

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.

Key references

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