Economic evaluation of oral valdecoxib versus diclofenac in the treatment of patients with rheumatoid arthritis in a randomized clinical trial

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In contrast to economic models that provide probabilistic estimates of economic impact, data extracted from clinical trials may be used to evaluate and compare actual resource utilization and costs. Health-care resource utilization and the costs of these resources were compared from the perspective of the UK National Health Service using data obtained in a 6-month clinical trial of oral valdecoxib 20 mg once daily and diclofenac 75 mg twice daily for the symptomatic treatment of rheumatoid arthritis. However, calculated health-care costs were exclusive of drug acquisition costs because the price of valdecoxib was not available at the time of analysis. While the efficacy of the two treatments was similar, use of valdecoxib was associated with a reduction in total health-care costs amounting to approximately £200 per patient. This lower cost was associated with reduced use of health-care resources for gastrointestinal serious adverse events (gastrointestinal SAEs). In particular, the incidence of hospitalization and number of hospital days for gastrointestinal SAEs was lower in the valdecoxib group. Analysis of cost per gastrointestinal SAE favoured valdecoxib (cost savings of £742), suggesting that even when these events did occur they were less severe. When costs of gastrointestinal SAEs were averaged over the entire population, valdecoxib was suggested to have lower total costs per patient compared with diclofenac (cost savings of £115 per patient), mainly resulting from significant savings in hospitalization costs (£76.49 per patient). These data are consistent with economic models and suggest that the favourable gastrointestinal profile of valdecoxib observed in clinical trials will be of economic benefit.

Key words: Valdecoxib, Diclofenac, Health economics, Outcomes, COX-2-specific inhibitors, Health resource utilization.

Health economic analyses have become an accepted and often required component of drug evaluation, in some countries representing a ‘fourth hurdle’ to the reimbursement process [1–4]. Simply stated, their purpose is to evaluate the economic value of a drug in the increasingly costly environment of health-care.

A variety of different types of economic analyses are used to evaluate or compare pharmacological or interventional strategies with respect to outcomes and the costs of these outcomes. Some economic analyses, such as the Arthritis Cost Consequence Evaluation System (ACCES) [5], which has been used to evaluate the economic impact of celecoxib in country-specific settings, rely on models [6, 7]. While models can provide a useful framework for comparing costs and consequences using alternative probabilities of events based on treatment choices, they may have limited generalizability to the clinical setting because of the inherent use of a series of assumptions.

An alternative approach captures outcomes from a trial and assigns costs based on actual resource utilization and established tariffs for the resources used.

This paper presents a health-economic analysis in which utilization of health-care resources and the costs of these resources are compared between the cyclooxygenase (COX)-2-specific inhibitor valdecoxib and diclofenac, a non-specific non-steroidal anti-inflammatory drug (NSAID). In contrast to economic models based
on probabilistic estimates of efficacy and safety, this analysis relies on documented health-care resource utilization in a randomized clinical trial.

The COX-2-specific inhibitors were developed to maintain the efficacy demonstrated by NSAIDs by inhibiting the proinflammatory COX-2 enzyme while improving upper gastrointestinal safety by sparing the gastroprotective COX-1. Valdecoxib is a COX-2-specific inhibitor that has demonstrated efficacy and safety for the symptomatic treatment of osteoarthritis [8, 9], rheumatoid arthritis [10] and primary dysmenorrhoea [11], and has been approved for these indications in the USA and the UK. The favourable upper gastrointestinal safety profile of valdecoxib may be expected to result in less health-care resource utilization, leading to a reduction in gastrointestinal-related treatment costs, as has been described for the COX-2-specific inhibitor celecoxib (N. M. Agrawal, G. Eisen, J. Fort et al., submitted for publication).

**Methods of data capture**

Evaluations of both clinical and economic outcomes were included as part of a prospective, double-blind, randomized, multicentre trial comparing oral valdecoxib 20 mg once daily with diclofenac 75 mg twice daily for the symptomatic treatment of rheumatoid arthritis [12]. Although the trial also included a valdecoxib 40 mg daily treatment group, economic outcomes were evaluated only for the recommended therapeutic dose of valdecoxib 20 mg.

The trial was international in scope, representing 26 countries, with 6.6% of the study population derived from the UK. Because this was a regulatory study, it was conducted according to the standards of good clinical practice and has been available to regulatory agencies including the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products.

Duration of treatment was 6 months. Clinical outcomes were evaluated using endpoints for efficacy, safety and tolerability. Efficacy endpoints included the American College of Rheumatology Responder Index (ACR-20), arthritis pain (visual analogue scale), global assessment of disease (patient and physician), the modified Health Assessment Questionnaire, swollen joint counts, and tender/painful joint counts and scores. Safety endpoints included the incidence of gastrointestinal ulceration observed by endoscopy at the end of the trial, the incidence of adverse events and withdrawal due to adverse events.

Additionally, utility analysis as an estimate of health-related quality of life was performed using the EuroQOL (European Quality of Life) questionnaire, which identifies health states reported by patients and converts them to quality-adjusted life years (QALYs) using utility weights derived from the EuroQOL time trade-off survey in the UK [13].

Health resource utilization, which may also be an indicator of safety and tolerability, was used as a measure of economic outcomes and provided the required information for a comparative cost analysis between the two treatment arms using the perspective of the UK National Health Service. Health-care resource utilization was obtained from the case report form, which was prospectively designed to specifically capture information on concomitant medications, unscheduled outpatient visits (general practitioner, specialist, hospital), hospitalization (stratified by intensive care or general medicine) and procedures (unscheduled endoscopy, surgery, blood transfusions, etc.). Unit costs for resources were obtained from the Monthly Index of Medical Specialties (MIMS) in the UK (2001 edition) and the National Health Service for the year 2000. Costs and analysis of differences in costs between the two treatments were exclusive of drug acquisition costs, because the price of valdecoxib had not been established in the UK at the time of the analysis.

Comparative economic endpoints to be included in the cost analysis were prespecified in the analysis plan. These endpoints included total cost per patient over the 6-month period and total cost per patient per day. These costs included the costs of treating all adverse events occurring in both treatment groups. Additionally, a subanalysis focused on gastrointestinal events. This analysis included costs per patient for total study duration and per day for ulcer and gastrointestinal complications, defined as gastrointestinal serious adverse events (SAEs) in the clinical report.

The cost analysis was performed by determining the mean difference in costs between the two treatments (valdecoxib minus diclofenac), and 95% confidence intervals (CI) for the point estimates were generated by bootstrapping (5000 iterations) [14, 15]. We used a bias-corrected form of bootstrapping that adjusts for the underlying natural non-parametric bias found in the bootstrap estimate of cost-effectiveness [15], although we are only showing the values of the cost differences.

**Results**

The cohorts evaluated consisted of the intent-to-treat population for each treatment group, which was defined as all randomized patients who took at least one dose of study medication. Demographic and baseline characteristics of the treatment arms are shown in Table 1. While age and ethnicity were similar between the two groups, there were significant differences in gender and gastrointestinal history. In the valdecoxib group, there was a significantly lower proportion of females and a significantly higher percentage of patients with a prior history of gastroduodenal ulcer. Use of low-dose acetylsalicylic acid was only about 6% and was similar between the groups.

As shown in Fig. 1, the mean differences between treatments for clinical efficacy outcomes approximated zero, suggesting that valdecoxib and diclofenac have similar efficacy. Consistent with their similar efficacy, no differences between the treatment groups were observed in health states as measured by utility analysis (data not shown).

The proportion of patients with endoscopic ulcers at end of trial was significantly lower in the valdecoxib group compared with the diclofenac group (5.6 vs 16.3%; \( P < 0.001 \)). Additionally, a smaller proportion of patients treated with valdecoxib withdrew from the trial for any reason compared with those patients taking diclofenac (19 vs 25%, 95% CI for between-group difference, \(-14\%, 1\%\)).

The improved safety profile of valdecoxib translated into a reduction in the utilization of health-care resources
that resulted in lower costs compared with diclofenac. As shown in Fig. 2, over the 6-month period, reductions in costs with the use of valdecoxib were obtained for all evaluated components of health-care resource utilization and were significantly lower for hospitalizations (−£136.30, 95% CI −£275.00, −£16.30) and procedures (−£25.24, 95% CI −£48.70, −£5.80). Also significant was the reduction in total cost per patient, which was almost £200 lower in the valdecoxib group (−£199.43, 95% CI −£417.00, −£9.00).

Because there was a lower withdrawal rate and consequently a longer treatment period among the patients treated with valdecoxib, the cost difference between the groups was standardized by calculating the cost difference per patient per day. This difference in daily treatment costs was determined to be −£3.40 (95% CI −£6.98, −£0.31), the minus signs indicating cost savings with use of valdecoxib.

The contribution of each evaluated component to the total cost per patient is presented in Table 2, which also shows that use of valdecoxib results in cost reductions of approximately 67 and 59% for hospital costs and procedures respectively, and a 37% reduction in total costs. These reductions are primarily due to reduced health-care resource utilization and a concomitant reduction in costs that are associated with a lower incidence of gastrointestinal SAEs.

Although valdecoxib resulted in a lower incidence of endoscopic gastroduodenal ulcers, this may not be a relevant endpoint for purposes of economic evaluation, as many endoscopically diagnosed ulcers are asymptomatic and the patient may not seek health-care. The protocol included the term ‘clinically significant events’ as a variable to identify clinically significant ulcer complications. However, there appeared to be some misclassification because some of the patients reported to have clinically significant events were not reported as SAEs, and patients hospitalized only with ulcers were not included. Therefore, a subgroup analysis was conducted in patients reported as having gastrointestinal SAEs in the clinical report as a surrogate for ulcer and gastrointestinal complications, with resource utilization and costs for these events serving as a marker for economic outcomes. As shown in Table 3, four patients in the valdecoxib group and 13 patients in the diclofenac group had gastrointestinal SAEs, with hospitalizations occurring in two and seven of these patients taking valdecoxib and diclofenac respectively.

Hospitalization, based on the number of days spent in a general ward and in intensive care, was tallied and costed using the SAE narrative in the case report form. When gastrointestinal SAEs were considered, valdecoxib resulted in a 94% reduction in hospital days for these events compared with diclofenac (Fig. 3). Among patients taking valdecoxib, two were hospitalized for a total of 5 days for gastrointestinal SAEs. In contrast, seven patients taking diclofenac were hospitalized for gastrointestinal SAEs for a total of 24 days.

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![Fig. 1. Point estimates and 95% CI for the mean difference between treatments (valdecoxib minus diclofenac) for efficacy outcomes.](https://academic.oup.com/rheumatology/article-abstract/42/suppl_3/iii53/1788142/34653178142/42?image=34653178142)
79 days. The number of days spent in hospital for non-gastrointestinal SAEs was also lower in the valdecoxib group.

A comparison of the mean costs per gastrointestinal SAE suggests lower total costs with valdecoxib, resulting mainly from significantly lower gastrointestinal-related hospitalization costs (£1206.26, 95% CI £2383.00, £185.22), although procedure costs were similar for the two treatment groups (Fig. 4). When the costs for gastrointestinal SAEs were averaged over the entire population in each treatment group and compared for differences, gastrointestinal SAE associated costs contributed £115.33 (95% CI £254.37, £1.63) of the total cost difference (£199.43) between the drugs (Fig. 5).

**Discussion**

A significant reduction in health-care resource utilization with the use of COX-2-specific inhibitors can be expected on the basis of the more favourable upper gastrointestinal safety of these drugs compared with non-specific NSAIDs. Such reductions have been reported in outcomes trials of celecoxib (N. M. Agrawal, G. Eisen, J. Fort et al., submitted for publication) and rofecoxib [16, 17], the use of celecoxib resulting in a >50% reduction in hospitalizations due to a reduction in...
significant gastrointestinal adverse events or ulcer complications (N. M. Agrawal, G. Eisen, J. Fort et al., submitted for publication). Economic models such as ACCES [5], which has been used to model celecoxib [6, 7], have suggested the economic advantages of COX-2-specific inhibitors.

Although the present study did not evaluate cost-effectiveness, the results confirm what has been reported using the ACCES model for celecoxib [6, 7]: lower costs relating to reduced utilization of health-care resources. By identifying health-care resource utilization during a clinical trial and assigning costs for these resources using published tariffs, a more realistic estimate of treatment costs can probably be obtained than that obtained from models. However, it should be noted that this study was designed to be powered to detect statistically significant differences in the rate of endoscopic ulcers and was not powered for economic evaluation. Although large trials would be required to obtain stable estimates of ulcer complication rates, resource utilization is driven symptomatically, and thus may provide an approximation of the safety, tolerability and costs that may be expected.

Hospitalization costs for gastrointestinal SAEs represent the single highest cost per event in patients taking non-specific NSAIDs and are the predominant driver of overall treatment costs in this population. Consequently, any reduction in hospitalization is likely to reduce the economic burden. A reduction in hospitalization days for gastrointestinal adverse events has previously been observed with other COX-2-specific inhibitors compared with non-specific NSAIDs [17] (N. M. Agrawal, G. Eisen, J. Fort et al., submitted for publication). This reduction in hospitalization is consistent with the more favourable gastrointestinal safety profile suggested for COX-2-specific inhibitors and is relevant from the standpoints of both economics and patient health.

From the patient perspective, reduced hospitalization is a favourable outcome that suggests better health states and implies improved drug safety. Although no differences were observed between treatments on the EuroQOL assessment, this can be ascribed to the use of a generic instrument that may lack the discriminative ability to detect differences between drugs with similar efficacy, especially in a trial with a low incidence of SAEs in a small population.
However, the economic benefits are clear. Both the total hospitalization days and hospitalization days due to gastrointestinal SAEs were significantly reduced for valdecoxib (Fig. 3). The effect of reduced hospitalization costs in this study was to reduce total costs when the costs were averaged across the whole group (Fig. 2). Among the few patients who had serious gastrointestinal events, the differences in hospitalization days and costs favoured valdecoxib (Figs 3 and 4).

The implications of these data are twofold. They not only demonstrate a saving resulting from a reduced incidence of serious gastrointestinal events, but also suggest that, if these events do occur in patients taking valdecoxib, the event is less severe than in patients taking diclofenac. This latter point is indicated by the difference in the per event cost of treating the serious gastrointestinal events that favoured the valdecoxib group (Fig. 4).

While the main focus of this paper is economic outcomes associated with adverse events, it is nevertheless important to establish if there are differences in efficacy. The comparable efficacy of valdecoxib and diclofenac is consistent with what has generally been reported for COX-2-specific inhibitors for the treatment of arthritic conditions: efficacy comparable to that of non-specific NSAIDs [18, 19]. Thus, the benefit of these drugs lies in their improved gastrointestinal safety and tolerability, with the corollary of reduced resource utilization and costs as demonstrated in economic analyses.

The results of this study are subject to several limitations. Although the data suggest lower treatment costs resulting from use of valdecoxib, drug acquisition costs were not available and hence could not be included in the analysis. Drug acquisition costs for valdecoxib are likely to be higher than for diclofenac, and may significantly add to overall treatment costs. However, it may also be expected that the higher acquisition costs will be offset by the reduction in costs associated with lower rates of resource utilization. This type of cost offset relative to traditional NSAIDs has previously been suggested for celecoxib, in economic models that have demonstrated the cost-effectiveness of this drug in country-specific settings [6, 7], as well as for rofecoxib [20, 21].

Another limitation applies to the generalizability of taking data obtained in several countries and pooling them for use in the context of the UK health system. This may be especially pertinent when considering that paradigms for treatment of NSAID-associated gastrointestinal events may vary among countries, thereby resulting in differences in health resource utilization. Nevertheless, the lower incidence of gastrointestinal SAEs and the reduced number of hospitalization days suggest that valdecoxib can be expected to limit costs and improve patient outcomes.

Use of data from a randomized clinical trial rather than a more relevant population, such as would be represented by an observational or outcomes study, may also be considered a limitation. While these latter types of studies evaluate a clinically realistic population, information on resource utilization is generally provided by retrospective analysis of claims data, which is often associated with its own set of limitations. In the present study, the capture of health resource utilization was prospectively planned and incorporated into the method for reporting this information on the case report form.

It should also be noted that there was a significantly higher proportion of patients with a gastrointestinal history in the group randomized to valdecoxib. While this was unexpected and could not be accounted for other than by the fact that there is a 1 in 20 probability of finding something statistically significant purely by chance, the higher gastrointestinal risk among these patients potentially biases against valdecoxib. Nevertheless, the data demonstrate a clear superiority of this agent compared with diclofenac with respect to gastrointestinal outcomes (i.e. lower incidence of ulcers, fewer withdrawals due to gastrointestinal adverse events,

![Figure 5. Point estimates and 95% CI for the mean differences between treatment groups (valdecoxib minus diclofenac) in costs associated with serious gastrointestinal adverse events averaged over the entire population (n = 246 for valdecoxib, n = 237 for diclofenac).](https://academic.oup.com/rheumatology/article-abstract/42/suppl_3/iii53/1788142/3415531788142)
Conclusions
This study demonstrates that, in the setting of a clinical trial, valdecoxib resulted in reduced health-care resource utilization with favourable economic outcomes relative to diclofenac, a non-specific NSAID. These outcomes are consistent with, and are a direct result of, the more favourable gastrointestinal profile of this drug, which has previously been demonstrated in clinical trials and was manifested in this study by fewer and less severe gastrointestinal adverse events. The data presented here also validate the concept of using valdecoxib to maintain efficacy while reducing gastrointestinal toxicity and containing health-care costs. These results, combined with other economic studies of celecoxib and rofecoxib, support the overall rationale for the development of COX-2-specific inhibitors and suggest that their use can lessen the burden of NSAID-associated upper gastrointestinal adverse events.

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