Cost-effectiveness modelling of biological treatment sequences in moderate to severe rheumatoid arthritis in France
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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.

CRD summary
This study examined the cost-effectiveness of sequences of drugs for patients with rheumatoid arthritis that had not responded to an anti-tumour necrosis factor agent. A sequence of etanercept then abatacept then adalimumab was more effective and had a better average cost-effectiveness ratio than a sequence of etanercept then rituximab then adalimumab, over two years. The methods and analyses were not fully reported and the results had limitations, which make it unclear whether the authors’ conclusions were valid.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
The aim was to examine the costs and health outcomes of sequences of biological pharmacotherapies for patients with active rheumatoid arthritis and an insufficient response to at least one anti-tumour necrosis factor agent.

Interventions
The sequences of biological agents were: etanercept then abatacept then adalimumab; etanercept then rituximab then adalimumab; etanercept then adalimumab then abatacept; and etanercept then adalimumab then infliximab. Response was assessed at six months and patients remained on a drug if it was efficacious, otherwise they switched to the next drug in the sequence.

Location/setting
France/primary care.

Methods
Analytical approach:
A decision model was used to synthesise the data from a selection of relevant published studies. The time horizon was two years, which was split into four treatment intervals of six months. The authors stated that they undertook a national payer’s perspective.

Effectiveness data:
The effectiveness data were mainly from published clinical trials. The six-month disease activity score status for each drug was from available randomised controlled trials; the Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN) trial, the Research in Active Rheumatoid Arthritis (ReAct) trial, and the Randomized Evaluation of Long-term Efficacy of Rituximab (REFLEX) trial. Where necessary, post hoc analyses and open-label trial results were used. Statistical mean tests were performed to test for significant differences between the two sequences ending in adalimumab and between the two with adalimumab as the second option. The main clinical effectiveness estimates were a low Disease Activity Score (DAS) and the theoretical expected number of days (TENDs) in remission.

Monetary benefit and utility valuations:
Not relevant.

Measure of benefit:
The measures of benefit were the number of days with a low DAS or remission over two years.

Cost data:
The direct medical costs included medical visits, laboratory tests, hospitalisations, imaging, physiotherapy, nursing, adaptive aids, and transport. The dose and course of medications and all other resource items were provided by clinical experts, based on clinical practice guidelines. Published sources, such as Journal Officiel de la Republique Francaise and French National sickness funds, were used for the unit costs to value the resources. The costs were calculated for each disease activity category and reported in Euros (EUR) for the price year 2008.

Analysis of uncertainty:
The input values were varied over plausible ranges. Uniform distributions were assigned to all variables, except for hospitalisations, where triangular distributions were applied.

Results
Using the low DAS criterion, over two years, patients receiving abatacept as second-line therapy (sequence one), had 102 mean expected days in remission, while those receiving rituximab as second-line therapy (sequence two) had 82 days. Those receiving abatacept as third-line therapy (sequence three) had mean expected days in remission of 63, while those receiving infliximab as third-line therapy (sequence four) had 32 days.

Using the remission criterion, sequence one had a TENDs in remission of 52, sequence two had 32, sequence three had 21, and sequence four had nine.

For patients achieving a low DAS, the total costs were estimated to be EUR 905 for the first six months and EUR 696 for the remaining six-month periods, compared with EUR 1,215 for patients not achieving a low DAS. For patients achieving remission, the total costs were estimated to be EUR 771 for the first six months and EUR 511 for the remaining six-month periods, compared with EUR 1,159 for patients not achieving remission.

Using the low DAS criterion; the mean cost-effectiveness ratios were EUR 278 for sequence one, EUR 303 for sequence two, EUR 473 for sequence three, and EUR 817 for sequence four. Using the remission criterion, they were EUR 526 for sequence one EUR 742 for sequence two, EUR 1,521 for sequence three, and EUR 2,677 for sequence four.

Authors' conclusions
The authors' concluded that a treatment sequence of etanercept then abatacept then adalimumab was more effective and had a better average cost-effectiveness ratio than a sequence of etanercept then rituximab then adalimumab, over two years.

CRD commentary
Interventions:
The four strategies were well described, but the recommended doses were not stated. The authors acknowledged their assumption that the patients had the same clinical characteristics at baseline. These drug sequences might not be relevant, taking into account the pre-treatment requirements and the available substitutions, in other settings.

Effectiveness/benefits:
The effectiveness data were from a selection of randomised controlled trials that assessed the agents compared with placebo. The authors did not state how they calculated the relative clinical effects between the drug therapies in the absence of direct head-to-head evidence. The details of the main clinical trials were not provided and their publications should be consulted to assess their internal validity. The comparability of the participants’ baseline socio-demographic and clinical characteristics, the withdrawal rates, and the previous treatments for the trial populations were not discussed. No systematic review was reported to identify the trials to ensure that the best available evidence was used. It was not clear if the benefit measures were discounted, which increases the uncertainty. The disease-specific benefit measures make comparisons across health conditions impossible.

Costs:
The perspective was not reported, so it is unclear if all the relevant costs were included. The unit costs were from publicly available sources, but were not reported. The resource quantities and the category costs were not provided.

Analysis and results:
The model was described, with a diagram. The results were sufficiently reported. Average cost-effectiveness ratios were presented for each of the four sequences and the mean differences were analysed, but incremental cost-effectiveness ratios would have been more informative for decision makers. The authors stated that they performed a probabilistic sensitivity analysis, but the results were not reported and no one-way sensitivity analyses were performed. This makes it difficult to assess whether the findings were robust to variations in the modelled estimates. The authors discussed some limitations to their study.

Concluding remarks:
The methods and analyses were not fully reported and the results had limitations, which make it unclear whether the authors' conclusions were a good assessment of the evidence.

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