choice of utilities (0.650 for PFS and 0.470 for PD, whereas we favoured 0.428 for PFS and 0.279 for PD); the omission of 17p and 11q chromosomal deletions as factors in their Cox proportional hazards models for PFS and OS; and the omission of the costs of drugs in PD.

Conclusions

Areas of uncertainty

Several areas of uncertainty were identified:

- The true effect of ofatumumab on ORR, PFS and OS is uncertain. Although it is not self-evident that modelling patients on BSC as non-responders in the single arm trial of ofatumumab will necessarily lead to an overestimate of the treatment effect, it is superficially tempting to conclude that this is the most likely impact of the bias.
- In the absence of a control arm, it is not known whether AEs experienced by the treated population are related to the condition or the treatment.
- It is difficult to determine the impact of ofatumumab on global quality of life as it has not been measured.
- The impact on the measured effect of outcomes, for example infection, which could be attributable to lack of response or to AEs of ofatumumab.

There was considerable uncertainty concerning the base-case ICER for the following reasons:

- The effectiveness of the ofatumumab and BSC treatment arms was not taken from a randomised trial. Instead, the effectiveness for BSC was taken from non-responders in the single-arm ofatumumab trial, which is methodologically very dubious. However, as the survival data for the non-responder group in the ofatumumab trial are very similar to those in the Tam *et al.* observational study,⁴ this offers some support for the use of this group as an appropriate proxy for the BSC arm.
- There was extensive extrapolation of OS, with approximately 40% of patients still alive at maximum follow-up.
- There was considerable uncertainty surrounding the methodology of the study from which the utilities are taken.⁶ This is important because cost-effectiveness is sensitive to the utilities. The valuation of health-state descriptions in the Ferguson *et al.* study⁶ uses the time trade-off method (which is appropriate), from a representative sample of the general public ($n = 60$). However, the health-state descriptions were taken from the literature, the clinical guidelines and specialist nurses/clinicians, but the NICE reference case^{1,7} explicitly states that health-state descriptions should come from patients. Further information on the health-state descriptions, particularly the domains covered, was not available.
- GlaxoSmithKline's probabilistic sensitivity analyses overestimate the extent of parameter uncertainty in cost-effectiveness because GSK have assumed that the two parameters of the Weibull distributions for PFS and separately for OS are independent, whereas they will be correlated to some extent.

Key issues

The key issues for consideration by the appraisal committee were thus suggested to be as follows:

- The use of a non-randomised, single-arm study makes it difficult to determine the nature and extent of the bias in the treatment effect of ofatumumab relative to BSC.
- It is difficult to determine the impact of ofatumumab on global quality of life, as it has not been measured.
- The impact on the measured effect of outcomes, for example infection, which could be attributable either to lack of response or to AEs of ofatumumab.

Summary of NICE guidance issued as a result of the STA

The final appraisal determination was issued by NICE in September 2010 and states:

1.1 Ofatumumab is not recommended for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab.

1.2 People currently receiving ofatumumab for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab should have the option to continue treatment until they and their clinician consider it appropriate to stop.

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Trabectedin for the treatment of relapsed ovarian cancer

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

The paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of trabectedin for the treatment of relapsed platinum-sensitive ovarian cancer, based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The submission addressed only part of the decision problem and did not provide evidence to compare trabectedin (Yondelis[®], PharmaMar) and pegylated liposomal doxorubicin hydrochloride (PLDH) (Caelyx[®], Schering-Plough) with key comparators. The submission's

direct comparison evidence came from one reasonable-quality randomised controlled trial (RCT) of trabectedin and PLDH versus PLDH alone (ET743-OVA-301). The results of the RCT were subdivided into the entire platinum-sensitive population (>6-month relapse after initial platinum-based chemotherapy) and partially platinum-sensitive (≥ 6 - to 12-month relapse) and fully platinum-sensitive (>12-month relapse) populations. The outcomes included were overall survival, progression-free survival measured by three types of assessor, response rates, adverse effects of treatment, health-related quality of life and cost per quality-adjusted-life-year (QALY) gained. A mixed treatment comparison (MTC) meta-analysis comparing trabectedin and PLDH with single-agent PLDH within the entire platinum-sensitive population, with paclitaxel or with topotecan also formed part of the submission. The RCT data showed that trabectedin plus PLDH compared with PLDH monotherapy had a significant effect on overall survival only within the partially platinum-sensitive subgroup. PFS results reported by the independent radiologists showed significant effects in favour of the trabectedin and PLDH arm for the entire and partially platinum-sensitive populations only. Rates of grade 3 and 4 adverse events were mostly higher in the trabectedin and PLDH arm than in the PLDH alone arm. There were several issues regarding the undertaking of the MTC, and thus the data were not considered robust. Furthermore, the ERG did not believe the MTC to be necessary to answer the decision problem. The manufacturer submitted a de novo cost-effectiveness model. The main analysis compared trabectedin in combination with PLDH versus paclitaxel, topotecan and PLDH (each as monotherapy) in the entire platinum-sensitive population, using results estimated from the MTC. Additional analyses were presented comparing trabectedin in combination with PLDH versus PLDH monotherapy using direct evidence from the OVA-301 trial for the fully, partially and entire platinum-sensitive populations. The cost per QALY gained for trabectedin in combination with PLDH versus PLDH monotherapy was estimated to be £70,076 in the main analysis. In the additional analyses, the cost per QALY gained for trabectedin in combination with PLDH versus PLDH monotherapy was £94,832, £43,996 and £31,092 for the entire, partially and fully platinum-sensitive populations, respectively. Additional work was undertaken by the ERG using patient-level data and amending some assumptions to provide a better statistical fit to the Kaplan–Meier data than the exponential distribution assumed by the manufacturer. The ERG base-case estimate of the cost per QALY of trabectedin in combination with PLDH ranged from £46,503 to £54,607 in the partially platinum-sensitive population. At the time of writing, trabectedin in combination with PLDH for the treatment of women with relapsed platinum-sensitive ovarian cancer is not recommended by NICE in the final appraisal determination.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.¹ Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Trabectedin for the treatment of relapsed ovarian cancer*.²

Description of the underlying health problem

Trabectedin (Yondelis[®], PharmaMar) in combination with pegylated liposomal doxorubicin hydrochloride (PLDH) (Caelyx[®], Schering-Plough) is licensed for patients with platinum-sensitive ovarian cancer (OC).³ OC is asymptomatic in the early stages, with diagnosis in $\geq 75\%$ cases made when OC is at an advanced stage (stage III/IV disease). Of women with OC, 80% will relapse and require second-line chemotherapy; the long-term prognosis is poor, with the UK 5-year survival rate reported as around 30%.⁴ The number of new cases of OC in 2010 was estimated as 5423, based on Cancer Research UK incidence rates.⁵ The estimated number of stage III/IV OC cases will be 4067; the number who will relapse will be 3253. Expert opinion^{2,6} suggests that, of those patients who relapse, 15–25% are platinum refractory (OC that does not respond to initial platinum-based chemotherapy). Of the remaining patients, expert opinion in the UK indicates that 20–25% are platinum resistant (i.e. relapse within <6 months), 25–30% (813–976 in 2010) are partially platinum sensitive (relapse within 6–12 months) and 50% (1626 in 2010) are fully platinum sensitive (relapse > 12 months after initial chemotherapy). In total, therefore, 75–80% of relapsing patients are potentially eligible for treatment: 2440–2602 patients in 2010.^{2,6}

Scope of the evidence review group report

The principal research question was to appraise the clinical effectiveness and cost-effectiveness of trabectedin in combination with PLDH within its licensed indication for the treatment of relapsed cases of platinum-sensitive OC. The comparator defined in the NICE scope was platinum-based chemotherapy (single agent or in combination) for the fully and partially platinum-sensitive populations. Additional comparators for the partially platinum-sensitive population were single-agent PLDH, paclitaxel or topotecan. Relevant clinical outcomes were overall survival (OS), progression-free survival (PFS) and overall response rate, with the last two outcomes being measured by three types of assessor – independent radiologists, independent oncologists and an investigator – and adverse effects of treatment. Health-related quality-of-life outcomes were measured by subscales from two cancer-specific quality-of-life instruments [European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EORTC QLQ-QV28], and the EQ-5D (European Quality of Life-5 Dimensions). Cost per quality-adjusted life-year (QALY) gained was the relevant outcome for the cost-effective analysis.

The manufacturer submitted a cost-effectiveness model developed in Microsoft[®] EXCEL (Microsoft Corporation, Redmond, WA, USA). The main analysis compared trabectedin in combination with PLDH versus paclitaxel, topotecan and PLDH (each as monotherapy) in the entire platinum-sensitive population only (>6-month relapse) using results estimated from a mixed treatment comparison (MTC). Additional analyses were presented by the manufacturer comparing trabectedin in combination with PLDH versus PLDH as monotherapy using direct evidence from the ET743-OVA-301 trial⁷ for the fully, partially and entire platinum-sensitive populations. The model used a lifetime horizon and the main outcome was the cost per QALY gained.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The review of the clinical evidence included repeating the searches undertaken by the manufacturer. The ERG does not believe that any relevant clinical effectiveness or

cost-effectiveness studies have been missed. The ERG critiqued the economic model supplied. In addition, the ERG made changes to the model structure and data used to form an ERG base-case cost per QALY.

Results

Summary of submitted clinical evidence

The main evidence in the manufacturer's submission (MS)⁶ is derived from one phase III randomised controlled trial (RCT) comparing the efficacy and safety of a combination of 1.1 mg/m² trabectedin and 30 mg/m² PLDH with 50 mg/m² PLDH.⁷ Table 1 presents the OS and PFS data for the trial. The largest and only significant effect on OS was seen within the partially platinum-sensitive subgroup, for which the median OS for the trabectedin plus PLDH arm was 23.0 months compared with 17.1 months for patients treated with PLDH alone.

The MS presented PFS results from the independent radiologists' assessment. Within the partially platinum-sensitive subgroup, there was a significant effect on PFS where the median PFS for the trabectedin and PLDH arm was 7.4 months compared with 5.5 months for PLDH alone [hazard ratio 0.65 (95% confidence interval 0.45 to 0.92); $p=0.0152$]. Significant effects were also seen in the entire platinum-sensitive population but not in the fully platinum-sensitive population.

Progression-free survival results from assessments by the independent oncologists and the investigator are available in the ERG report.²

Discontinuation of treatment owing to adverse events and most grade 3 and 4 adverse events were higher in the trabectedin and PLDH combination arm than in the PLDH monotherapy. The

TABLE 1 Summary of OS and PFS from the OVA-301 trial

	Numbers included in analysis	Median OS (months)	HR (95% CI, p -value)	Numbers included in analysis	Median PFS by independent radiologists' assessment ^a (months)	HR (95% CI, p -value)
Population > 6 months						
Trabectedin + PLDH	218	27	0.82 (0.630 to 1.060), $p=0.1259$	215	9.2	0.73 (0.56 to 0.95), $p=0.0170$
PLDH	212	24.3		202	7.5	
Population > 12 months						
Trabectedin + PLDH	95	Not reached	0.887 (0.584 to 1.348), $p=0.5746$	93	11.1	0.70 (0.47 to 1.03), $p=0.0707$
PLDH	122	31.7		117	8.9	
Population 6–12 months						
Trabectedin + PLDH	123	23.0	0.59 (0.420 to 0.820), $p=0.0015$	122	7.4	0.65 (0.45 to 0.92), $p=0.0152$
PLDH	91	17.1		86	5.5	
Population < 6 months						
Trabectedin + PLDH	119	14.2	0.901 (0.675 to 1.203), $p=0.4806$	113	4.0	0.95 (0.70 to 1.30), $p=0.7540$
PLDH	123	12.4		115	3.7	

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride.
 a PFS by independent oncologists and the investigator are available in the ERG report.²

main adverse events were neutropenia, febrile neutropenia, thrombocytopenia, anaemia, elevated aminotransaminase levels, fatigue, fever, diarrhoea, nausea and vomiting.

The MS also presented the results of an MTC to allow a coherent comparison of trabectedin and PLDH with PLDH, paclitaxel and topotecan (each as monotherapy). This was undertaken for the entire platinum-sensitive population only, and based on an MTC that had previously been performed as part of a NICE Multiple Technology Assessment (TA) – NICE TA91.⁴

Summary of submitted cost-effectiveness evidence

The model structure was derived from a previously published NICE Multiple TA (TA91⁴), and the effectiveness was modelled using the mean survival time derived from the median survival time, using an assumption that data were exponentially distributed. Utilities were extracted from the OVA-301 trial,⁷ and costs were assessed from an NHS perspective. In the main analysis, the manufacturer reported that paclitaxel provided the least number of QALYs, followed by topotecan, PLDH as monotherapy and trabectedin in combination with PLDH. The incremental cost-effectiveness ratio (ICER) for trabectedin in combination with PLDH versus PLDH as monotherapy was estimated to be £70,076 per QALY gained.

The manufacturer also presented the ICERs for the three direct comparisons for the entire, partially and fully platinum-sensitive populations. The ICERs between trabectedin in combination with PLDH versus PLDH as monotherapy, using the independent radiologists' assessment, were £94,832, £43,996 and £31,092 by population, respectively. Results using the independent oncologists' assessment and the investigator's assessment are available in the clarification letter provided by the manufacturer.⁸

Uncertainties were examined in univariate sensitivity analyses only for the main analysis, whereas probabilistic sensitivity analyses (PSA) were undertaken for each scenario.

Commentary on the robustness of submitted evidence

Limited data were available and the MS addressed only one part of the final scope issued by NICE, i.e. trabectedin and PLDH versus PLDH alone for the partially platinum-sensitive population. The remainder of the final scope issued by NICE was not addressed within the MS, i.e. trabectedin and PLDH versus platinum-based chemotherapy (single agent or in combination) in the fully or partially platinum-sensitive populations, and trabectedin and PLDH versus paclitaxel or topotecan monotherapy in the partially platinum-sensitive population.

The main evidence in the MS is derived from one phase III RCT that is of reasonable methodological quality and measured a range of outcomes that were appropriate and clinically relevant. The included RCT is not an absolute reflection of the population with advanced relapsed OC in the UK, hence its external validity may be questionable. There appeared to be a high degree of censoring within the PFS analysis; reasons for censoring a large number of trial participants ($n = 178$) were not made explicitly clear within the MS. PFS analysis was also based on the independent radiologists' assessment. Clinical advice sought by the ERG suggested that the independent oncologists' assessment of PFS was more appropriate. OS results presented in the MS are based on an interim analysis.

The ERG did not believe that the MTC was necessary to answer the scope set by NICE. This is because PLDH had previously been estimated to be the most clinically effective and cost-effective treatment within the platinum-sensitive population when compared with paclitaxel or topotecan monotherapy,⁴ and clinical advice sought by the ERG indicated that in instances whereby PLDH monotherapy is contraindicated, a trabectedin and PLDH combination would also be contraindicated. Therefore, the relative cost-effectiveness of trabectedin and PLDH compared

with paclitaxel or topotecan monotherapy is not needed, as there would never be a choice between these interventions. As such, a direct comparison of trabectedin and PLDH was deemed sufficient to address the decision problem.

The ERG requested individual patient data from the manufacturer. From these it was shown that the PFS and OS data were not exponentially distributed, and the ERG conducted analyses using alternative distributions. Secondly, the use of the average number of cycles of treatment across all the populations included in the trials for the main analysis only (i.e. platinum-sensitive and platinum-resistant individuals) is likely to have biased the cost-effectiveness estimate. Thirdly, there was uncertainty regarding the estimates of the mean dose per cycle. Fourthly, the ERG was concerned about the absence of discounting for costs and an incorrect approach used to discount health outcomes. Finally, there were problems concerning the implementation of the PSA, which limit its interpretation. This notably included the lack of variation for some main parameters, the choice of distribution and assumptions used.

Additional work was undertaken by the ERG only for the partially platinum-sensitive population. This included fitting more appropriate distributions for PFS and OS using individual patient-level data and estimating the mean dose per cycle from the mean number of cycles and mean cumulative dose from the trial, discounting costs and health outcomes using a conventional methodology, and amending the PSA. Assuming a Weibull or Gompertz distribution for both OS and PFS, and using the independent oncologists' assessment, the ERG estimated that the ICER of trabectedin in combination with PLDH when compared with PLDH as monotherapy would range from £46,503 to £54,607, respectively, in the partially platinum-sensitive population. The ICER reported by the manufacturer was £39,262 using the independent oncologists' assessment.

Conclusions

The MS contained only one phase III RCT, which may not be an absolute reflection of the population with advanced relapsed OC in the UK, and had some trial design limitations, such as the open-label design and a high degree of censoring. This RCT showed a significant increase in OS for the trabectedin and PLDH arm in the partially platinum-sensitive population compared with PLDH monotherapy. Non-significant improvements in OS were seen in the fully and entire platinum-sensitive populations. However, clinical evidence is based on only one RCT. In addition, the MS answered only part of the final scope issued by NICE, and so the clinical effectiveness of trabectedin and PLDH versus the key comparator, platinum-based chemotherapy (single agent or combination), is unknown.

The cost-effectiveness estimates presented in the MS are limited owing to the assumptions used and limitations of the submitted cost-effectiveness model. Additional work was undertaken by the ERG to provide an alternative estimate of the cost-effectiveness of trabectedin in combination with PLDH versus PLDH as monotherapy in the partially platinum-sensitive population. Despite the additional work, uncertainties still exist, as no comparison between platinum-based chemotherapy (single agent or in combination) and trabectedin was provided.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance issued by NICE in the final appraisal determination in March 2011 states that:⁹

- Trabectedin in combination with pegylated liposomal doxorubicin hydrochloride (PLDH) is not recommended for the treatment of women with relapsed platinum-sensitive ovarian cancer.
- Women with relapsed platinum-sensitive ovarian cancer currently receiving trabectedin plus PLDH should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

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Liraglutide for the treatment of type 2 diabetes

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of liraglutide in the treatment of type 2 diabetes mellitus, based upon the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The manufacturer proposed the use of liraglutide as a second or third drug in patients with type 2 diabetes whose glycaemic control was unsatisfactory with metformin, with or without a second oral glucose-lowering drug. The submission included six manufacturer-sponsored trials that compared the efficacy of liraglutide against other glucose-lowering agents. Not all of the trials were relevant

to the decision problem. The most relevant were Liraglutide Effects and Actions in Diabetes 5 (LEAD-5) (liraglutide used as part of triple therapy and compared against insulin glargine) and LEAD-6 [liraglutide in triple therapy compared against another glucagon-like peptide-1 agonist, exenatide]. Five of the six trials were published in full and one was then unpublished. Two doses of liraglutide, 1.2 and 1.8 mg, were used in some trials, but in the two comparisons in triple therapy, against glargine and exenatide, only the 1.8-mg dose was used. Liraglutide in both doses was found to be clinically effective in lowering blood glucose concentration [glycated haemoglobin (HbA_{1c})], reducing weight (unlike other glucose-lowering agents, such as sulphonylureas, glitazones and insulins, which cause weight gain) and also reducing systolic blood pressure (SBP). Hypoglycaemia was uncommon. The ERG carried out meta-analyses comparing the 1.2- and 1.8-mg doses of liraglutide, which suggested that there was no difference in control of diabetes, and only a slight difference in weight loss, insufficient to justify the extra cost. The cost-effectiveness analysis was carried out using the Center for Outcomes Research model. The health benefit was reported as quality-adjusted life-years (QALYs). The manufacturer estimated the cost-effectiveness to be £15,130 per QALY for liraglutide 1.8 mg compared with glargine, £10,054 per QALY for liraglutide 1.8 mg compared with exenatide, £10,465 per QALY for liraglutide 1.8 mg compared with sitagliptin, and £9851 per QALY for liraglutide 1.2 mg compared with sitagliptin. The ERG conducted additional sensitivity analyses and concluded that the factors that carried most weight were:

- in the comparison with glargine, the direct utility effects of body mass index (BMI) changes and SBP, with some additional contribution from HbA_{1c}
- in the comparison with exenatide, HbA_{1c}, with some additional effects from cholesterol and triglycerides
- in the comparison with sitagliptin, HbA_{1c} and direct utility effects of BMI changes.

The European Medicines Agency has approved liraglutide in dual therapy with other oral glucose-lowering agents. NICE guidance recommends the use of liraglutide 1.2 mg in triple therapy when glycaemic control remains or becomes inadequate with a combination of two oral glucose-lowering drugs. The use of liraglutide 1.2 mg in a dual therapy is indicated only in patients who are intolerant of, or have contraindications to, three oral glucose-lowering drugs. The use of liraglutide 1.8 mg was not approved by NICE. The ERG recommends research into the (currently unlicensed) use of liraglutide in combination with long-acting insulin.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.¹ Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Liraglutide for the treatment of type 2 diabetes*.²

Description of the underlying health problem

Type 2 diabetes mellitus is one of the most common chronic metabolic disorders found in both England and Wales. In England, it is estimated that > 2.1 million people have diabetes mellitus and the majority, i.e. about 90% of them, have type 2 diabetes.³

Type 2 diabetes is treated first with lifestyle measures aiming at weight loss and increased physical activity, but most patients will need drug treatment as well, partly because most do not achieve sufficient weight loss. However, type 2 diabetes is a progressive disease because of loss over time of beta-cell capacity and falling insulin production. Standard therapy in the UK is to add metformin as first drug when lifestyle measures fail, and then to add a sulphonylurea. When dual therapy fails, triple therapy with insulin or a glitazone is next.⁴ However, many patients fail to achieve good control on insulin, and weight gain is a common unwanted side effect.

Scope of the decision problem

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. Naturally occurring GLP-1 is released by the small intestine in response to food, and has a number of actions, including stimulating insulin release, inhibiting glucagon release, delaying gastric emptying and promoting a feeling of satiety. Liraglutide is taken once daily and has a plasma half-life of approximately 13 hours (compared with that of native GLP-1, 1.5–2.1 minutes).⁵ Liraglutide (Victoza[®], Novo Nordisk) received marketing authorisation by the European Medicines Agency on 30 June 2009. It was subsequently launched in the UK on 6 July 2009. Liraglutide is licensed for treatment of adults with type 2 diabetes mellitus in combination with (1) metformin or a sulphonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea or (2) metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

The Novo Nordisk submission provided data on the clinical effectiveness of liraglutide as a second- and third-line drug for type 2 diabetes, taken from a suite of trials known as the LEAD (Liraglutide Effects and Actions in Diabetes) trials. Two doses are available in the UK: 1.2 or 1.8 mg once daily. The trials compared liraglutide with glargine and exenatide in triple therapy, and with sitagliptin, rosiglitazone and glimepiride in dual therapy.

The annual costs are £954.84 for the 1.2-mg dose and £1432.26 for the 1.8-mg dose.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE. The ERG review was also informed by a Cochrane review⁶ of the GLP-1 agonists being undertaken by the Diabetes and Health Technology Assessment group at the University of Aberdeen.

The ERG ran searches to identify studies that compared safety and efficacy of liraglutide with other drugs. To compare data and also to resolve some discrepancies, the ERG used the submission, the published papers and the full clinical trial reports of some trials (LEAD-5,⁷ LEAD-6⁸ and Pratley and colleagues⁹) provided by the manufacturer.

The Novo Nordisk submission used the Center for Outcomes Research (CORE) model for economic analysis. Although this model is not one of the standard software packages defined by NICE, it was agreed by NICE and the ERG that it would be acceptable because the complexity of

economic modelling in diabetes made it sensible to use an existing and tried-and-tested model rather than develop a new one.

The ERG carried out additional sensitivity analyses using the CORE model.

Results

Summary of submitted clinical evidence

Of the six clinical trials^{8–12} included in the submission report, five were published in full and one was then unpublished.⁹ All were sponsored by the manufacturer. The main evidence was from the LEAD phase III randomised controlled trials. All trials were multicentred and had glycated haemoglobin (HbA_{1c}) level as the primary outcome. Secondary outcomes measured included percentage of patients reaching HbA_{1c} level of 7%, percentage of patients reaching HbA_{1c} level of <6.5%, changes in body weight, body mass index (BMI), fasting plasma glucose (FPG), systolic blood pressure (SBP) and lipids, and numbers of patients experiencing adverse events, such as hypoglycaemia and nausea. Patients aged 18–80 years were included and all trials had a duration of 26 weeks.

All studies analysed data for the intention-to-treat population for subjects who were exposed to at least one dose of the drug and had one postbaseline measurement of the parameter. Each end point was analysed using an analysis of covariance model with treatment, pretreatment and country as fixed effects and baseline as a covariate. Missing data were imputed as last observation carried forward.

One of the recommendations in the NICE guideline is that GLP-1 agonists should be used as a triple therapy only in people whose control is unsatisfactory on a combination of two oral agents, usually metformin and a sulphonylurea. Some people would be unable to tolerate these and might take a glitazone or a gliptin instead. Therefore, on the basis of this guideline, not all LEAD trials were relevant. Therefore, the ERG paid most attention to the studies that compared liraglutide in triple therapy, but studies that used liraglutide in dual therapy were reviewed in case NICE decided to approve it for such use.

The two trials that were most relevant were LEAD-5,⁷ in which liraglutide 1.8 mg was compared with the long-acting insulin glargine (in combination with metformin and glimepiride), and LEAD-6,⁸ in which liraglutide 1.8 mg was compared with another GLP-1 agonist, exenatide. Approximately 63% of patients in both arms were on metformin plus a sulphonylurea, with 27.5% on metformin only and ~9.5% on sulphonylurea only.⁸

In LEAD-5,⁷ liraglutide 1.8 mg daily reduced HbA_{1c} level by 0.24% ($p=0.0015$) more than glargine 24 units/day. Liraglutide also resulted in statistically significant reductions in weight (3.4 kg) and SBP (4.51 mmHg) compared to glargine, but no difference in FPG. The ERG wondered if the dose of glargine had been sufficiently titrated, being only 24 units a day at study end.

In LEAD-6,⁸ liraglutide reduced HbA_{1c} level by 0.33% ($p<0.0001$) more than exenatide twice daily. FPG was reduced by 1.01 mmol/l ($p<0.0001$) in favour of liraglutide, but weight and SBP showed no significant difference. There was less nausea with liraglutide.

Three trials^{9–11} examined liraglutide in dual therapy. LEAD-1¹⁰ compared liraglutide 1.2 and 1.8 mg with rosiglitazone 4 mg daily, added to existing sulphonylurea in both arms. Liraglutide showed a significant improvement in HbA_{1c} level, but no difference in weight and SBP.

LEAD-2¹¹ investigated patients who were inadequately controlled on metformin alone, and compared liraglutide 1.2 and 1.8 mg daily with glimepiride (a sulphonylurea) as the second drug. There was no difference in HbA_{1c} level between the drugs, but liraglutide showed a favourable difference in weight of 3.7 kg and SBP of 3.2 mmHg compared with glimepiride.

Pratley and colleagues⁹ compared the efficacy and safety of liraglutide 1.2 or 1.8 mg once daily with sitagliptin 100 mg once daily. All groups continued on metformin therapy. Compared with sitagliptin, liraglutide 1.2 mg showed a reduction in HbA_{1c} level of 0.34%, a reduction in weight of 1.9 kg and an increase in SBP of 0.39 mmHg.

Because of the significant cost difference between the two doses of liraglutide, the ERG compared the relative benefits between the two in the meta-analyses shown in *Figures 1–4*. Data used in the meta-analyses come from a fully published paper.^{9–12} There were no significant differences in changes in HbA_{1c}, in proportions achieving HbA_{1c} level or in SBP. There was a statistically significant difference in weight, of 0.48 kg, where the clinical significance is doubtful.

As the trials were of short duration, there was a lack of data on the long-term safety of liraglutide. Concerns have been raised about the risk of pancreatitis with GLP-1 agonists.

The ERG concluded that liraglutide was effective in lowering blood glucose, while avoiding weight gain and hypoglycaemia, and was a useful addition to the therapeutic options available for type 2 diabetes.

Summary of submitted cost-effectiveness evidence

The manufacturer based cost-effectiveness analysis on data from LEAD-5⁷ (liraglutide 1.8 mg vs glargine), LEAD-6⁸ (liraglutide 1.8 mg vs glargine) and a trial by Pratley and colleagues⁹ (liraglutide 1.2 and 1.8 mg vs sitagliptin). The ERG re-ran the base cases in the CORE model, using the manufacturer's assumptions, and the results matched with those reported in the submission. The measure of health benefits was quality-adjusted life-years (QALYs). The manufacturer estimated the incremental cost-effectiveness ratios to be £15,130 per QALY for liraglutide 1.8 mg compared with glargine, £10,054 per QALY for liraglutide 1.8 mg compared with exenatide, £10,465 per QALY for liraglutide 1.8 mg compared with sitagliptin and £9851 per QALY for liraglutide 1.2 mg compared with sitagliptin. It was also reported that liraglutide was more cost-effective for patients with higher BMI; however, the cost-effectiveness for patients with lower BMI was not reported.

The ERG conducted additional sensitivity analyses and concluded that the factors that carried most weight were:

- in the comparison with glargine, the direct utility effects of BMI changes and SBP, with some additional contribution from HbA_{1c}
- in the comparison with exenatide, HbA_{1c}, with some additional effects from cholesterol and triglycerides
- in the comparison with sitagliptin, HbA_{1c} and direct utility effects of BMI changes.

Because the trials were of short duration, the costs and outcomes in the CORE model had to be modelled far beyond the duration of the trials.

Commentary on the robustness of submitted evidence

The manufacturer gives an accurate description of type 2 diabetes and of the current treatments available, correctly noting that existing treatments are not wholly satisfactory and that patients often suffer from adverse events, such as hypoglycaemia and weight gain. However, the

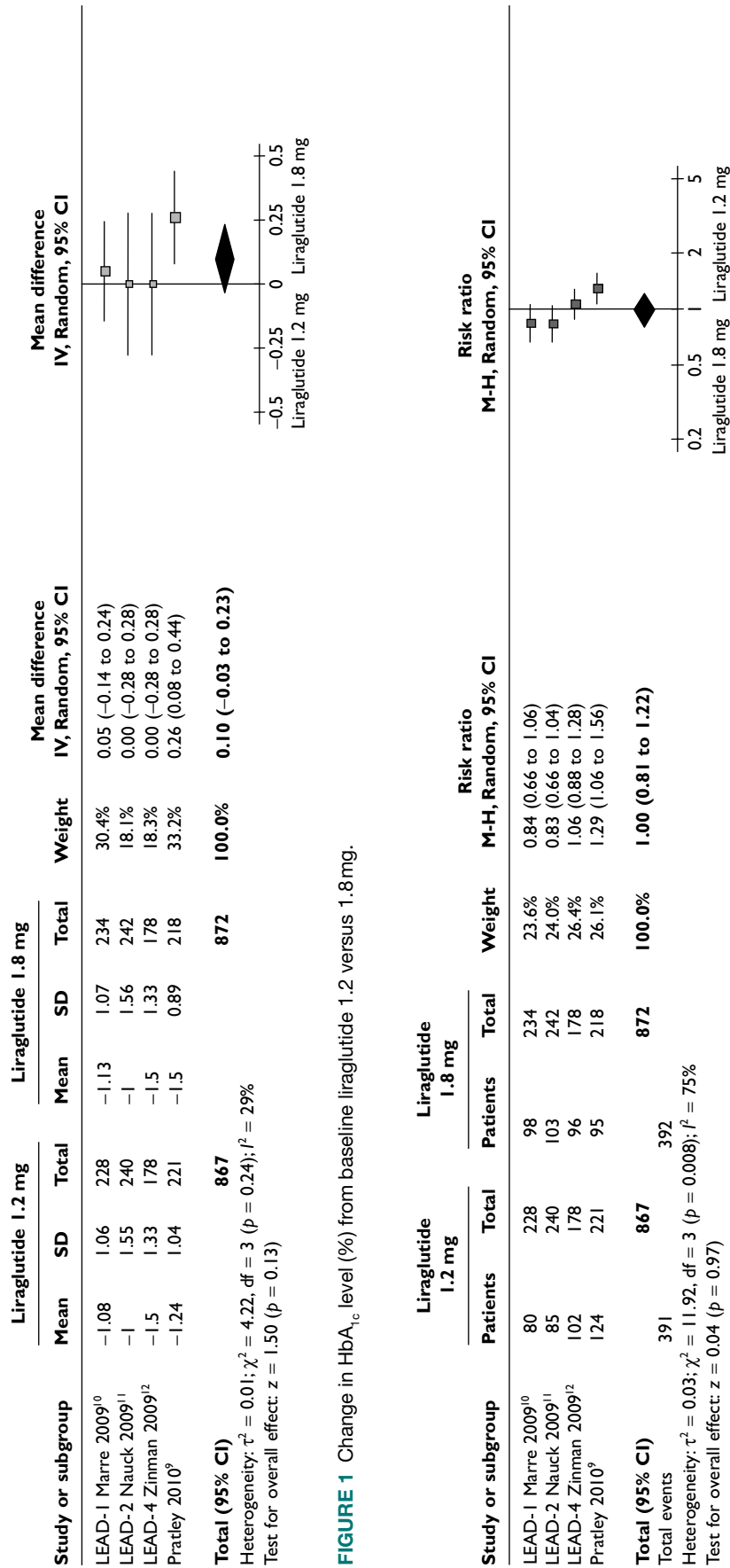


FIGURE 1 Change in HbA_{1c} level (%) from baseline liraglutide 1.2 versus 1.8 mg.

FIGURE 2 Patients reaching HbA_{1c} level of <7% liraglutide 1.2 versus 1.8 mg.

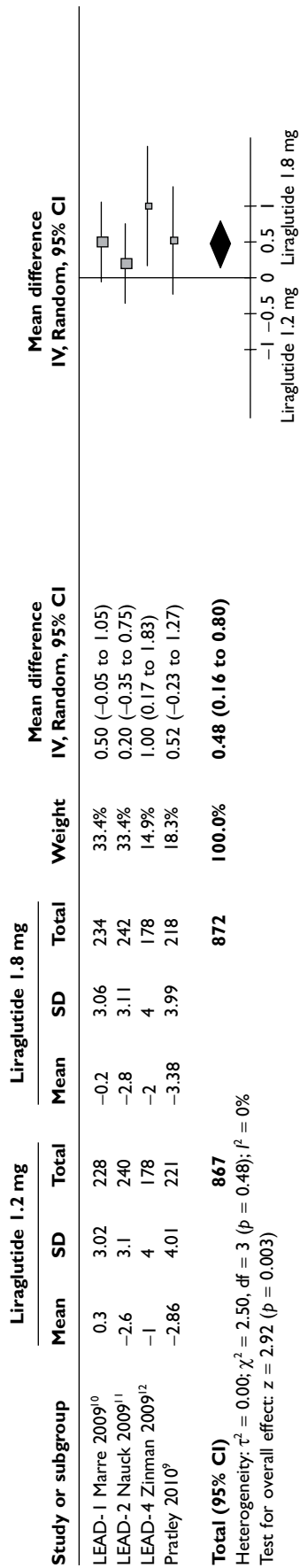


FIGURE 3 Change in weight (kg) from baseline liraglutide 1.2 versus 1.8 mg.

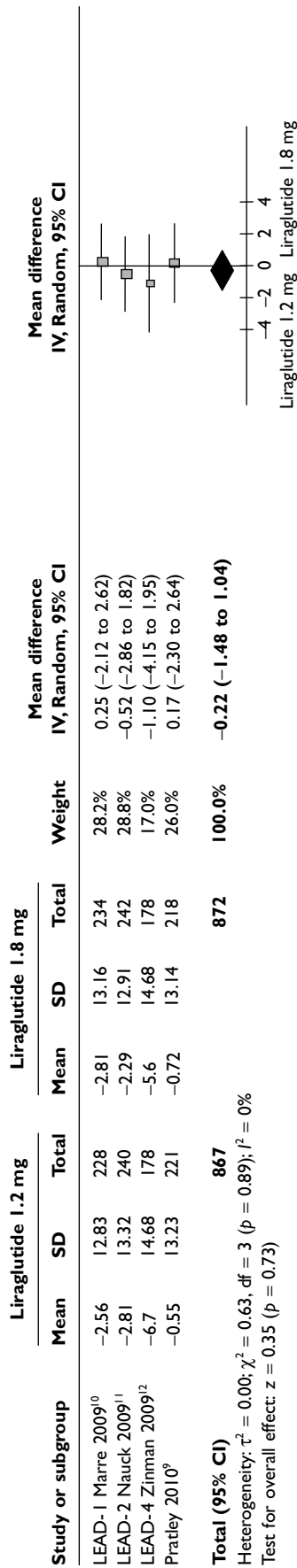


FIGURE 4 Change in SBP (mmHg) from baseline liraglutide 1.2 versus 1.8 mg.

manufacturer did not report the findings of a trial that compared insulin against an intensive lifestyle intervention in patients poorly controlled by combination oral glucose-lowering agents. Aas and colleagues¹³ reported that intensive life modification was better than starting insulin. However, the findings of Aas and colleagues¹³ were not confirmed in the TULIP (Testing the Usefulness of gLargine when Initiated Promptly) study.¹⁴ The latter,¹⁴ sponsored by the manufacturer of glargine, reported that adding glargine early in the conventional treatment with oral glucose-lowering drugs and lifestyle interventions resulted in better glycaemic control than intensifying lifestyle interventions.

The LEAD studies are of good quality. The trials were conducted in multiple settings in multiple countries, therefore increasing the generalisability of the results, though only a few patients were from the UK.

NICE recommends neutral protamine Hagedorn (NPH) as the first-choice basal insulin in type 2 diabetes, and none of the liraglutide trials provides a comparison with NPH. This might be justified on the grounds that glargine is now the most commonly used long-acting insulin,¹⁵ but NPH is considerably cheaper. The advantages of glargine over NPH in type 2 diabetes are slight.¹⁶

One weakness was the short durations of the trials. We do not have data on how long the GLP-1 agonists will be effective for in this progressive disease. The ERG and the manufacturer assumed a mean duration of use of 5 years.

Conclusions

The Novo Nordisk submission was considered to be of good quality. All of the relevant studies were included. Evidence from the trials shows that liraglutide is a useful addition to options for treating type 2 diabetes, being effective in reducing blood glucose while avoiding hypoglycaemia and weight gain. The ERG did not think the marginal benefits of the 1.8-mg dose over the 1.2-mg dose justified the much higher cost. Data are required on long-term safety of the drug, as are trials against other options in triple therapy. The ERG noted that trials were under way on use in combination with long-acting insulin, a use that seems logical but which is not currently licensed.

Summary of NICE final guidance issued as a result of the STA

1.1 Liraglutide 1.2 mg daily in triple-therapy regimens (in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione) is recommended as an option for the treatment of people with type 2 diabetes, only if used as described for exenatide in *Type 2 diabetes: The Management of Type 2 diabetes* (NICE clinical guideline 87), that is, when control of blood glucose remains or becomes inadequate ($\text{HbA}_{1c} \geq 7.5\%$, or other higher level agreed with the individual), and the person has:

- a BMI of $\geq 35 \text{ kg/m}^2$, is of European descent (with appropriate adjustment for other ethnic groups) and has specific psychological or medical problems associated with high body weight, or
- a BMI of $< 35 \text{ kg/m}^2$, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

1.2 Treatment with liraglutide 1.2 mg daily in a triple-therapy regimen should only be continued as described for exenatide in *Type 2 Diabetes: The Management of Type 2 Diabetes* (NICE clinical guideline 87), that is, if a beneficial metabolic response has been shown (defined as a reduction

of at least 1 percentage point in HbA_{1c} and a weight loss of at least 3% of initial body weight at 6 months).

1.3 Liraglutide 1.2 mg daily in dual-therapy regimens (in combination with metformin or a sulphonylurea) is recommended as an option for the treatment of people with type 2 diabetes, only if:

- the person is intolerant of either metformin *or* a sulphonylurea, or treatment with metformin *or* a sulphonylurea is contraindicated, *and* the person is intolerant of thiazolidinediones *and* dipeptidyl peptidase-4 (DPP-4) inhibitors, or treatment with thiazolidinediones *and* DPP-4 inhibitors is contraindicated.

1.4 Treatment with liraglutide 1.2 mg daily in a dual-therapy regimen should only be continued if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA_{1c} at 6 months).

1.5 Liraglutide 1.8 mg daily is not recommended for the treatment of people with type 2 diabetes.

1.6 People with type 2 diabetes currently receiving liraglutide who do not meet the criteria specified in section 1.1 or 1.3, or who are receiving liraglutide 1.8 mg, should have the option to continue their current treatment until they and their clinicians consider it appropriate to stop.

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Golimumab for the treatment of psoriatic arthritis

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Declared competing interests of authors: MS has a financial interest in a consulting company that has undertaken work for Abbott, Schering-Plough and Wyeth, but not relating to psoriatic arthritis, and he has not personally participated in this consultancy work. He has personally undertaken paid consultancy for some of the comparator manufacturers, again not relating to psoriatic arthritis.

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The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

This paper presents a summary of the evidence review group (ERG) report into the use of golimumab for the treatment of psoriatic arthritis (PsA). The main clinical effectiveness data were derived from a single phase III randomised controlled trial (RCT: GO-REVEAL) that

compared golimumab with placebo for treating patients with active and progressive PsA who were symptomatic despite the use of previous disease-modifying antirheumatic drugs or non-steroidal anti-inflammatory drugs. The 14-week data showed that, compared with placebo, golimumab 50 mg significantly improved joint disease response as measured by American College of Rheumatology (ACR) 20 [relative risk (RR) 5.73, 95% confidence interval (CI) 3.24 to 10.56] and Psoriatic Arthritis Response Criteria (PsARC) (RR 3.45, 95% CI 2.49 to 4.87), and skin disease response as measured by the Psoriasis Area and Severity Index (PASI) 75 (RR 15.95, 95% CI 4.62 to 59.11). The 24-week absolute data showed that these treatment benefits were maintained. There was a significant improvement in patients' functional status as measured by the Health Assessment Questionnaire (HAQ) change from baseline at 24 weeks (-0.33 , $p < 0.001$). The open-label extension data showed that these beneficial effects were also maintained at 52 and 104 weeks. However, PASI 50 and PASI 90 at 14 weeks, and all of the PASI outcomes at 24 weeks, were not performed on the basis of intention-to-treat analysis. Furthermore, analyses of the 24-week data were less robust, failing to adjust for treatment contamination due to patient crossover at week 16. The manufacturer conducted a mixed treatment comparison (MTC) analysis. The ERG considered the assumption of exchangeability between the trials for the purpose of the MTC analysis to be acceptable, and the statistical approach in the MTC analysis to be reliable. Regarding the safety evaluation of golimumab, the manufacturer failed to provide longer-term data or to consider adverse event data of golimumab from controlled studies in other conditions, such as rheumatoid arthritis and ankylosing spondylitis. Although the adverse effect profile of golimumab appears similar to other anti-tumour necrosis factor (TNF) agents, the longer-term safety profile of golimumab remains uncertain. The manufacturer's submission presented a decision model to compare etanercept, infliximab, golimumab and adalimumab versus palliative care for patients with PsA. In the base-case model, 73% of the cohort of patients were assumed to have significant psoriasis ($> 3\%$ of body surface area). Estimates of the effectiveness of anti-TNF agents in terms of PsARC, HAQ change and PASI change were obtained from an MTC analysis of RCT data. The manufacturer failed to calculate incremental cost-effectiveness ratios (ICERs) correctly by comparing golimumab with palliative care instead of the most cost-effective alternative (etanercept). Despite the manufacturer's claim that golimumab is a cost-effective treatment option, the manufacturer's own model showed that golimumab is not cost-effective compared with other biologics when the ICERs are correctly calculated. None of the sensitivity analyses carried out by the manufacturer or the ERG regarding uncertainty in the estimates of clinical effectiveness, the acquisition and administration cost of drugs, the cost of treating psoriasis and the utility functions estimated to generate health outcomes changed this conclusion. However, a key area in determining the cost-effectiveness of anti-TNF agents is whether they should be treated as a class. If all anti-TNF agents are considered equally effective then etanercept, adalimumab and golimumab have very nearly equal costs and equal quality-adjusted life-years (QALYs), and all have an ICER of about £15,000 per QALY versus palliative care, whereas infliximab with a higher acquisition cost is dominated by the other biologics.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant

evidence lies with one manufacturer or sponsor (Schering-Plough). Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology.¹ In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute. This paper presents a summary of the ERG report for the STA entitled *Golimumab for the treatment of psoriatic arthritis*.²

Description of the underlying health problem

Psoriatic arthritis (PsA) is defined as a unique inflammatory arthritis affecting the joints and connective tissue and is associated with psoriasis of the skin or nails.³ The prevalence of psoriasis in the general population has been estimated at between 2% and 3%,³ and the prevalence of inflammatory arthritis in patients with psoriasis has been estimated to be up to 30%.⁴ PsA affects males and females equally. The figures for the UK have estimated the adjusted prevalence of PsA in the primary care setting to be 0.3%.⁵ Severe PsA with progressive joint lesions can be found in at least 20% of patients with psoriasis.⁶

The current UK treatment for PsA aims to improve psoriasis, arthritis or both. Non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) are widely used to relieve symptoms, slow disease progression and prevent disability. For active and progressive patients with PsA, who have responded inadequately to at least two DMARDs, NICE clinical guideline 199 recommends three licensed anti-tumour necrosis factor (TNF) agents (etanercept, infliximab and adalimumab) as standard biological therapies.⁷

Scope of the evidence review group report

The scope specified by NICE was the use of golimumab (Simponi[®], Merck & Co.) for the treatment of active and progressive PsA that has responded inadequately to previous DMARDs. Golimumab is licensed for the treatment of active and progressive PsA.⁸ The NICE scope specified the following comparators to be of interest: (1) alternative TNF- α inhibitors and (2) conventional management strategies for active and progressive PsA that has responded inadequately to previous DMARD therapy excluding TNF- α inhibitors.

The outcome measures considered were pain and other symptoms, functional capacity, effect on concomitant skin condition, joint damage, disease progression (e.g. imaging), adverse effects of treatment, and health-related quality of life (HRQoL). The outcome of economic evaluation was incremental cost per quality-adjusted life-year (QALY) gained.

Methods

The ERG report comprised a critical review of evidence for clinical evidence and cost-effectiveness of the technology based upon the manufacturer's submission (MS) to NICE as part of the STA process. The ERG appraised the literature searches and carried out a search for ongoing trials. The systematic review methodology was appraised. The ERG also performed quality assessment of included trials using the Centre for Reviews and Dissemination guidelines for the critical appraisal of randomised controlled trials (RCTs).

The manufacturer's model was checked for any discrepancies and the results were validated. A series of sensitivity analyses was also conducted. A critical appraisal of the submission was conducted with the aid of a checklist⁹ to assess the quality of economic evaluations and a narrative review to highlight key assumptions and possible limitations.

Results

Summary of submitted clinical evidence

The main clinical effectiveness data were derived from a single phase III RCT (GO-REVEAL^{10,11}) that compared golimumab with placebo for treating active and progressive patients with PsA who were symptomatic despite the use of current or previous DMARDs or NSAIDs. The 14-week data (Table 1) showed that, compared with placebo, golimumab 50 mg significantly improved joint disease response as measured by ACR 20 [relative risk (RR) 5.73, 95% confidence interval (CI) 3.24 to 10.56] and the Psoriatic Arthritis Response Criteria (PsARC) (RR 3.45, 95% CI 2.49 to 4.87), and skin disease response as measured by the Psoriasis Area and Severity Index (PASI) 75 (RR 15.95, 95% CI 4.62 to 59.11). The 24-week absolute data showed that these treatment benefits were maintained (see Table 1). There was a statistically significant improvement in patients' functional status as measured by the Health Assessment Questionnaire (HAQ) change from baseline at 24 weeks (-0.33 , $p < 0.001$), thereby achieving the minimum clinically significant threshold for PsA (-0.3).¹² Golimumab 100 mg significantly achieved a similar magnitude of treatment effects at 14 and 24 weeks. The open-label extension data showed that these beneficial effects were also maintained at 52 and 104 weeks.

TABLE 1 Efficacy data of golimumab in the GO-REVEAL trial^{10,11}

Duration	Outcomes	Golimumab (n, %)		Placebo (n, %)	Golimumab (RR or mean difference, 95% CI)	
		50 mg	100 mg		50 mg	100 mg
14 weeks	PsARC	107/146 (73.3)	105/146 (71.9)	24/113 (21.2)	3.451 (2.49 to 4.87)	3.386 (2.43 to 4.80)
	ACR 20	74/146 (50.7)	66/146 (45.2)	10/113 (8.8)	5.727 (3.24 to 10.56)	5.108 (2.86 to 9.48)
	ACR 50	44/146 (30.1)	41/146 (28.1)	2/113 (1.8)	17.027 (4.81 to 63.32)	15.866 (4.47 to 59.11)
	ACR 70	18/146 (12.3)	25/146 (17.1)	1/113 (0.9)	13.932 (2.46 to 81.82)	19.349 (3.48 to 112.44)
	HAQ change from baseline, mean (SD)	NA	NA	NA	–	–
	PASI 50 ^a	63/106 (59.4)	83/107 (77.6)	7/73 (9.6)	6.198 (3.22 to 12.7)	8.089 (4.38 to 16.04)
	PASI 75 ^a	44/109 (40.4)	63/108 (58.3)	2/79 (2.5)	15.945 (4.62 to 59.11)	23.042 (6.85 to 84.59)
	PASI 90 ^a	22/106 (20.8)	26/107 (24.3)	0/73 (0.0)	∞ (4.21 to ∞)	∞ (4.95 to ∞)
24 weeks	PsARC	102/146 (69.9)	124/146 (84.9)	33/113 (29.2)	2.392 (1.81 to 3.20)	2.908 (2.28 to 3.68)
	ACR 20	76/146 (52.1)	89/146 (61.0)	14/113 (12.4)	4.202 (2.60 to 7.03)	4.920 (3.09 to 8.13)
	ACR 50	47/146 (32.2)	55/146 (37.7)	4/113 (3.5)	9.094 (3.62 to 23.94)	10.642 (4.27 to 27.85)
	ACR 70	27/146 (18.5)	31/146 (21.2)	1/113 (0.9)	20.897 (3.77 to 121.19)	23.993 (4.35 to 138.68)
	HAQ change from baseline, mean (SD)	0.33 ± 0.55, $p < 0.001$	0.39 ± 0.50, $p < 0.001$	−0.01 ± 0.49	–	–
	PASI 50 ^a	77/102 (75.5)	87/106 (82.1)	6/73 (8.2)	9.185 (4.69 to 19.45)	9.986 (5.21 to 20.76)
	PASI 75 ^a	57/102 (55.9)	70/106 (66.0)	1/73 (1.4)	40.794 (7.86 to 232.88)	48.208 (9.44 to 274.39)
	PASI 90 ^a	33/102 (32.4)	34/106 (32.1)	0/73 (0.0)	∞ (6.65 to ∞)	∞ (6.59 to ∞)

BSA, body surface area; CI, confidence interval; HAQ, Health Assessment Questionnaire; NA, not available; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; RR, relative risk; SD, standard deviation.

a Reported for patients with at least 3% BSA psoriasis.

In the absence of head-to-head comparisons of the relative efficacy between different anti-TNF agents, the manufacturer conducted a mixed treatment comparison (MTC) analysis to estimate the relative efficacy of the four relevant anti-TNF agents: golimumab, etanercept, adalimumab and infliximab. The results of MTC analyses in the MS were marked as confidential and therefore cannot be reported. *Table 2* presents the ERG's recalculated results of the MTC analyses based on the data provided in the MS. These results are generally similar to the results of MTC analyses from the MS. The results (see *Table 2*) show that infliximab appears to be the most effective of the four anti-TNF agents, being associated with the highest probabilities of response in terms of joint and skin disease outcomes. Golimumab achieves the second highest PsARC response (joint disease), and golimumab has the third highest response for skin disease in terms of PASI change from baseline. In those patients who achieved a PsARC response, the highest mean improvement in the functional status (HAQ) is seen with infliximab (−0.659), and the lowest mean improvement in HAQ is seen with golimumab (−0.440). For all four of the anti-TNF agents, the changes in HAQ for those patients who did not achieve a PsARC response are below the minimum clinically significant threshold (−0.3).¹² The credible intervals of most outcomes for all four anti-TNF agents overlap each other.

Short-term radiographic data from the GO-REVEAL trial^{10,11} indicated that golimumab 50 mg significantly slowed joint disease progression during the 24 weeks. There was a lack of follow-up radiographic data to determine whether these effects persisted in the longer term.

The limited available evidence for the safety evaluation from the single GO-REVEAL trial^{10,11} suggested that the most frequently reported adverse events associated with golimumab therapy were infections and infestations, upper respiratory tract infection and nasopharyngitis. Serious adverse events including serious infection and malignancy were rare. No active tuberculosis in any treatment arm was observed.

Summary of submitted cost-effectiveness evidence

The MS included a decision model to compare etanercept, infliximab, golimumab and adalimumab versus palliative care for patients with PsA. In the base-case model, 73% of the cohort of patients were assumed to have significant psoriasis (> 3% body surface area). Estimates of the effectiveness of anti-TNF agents in terms of PsARC, HAQ change and PASI change were obtained from an MTC analysis of RCT data.

TABLE 2 Results of MTC analyses from the ERG's evidence synthesis

Outcomes		Placebo	Infliximab	Etanercept	Adalimumab	Golimumab
PsARC response	Mean (SD)	0.247 (0.036)	0.793 (0.057)	0.712 (0.070)	0.585 (0.070)	0.764 (0.065)
	95% CrI	0.175 to 0.318	0.001 to 0.799	0.562 to 0.832	0.441 to 0.716	0.622 to 0.871
HAQ change from baseline, in PsARC responders	Mean (SD)	−0.2663 (0.044)	−0.659 (0.709)	−0.635 (0.091)	−0.4818 (0.065)	−0.4404 (0.085)
	95% CrI	−0.3555 to −0.1816	−1.026 to −0.286	−0.8144 to −0.4563	−0.6053 to −0.3488	−0.6088 to −0.2756
HAQ change from baseline, in PsARC non-responders	Mean (SD)	0	−0.1981 (0.073)	−0.1949 (0.099)	−0.136 (0.068)	−0.0308 (0.088)
	95% CrI	0	−0.3382 to 0.056	−0.3917 to 0.00023	−0.2684 to 0.0017	−0.2608 to 0.1418
PASI change from baseline, in patients ≥3% BSA psoriasis at baseline	Mean (SD)	–	−7.2168	−2.5044	−5.17769	−4.486
	95% CrI					

BSA, body surface area; CrI, credible interval; HAQ, Health Assessment Questionnaire; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; SD, standard deviation.

Patients in the model were assumed to continue with biologic therapy after 12 weeks if they achieved a PsARC response (Figure 1). HRQoL and costs were estimated as a function of HAQ and PASI score. The acquisition costs of anti-TNF agents (other than golimumab) were taken from the *British National Formulary*.¹³ The acquisition, administration and monitoring costs of golimumab were stated by the manufacturer to be equivalent to the list price of adalimumab. The unit price for golimumab is £774.58 for a 0.5-ml pre-filled pen/syringe containing 50 mg of golimumab. The annual drug acquisition cost is £9294.96.

The original MS base-case model was revised following requests for clarifications from the ERG. The revised MS model amended the functional form of the utility algorithm linking HAQ and PASI to HRQoL. The revised model also assumed that infliximab was administered without vial sharing.

The revised decision model found that the incremental cost-effectiveness ratio (ICER) of golimumab versus palliative care was just under £20,000 per QALY. However, the comparison with palliative care does not meet the NICE requirement for an incremental cost-effectiveness analysis to be conducted, in which each strategy should be compared with the next best alternative.

Commentary on the robustness of submitted evidence Strengths of the manufacturer's submission

The manufacturer's systematic review identified the single double-blind phase III RCT (GO-REVEAL^{10,11}) that was conducted in a relevant population, and the dosing regimen

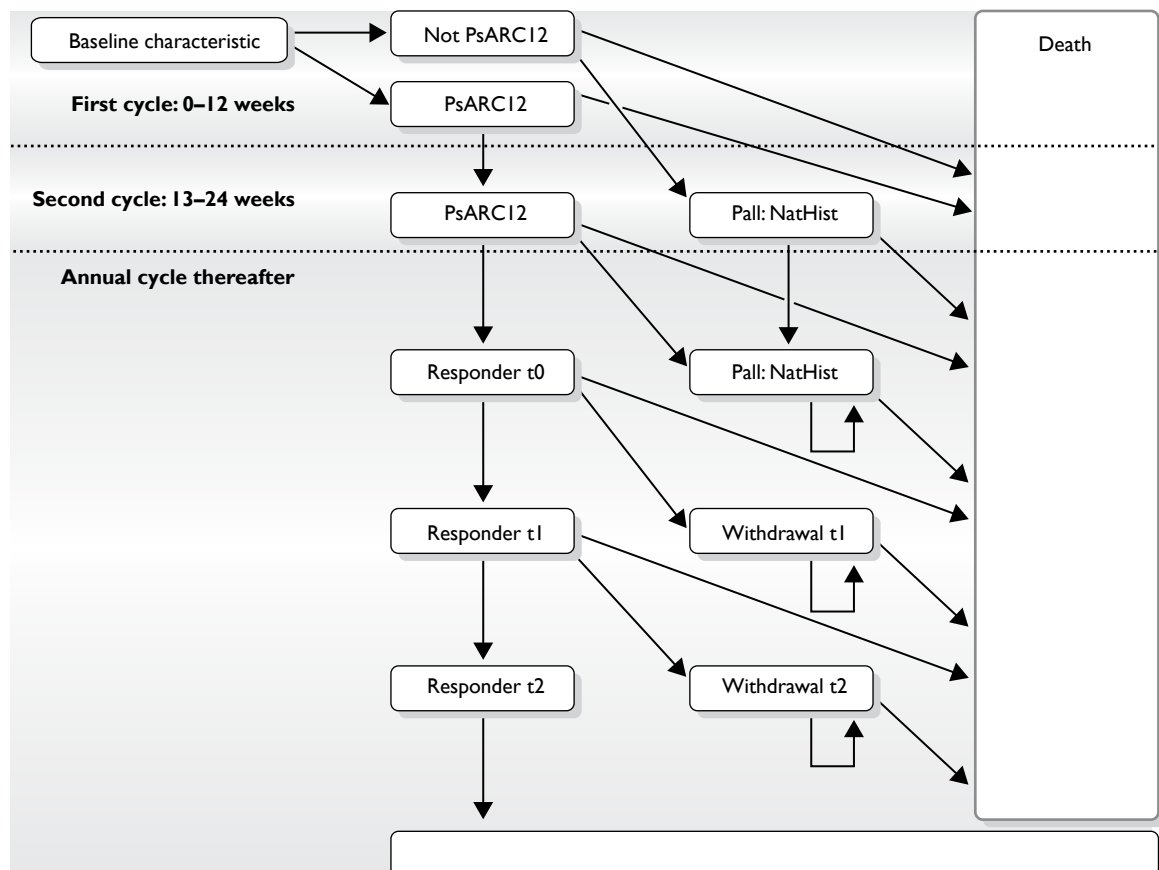


FIGURE 1 Model structure. NatHist, natural history; Pall, palliative care.

(including dose adjustment) for the golimumab 50 mg group was generally reflective of clinical practice. The results from the 14-week data analyses of this trial were considered to be robust.

The degree of clinical heterogeneity between the included trials in the MTC was considered reasonable, and the assumption of exchangeability between the trials for the purpose of the MTC analysis was acceptable. The ERG also considered the statistical approach in the manufacturer's MTC analysis to be reliable.

For the economic evaluation, the manufacturer's model took account of all important elements of the decision problem, in terms of the rules for continuation of biological therapy, natural history of arthritis and psoriasis in these patients, the treatment effects, the relationship between psoriasis, arthritis and HRQoL, and its associated costs.

Weaknesses of the manufacturer's submission

The manufacturer did not adequately apply the intention-to-treat approach for all outcomes in the efficacy analysis in the MS. Based on the revised data table provided by the manufacturer, PASI 50 and PASI 90 at 14 weeks and all the PASI outcomes at 24 weeks were also not performed on the basis of intention-to-treat analysis. Such analyses may have potentially compromised the internal validity of the results in terms of these skin disease outcomes.

There was further concern about the robustness for the analyses on the 24-week data in the GO-REVEAL trial,^{10,11} which failed to adjust the treatment contamination due to patients crossing over at week 16. This may have threatened the internal validity of trial results for all the efficacy and safety outcomes at 24 weeks.

In terms of safety evaluation, the manufacturer did not present data to facilitate a comparison between the adverse events of golimumab with those of the comparator anti-TNF agents. The longer-term follow-up safety data (e.g. at 52 and 104 weeks) from the GO-REVEAL trial^{10,11} were not available. Furthermore, the manufacturer failed to consider adverse event data of golimumab from controlled studies in other conditions, such as rheumatoid arthritis and ankylosing spondylitis.

Regarding the cost-effectiveness analysis, there was some concern about the robustness of the estimates of the cost associated with psoriasis. This was based on a survey of 22 dermatologists. The manufacturer stated that, based on the results from survey, the cost per PASI point was £53 per year if phototherapy is excluded and £167 per PASI point per year if phototherapy is included as a treatment for psoriasis. This implies that reducing PASI from, for example, 9.9 to 3.3 (a reduction of 6.6 points estimated for infliximab) would reduce the expected cost of treating psoriasis by £1100 per year if phototherapy was used and by £350 per year if phototherapy was not used. However, the MS provided insufficient detail of these calculations for the ERG to check whether or not these estimated costs were valid. No estimates of variability or sampling uncertainty were provided. The manufacturer provided raw data from the survey of dermatologists on request for clarification, but these data did not show the unit costs or details of how the results of the survey were synthesised to generate the mean cost per PASI point.

The MS did not correctly calculate the ICERs used to compare the cost-effectiveness of the treatments. The MS did not exclude extendedly dominated alternatives. The ERG recalculated the ICERs using the results of the MS model. The corrected ICER from the MS model for etanercept versus palliative care is about £17,000 per QALY. According to the MS model, with the ICERs correctly calculated, other anti-TNF agents (golimumab, adalimumab and infliximab) are not cost-effective because they are either dominated or extendedly dominated by etanercept.

Areas of uncertainty

While MTC analyses provide evidence of the relative efficacy of these anti-TNF agents, those findings may be considered more uncertain than would be provided in head-to-head RCTs. In particular, there were substantial uncertainties for the estimates of PASI change from baseline owing to a small sample size of patients evaluable for psoriasis.

No trial specified the failure to respond to at least two DMARDs (patients whom the current British Society for Rheumatology guidelines and NICE guidance for etanercept, infliximab and adalimumab consider eligible for the biologic treatment) as a recruitment criterion. As trial participants were not precisely representative of the active and progressive PsA population recommended for anti-TNF agents by the current guidelines, it remains unclear that the beneficial effects observed in these trial participants were similar in those treated in routine clinical practice.

Other areas of uncertainty that were explored in sensitivity analyses by the ERG were the effects of alternative estimates of clinical effectiveness in terms of PsARC; HAQ change and PASI change from the ERG evidence synthesis; the cost of administration of drugs; alternative values for NHS cost of psoriasis, measured by PASI; alternative utility functions; and the possibility of increasing the dose of golimumab (to 100 mg) for patients who do not achieve adequate response at 12 weeks, in accordance with the licence. None of these sensitivity analyses changed the conclusion that golimumab is extendedly dominated by etanercept. Further analyses were also conducted using the ERG model developed by the York Assessment Group during the recent appraisal of etanercept, infliximab and adalimumab. These analyses were used to validate the MS model by comparing the results with an independently constructed model. The MS model and the ERG alternative model have a broadly similar structure and data inputs, and gave similar results.

A key area of uncertainty is whether the anti-TNF agents should be considered equally clinically effective, i.e. to treat them as a class. This was the position adopted by the recent guidance issued by NICE regarding the previous appraisal of etanercept, adalimumab and infliximab for PsA.⁷ If all anti-TNF agents are considered equally effective (in terms of PsARC, HAQ and PASI responses) then etanercept, adalimumab and golimumab have very nearly equal costs and QALYs, and all have an ICER of about £15,000 per QALY versus palliative care, whereas infliximab, with a higher acquisition cost, is dominated by the other biologic.

The licence for golimumab indicates that patients who are > 100 kg in weight and who fail to respond to golimumab 50 mg at 3 months can be trialled on a higher dose of 100 mg. A full economic analysis of this option could not be undertaken because of a lack of clinical data for this subgroup of patients. The ERG notes that if patients are titrated and maintained on a higher dose then the additional acquisition costs will be around £2145 per 3 months. However, the clinical adviser to the ERG suggests that, in practice, this scenario is unlikely because of the additional cost; eligible patients are more likely to be tried on an alternative biologic agent.

A remaining source of uncertainty is the annual cost of treating psoriasis. Although the MS conducted a survey of dermatologists and presented the raw data from the survey, there was no detail of the statistical methods used to calculate the mean costs from the raw data and, therefore, the ERG could not validate the calculations. However, the ERG conducted sensitivity analysis on the PASI cost using the ERG model. Doubling or halving the cost per PASI point of £167 per year did not materially affect the results of the ERG model.

Conclusions

The data from the GO-REVEAL trial^{10,11} provide evidence to suggest that golimumab appears to be an efficacious treatment for patients with active and progressive PsA despite the use of previous DMARDs or NSAIDs. The effect sizes of point estimates of joint and skin disease response and functional status were moderate to large, implying that these treatment effects could be clinically significant. However, the analyses for efficacy outcomes were limited to only one RCT (GO-REVEAL^{10,11}) with limited sample size. In particular, few patients provided data on the psoriasis response to golimumab treatment.

The ERG further considered the evidence for safety evaluation of golimumab to be inadequate. The evidence was exclusively based on 24-week data from the single RCT with patients with PsA (GO-REVEAL^{10,11}). The manufacturer failed to provide longer-term data or to consider adverse event data of golimumab from controlled studies in other conditions, such as rheumatoid arthritis and ankylosing spondylitis. Although the adverse effects profile of golimumab appears similar to other anti-TNF agents, the longer-term safety profile of golimumab remains uncertain. Given these limitations and uncertainties, the manufacturer's conclusion that golimumab is a safe treatment option similar to other anti-TNF agents may be premature and may not be reliable.

Despite the claim made by the manufacturer that golimumab is a cost-effective treatment option, the manufacturer's own model showed that golimumab is not cost-effective when the ICERs are correctly calculated. None of the sensitivity analyses carried out by the manufacturer or the ERG regarding uncertainty in the estimates of clinical effectiveness, the acquisition and administration cost of drugs, the cost of treating psoriasis and the utility functions estimated to generate health outcomes changed this conclusion.

However, a key area in determining the cost-effectiveness of anti-TNF agents is whether they should be treated as a class. If all anti-TNF agents are considered equally effective (in terms of PsARC, HAQ and PASI responses) then etanercept, adalimumab and golimumab are all cost-effective, whereas infliximab is dominated by the other biologic agents.

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE in April 2011 states that:

Golimumab is recommended as an option for the treatment of active and progressive psoriatic arthritis in adults only if:

- it is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis' (NICE technology appraisal guidance 199)⁷ and
- the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50-mg dose.

When using the Psoriatic Arthritis Response Criteria (PsARC; as set out in NICE technology appraisal guidance 199), health-care professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate.

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External Devices and Physical Therapies Panel

Members

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Professor Bipin Bhakta, Charterhouse Professor in Rehabilitation Medicine, University of Leeds	Mrs Anthea De Barton-Watson, Public contributor	Dr Lorraine Pinnigton, Associate Professor in Rehabilitation, University of Nottingham	Dr Pippa Tyrrell, Senior Lecturer/Consultant, Salford Royal Foundation Hospitals' Trust and University of Manchester
Mrs Penny Calder, Public contributor	Professor Nadine Foster, Professor of Musculoskeletal Health in Primary Care Arthritis Research, Keele University	Dr Kate Radford, Senior Lecturer (Research), University of Central Lancashire	Dr Nefyn Williams, Clinical Senior Lecturer, Cardiff University

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Interventional Procedures Panel

Members

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We look forward to hearing from you.