Modelling cost effectiveness and cost utility of sequential DMARD therapy including leflunomide for rheumatoid arthritis in Germany: II the contribution of leflunomide to efficiency


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The health intervention examined in the study was leflunomide (LEF) added to conventional sequential therapy consisting of the most frequently used disease-modifying antirheumatic drugs (DMARDs), for patients with rheumatoid arthritis (RA). LEF was given at a dosage of 20mg/day.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of adult patients with active RA. Two groups of DMARD-naive patients were considered: RA patients with severe disease and poor prognosis, and RA patients with mild-to-moderate disease or low disease activity.

Setting
The setting was secondary care. The economic study was carried out in Germany.

Dates to which data relate
Effectiveness data were derived from studies published between 1987 and 2001. Resource use data were derived from a sample of patients followed in 1998 and from data published between 1989 and 2001. Costs were estimated using 1998-2001 values.

Source of effectiveness data
The effectiveness evidence came from a synthesis of previous studies.

Modelling
An international model of treatment patterns for RA patients was used. The conceptual framework of the model was reported graphically. The model considered DMARD sequences that might or not include LEF. Patients moved at six-month intervals across different DMARD sequences. Patients could be switched to the next DMARD in the sequence due to loss of effectiveness or adverse drug reaction (ADR) at the beginning of each successive treatment interval. The model had a three year time horizon, and 6 six-month cycles were considered.
Outcomes assessed in the review
The outcomes estimated from published sources were the probabilities of remaining on treatment and data on the effectiveness of treatments. The proportion of each sequence used in Germany was also reported. The efficacy of treatment was estimated using the measure response years gained (RYGs) according to the American College of Rheumatology (ACR) criteria for 20%, 50% and 70% improvement (ACR20/50/70RYs). Quality of life was estimated using the Health Assessment Questionnaire Functional Disability Index (HAQ-FDI) and the Hannover functional ability questionnaire. Details of the tools used to derive treatment efficacy were given.

Study designs and other criteria for inclusion in the review
Primary studies appear to have been identified selectively rather than using a systematic search and review of the literature. ACR results for LEF and MET were taken from two clinical trials that were described in detail. The clinical responses for the other DMARDs were derived by applying their relative effect with respect to MTX using data from an international model. Observational studies were used to estimate the rate of ADR with MTX while the rate of ADR with LEF was obtained by applying the ratio between the withdrawal rate with LEF and MTX obtained from the clinical trials to the baseline rate for MTX in the observational studies. Other data were obtained from German national databases. Quality of life data were derived from a Swedish database, due to the lack of German utility data.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
The authors did not investigate the validity of primary sources. However, the data obtained from the clinical trials are more likely to have been valid due to the robust design. In addition, the use of observational studies to estimate the baseline rate of ADR with MTX appears appropriate.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Seventeen primary studies were used as the source of clinical data.

Methods of combining primary studies
A narrative approach appears to have been used to combine primary estimates. Average values for the two main clinical trials were used. The treatment effect for all the DMARDs with respect to MTX was used to estimate clinical effectiveness.

Investigation of differences between primary studies
The authors stated that the two main clinical trials used to derive some data had comparable populations. However, the issue of heterogeneity across studies was not addressed.

Results of the review
Details of the migration of 10,000 DMARD-naive patients starting on sequence 1 as well as other data derived from the literature were extensively reported in the article.

For example, in the first six months, the average ACR20RYs were 19.8 with MTX, 21.2 with LEF, 18.4 with SSZ, 16.1 with IMG, 16.1 with AZA, and 15.4 with CQ/HCQ; the average ACR50RYs were 8.8 with MTX, 9.7 with LEF, 8.2 with SSZ, 7.2 with IMG, 7.2 with AZA, and 6.9 with CQ/HCQ; the average ACR70RYs were 2.6 with MTX, 3.3 with
LEF, 2.4 with SSZ, 2.1 with IMG, 2.1 with AZA, and 2.0 with CQ/HCQ.

In each following six months, the average ACR20RYs were 29.4 with MTX, 27.2 with LEF, 27.4 with SSZ, 23.9 with IMG, 23.9 with AZA, and 22.9 with CQ/HCQ; the average ACR50RYs were 16.7 with MTX, 15.3 with LEF, 15.6 with SSZ, 13.6 with IMG, 13.6 with AZA, and 13.1 with CQ/HCQ; the average ACR70RYs were 6.2 with MTX, 6.7 with LEF, 5.8 with SSZ, 5.1 with IMG, 5.1 with AZA, and 4.8 with CQ/HCQ.

The utility values were 0.7154 in patients with HFAQ >94% and HAQ-FD <= 0.5; 0.6197 in patients with HFAQ 94%-74% and HAQ-FD >0.5 to <=1.1; 0.5190 in patients with HFAQ 73%-56% and HAQ-FD >1.1 to <=1.6; 0.5388 in patients with HFAQ 55%-38% and HAQ-FD >1.6 to <=2.1; 0.4210 in patients with HFAQ 37%-20% and HAQ-FD >2.1 to <=2.6; and 0.2245 in patients with HFAQ <20 and HAQ-FD >2.6.

The proportion of DMARD sequences specific to Germany was also reported.

Measure of benefits used in the economic analysis
The summary benefit measures were ACR20 response years, ACR50 response years, and ACR70 response years in the cost-effectiveness analysis, and Quality-Adjusted Life-Years (QALYs) in the cost-utility analysis. Utility values were derived from a Swedish database using a specific approach that was described in the paper. A 5% annual discount rate was applied to all benefits.

Direct costs
The costs analysis was carried out from a societal perspective and included the following categories of direct costs: drugs (DMARDs and LEF), monitoring and treatment of adverse events incurred by DMARD and RA-related non-DMARD medication, outpatient and inpatient services, long-term care insurance, and rehabilitation treatment. Costs were related to the functional capacity of RA patients, which was based on the HAQ-FDI score. Unit costs and the quantities of resources used were not reported for most items. Resource use data were estimated from national statistics and databases as well as from a sample of 583 patients from the German rheumatological database of 1998. Recommended dosages for drugs were considered. Direct costs were borne by the German Statutory Health Insurance (SHI), the Social Long-Term Care Insurance (SLTCI), and the Statutory Pension Insurance (SPI), and these were the sources used for unit costs. Discounting was relevant as costs were incurred over a long time period and a 5% annual rate was used. Costs were given in 1998-2001 values.

Statistical analysis of costs
Costs were treated deterministically in the base case.

Indirect Costs
Indirect costs, namely productivity losses and premature retirement, were included in the analysis which was appropriate given that a societal perspective was adopted. Unit costs and the quantities of resources used were presented separately. Resource consumption was derived from an anonymous sample of RA patients in 1998, while unit costs came from German statistics. Costs were discounted at an annual rate of 5% and were given in 1998-2001 values.

Currency
Euros (EUR). The exchange rate between Euros and US dollars ($) was: EUR 1 = $0.91 (the average rate for the period 2000 to 2001).

Sensitivity analysis
Three types of sensitivity analyses were carried out to address the issue of the robustness of cost-effectiveness and cost-utility estimates: analysis of extremes (with different combinations of average, best, and worst values); scenario analysis (which address the issue of uncertainty in the number and order of the selected DMARDs, while keeping constant cost...
and effectiveness variables); and accounting for sequence effects (where the effectiveness of therapies given as second-line strategies or later in the sequence of drugs was reduced). Most ranges of values were based on published data.

**Estimated benefits used in the economic analysis**
In all the hypothetical sequences (1, 2, 3 and 4) assumed for DMARD-naive patients the addition of LEF resulted in higher QALYs and better results in terms of ACR20, ACR50 and ACR70 response.

Using the German-specific sequences of DMARDs in a hypothetical cohort of 100 patients over a three-year period, the expected response years and QALYs were as follows:

- ACR20 response years = 145.0; ACR50 response years = 78.3; ACR70 response years = 31.4, and QALYs = 173.0 with LEF; and
- ACR20 response years = 136.8; ACR50 response years = 74.0; ACR70 response years = 26.4; and QALYs = 168.1 with sequence without LEF.

The differences were 8.1 (5.9%) for ACR20 response years, 4.3 (5.8%) for ACR50 response years, 5.1 (19.3%) for ACR70 response years and 4.9 (2.9%) for QALYs.

**Cost results**
In general, the addition of LEF to the 4 hypothetical sequences or DMARD-naive patients resulted in an increase of direct costs but a reduction of total costs.

Using the German-specific sequences of DMARDs in the hypothetical cohort of 100 patients over a three-year period, the expected direct costs were EUR 1,314,238 for LEF and EUR 1,273,517 for the sequence without LEF. The difference in direct costs was EUR 40,721 (3.2%).

In the same cohort, the expected total costs were EUR 4,816,226 for the LEF sequence and EUR 5,087,343 for the sequence without LEF. The difference in total direct costs was -EUR 271,117 (-5.3%).

**Synthesis of costs and benefits**
Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of the alternative strategies.

The incremental analysis showed that, when the societal perspective was adopted, LEF was the dominant strategy since it led to lower costs and better benefits in comparison with standard DMARDs. However, when only direct costs were taken into account, the following cost-effectiveness ratios were calculated: EUR 5,004 per ACR20RY gained, EUR 9,535 per ACR50RY gained, and EUR 7,996 per ACR70RY gained. The incremental cost-utility ratio of including LEF was EUR 8,301 per QALY gained.

The analysis of extremes showed that, when total costs were considered, the sequence with LEF was dominant in 79% of the cases and less costly and less effective in 21% of the cases compared to the sequence without LEF.

When only direct costs were included, the sequence with LEF was dominant in 29% of the cases, more costly and more effective in 50% of the cases, and more costly and less effective in 21% of the cases compared to the sequence without LEF.

Base case results were basically corroborated both in the scenarios analysis and in the third analysis, where sequence effects were considered.

**Authors' conclusions**
The authors concluded that LEF added to the sequence of commonly used DMARDs in RA patients in Germany was a
cost-effective strategy. LEF was both less costly and more effective than standard DMARD sequences from the perspective of society, and had a very favourable cost-effectiveness ratio when only direct costs were considered. Thus, LEF costs paid off due to the higher effectiveness of LEF sequences that significantly slowed the disabling disease progression of RA over time.

CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparators was clear, and all the relevant DMARD strategies in the German context were considered. The authors justified the choice of the interventions examined in the study. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was estimated from published studies, but it was not stated whether a systematic search and review of the literature was undertaken to identify primary studies, which may therefore have been included selectively. No details of any literature review methods were given. Some information on the studies used to estimate clinical inputs was provided, with the exception of the two clinical trials that were used as the main source of data and were extensively reported. The authors reported the design, the characteristics of the patients, the follow-up, and the main results. Some clinical data were derived from German databases and other publications, which were not extensively described. The issue of uncertainty around model parameters was addressed in the sensitivity analysis.

Validity of estimate of measure of benefit
Both disease-specific and generic benefit measures were used. The approach used to calculate the impact of the treatments on quality of life was reported, and the use of QALYs means that it will be possible to compare the current benefits with those associated with other studies. The ACR measures are widely used for patients with RA. Thus, they are also comparable with other studies on RA patients. Discounting was applied to all benefits. The authors noted that the impact of the interventions on mortality was not explicitly modelled since this represents a debated issue.

Validity of estimate of costs
The bulk of the data on the cost analysis were reported in a companion paper. The choice of adopting a societal perspective was appropriate since all costs incurred were accounted for, regardless of the payer. The results of the analysis were also reported in a scenario in which only direct costs were included. Extensive information on unit costs, quantities of resources used, source of data, and price year was provided in the primary cost analysis. This enhances the possibility of replicating the analysis and of making reflation exercises in other settings and time periods. Discounting was relevant and was applied. The authors stated that the impact of using alternative discount rates was not investigated because the discount rate was not a key parameter due to the relatively short time horizon of the analysis. No statistical analyses of costs were carried out but cost estimates were varied in the sensitivity analysis. The source of costs was consistent with the German health care system. Resource consumption reflected actual management of RA patients in Germany. The current analysis confirmed the dependency of RA costs on functional capacity of RA patients rather than on clinical activity of the disease. The sensitivity analysis also investigated the impact of altering the DMARD sequence, which might be a key assumption of the decision model.

Other issues
The authors pointed out that specific comparisons of their findings with those from other studies would be difficult due to apparent differences in terms of patient populations, cost categories, and treatment patterns, which might vary across countries and settings. However, the main characteristics and results of some published studies were reported. The issue of the generalisability of the study results to other settings was not explicitly stated but the extensive use of sensitivity analyses enhances the external validity of the study. The authors justified the use of a modelling approach in order to assess the cost-effectiveness of LEF on the grounds that comparisons of different DMARDs over the long-term is not feasible using clinical trials. Some potential limitations of the current analysis were also noted. For example, the analysis did not consider disease duration due to the lack of reliable data.
Implications of the study
The study results support the use of LEF for the management of RA patients from a therapeutic and economic perspective.

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