Cost-effectiveness of scheduled maintenance treatment with infliximab for pediatric Crohn's disease
Punekar YS, Sunderland T, Hawkins N, Lindsay J

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 investigated the cost-effectiveness of infliximab, compared with standard care, as maintenance therapy for paediatric patients with moderate-to-severe Crohn's disease. The authors concluded that infliximab was likely to be cost-effective compared with standard care. There were limited data available, but the methods appear to have been appropriate and comprehensive. The conclusions reached by the authors are uncertain, but it was stated that they were based on the best available evidence.

Type of economic evaluation
Cost-utility analysis

Study objective
The aim was to assess the costs and health outcomes of infliximab as maintenance treatment for active Crohn's disease in paediatric patients. A hypothetical cohort of children, aged six to 17 years with moderate-to-severe active Crohn's disease and a Crohn's Disease Activity Index (CDAI) of 30 or more at baseline, was considered. The patients' mean baseline weight was 40kg increasing by 5kg per year up to 60kg, and their mean age was 13 years.

Interventions
The study compared infliximab at a dose 5mg per kg, with standard care (no treatment), as maintenance therapy for severe Crohn's disease in paediatric patients. Infliximab was given as an infusion at week zero, followed by infusions for responders at weeks two and six, and every eight weeks thereafter.

Location/setting
UK/out-patient care.

Methods
Analytical approach:
A Markov model was used to synthesise published data from various sources, including key randomised controlled trials. The base analysis had a five-year time horizon. The cycle length was varied to match the efficacy estimates from the clinical trial and the infliximab dosing regimen (two, eight, and 20 weeks, then 24 weeks). The authors stated that the perspective was that of the UK NHS.

Effectiveness data:
The clinical data for the efficacy of infliximab included the remission rates, response rates, surgeries, post-surgical complications, and deaths. The clinical events were primarily from two pivotal randomised controlled trials, the Randomized, multicenter, open-label study to Evaluate the safety and efficacy of Anti-TNF-alpha Chimeric monoclonal antibody in pediatric subjects with moderate to severe Crohn's disease (REACH) and A Crohn's disease Clinical trial Evaluating infliximab in a New long-term Treatment regimen (ACCENT) 1, and a third study. Both the ACCENT 1 and the third study were of adult patients. The trials lasted 54 weeks, with the efficacy of infliximab extrapolated from the last treatment cycle, weeks 46 to 54.

Monetary benefit and utility valuations:
The health states values were adapted from a published study of adult patients that used the European Quality of life (EQ-5D) measure and UK tariffs. For the health states following surgery, a database of EQ-5D scores of 41 adult
Measure of benefit:
The measure of benefit was quality-adjusted life-years (QALYs). Discounting was applied at an annual rate of 3.5%.

Cost data:
The direct medical costs included infliximab acquisition and administration, concomitant medications, hospitalisations, and other direct costs. The estimates were from published studies of patients with Crohn's disease, the National Schedule of Reference Costs, and an expert Delphi panel of UK gastroenterologists. They were discounted at 3.5% and reported in UK pounds sterling (£) for the price year 2006 to 2007. Inflationary adjustments were made using the annual UK Health Price Index.

Analysis of uncertainty:
One-way sensitivity analyses were undertaken on the key parameters, and two scenarios tested the assumptions around infliximab efficacy. Probabilistic sensitivity analysis was undertaken, with beta distributions assigned to the health utilities and transition probabilities, and normal distributions assigned to the costs. Ten thousand Monte Carlo simulations were performed and 95% confidence intervals were generated. The results were presented in cost-effectiveness acceptability curves (CEACs).

Results
For paediatric patients with severe Crohn's disease, the mean cost per patient, over five years, was £34,012 with infliximab compared with £25,987 with standard care. In the scenario in which no treatment effect was assumed beyond 54 weeks, the mean cost per patient was £31,010 with infliximab and £25,987 with standard care, and in the scenario using only REACH efficacy data (the only data for children), it was £37,181 with infliximab, and £23,186 with standard care.

In the base case, the mean QALYs were 3.224 for infliximab, and 2.675 for standard care. In the two scenarios, the mean QALYs per patient were 2.943 with infliximab and 2.675 with standard care, where no treatment effect was assumed beyond 54 weeks, and 3.468 with infliximab and 3.090 with standard care, where only REACH data were used.

The incremental cost per QALY gained with infliximab over standard care was £14,607. Based on the CEAC, there was a 78.6% likelihood that the incremental cost per QALY gained would be below £30,000, the accepted UK willingness-to-pay threshold. The results were most sensitive to variations in the efficacy of standard care, resulting in an incremental cost per QALY gained of £37,017, using data from REACH only.

Authors' conclusions
The authors concluded that regular maintenance therapy with infliximab was likely to be cost-effective for children with moderate-to-severe Crohn’s disease, despite the uncertainty in the results.

CRD commentary
Interventions:
The authors provided a good description of the infliximab maintenance therapy in the intended population. What was not clear was if infliximab was the only relevant treatment for this population or if other comparators should have been included or discussed.

Effectiveness/benefits:
The key effectiveness parameters were from two randomised controlled trials, which were chosen because, together, they provided the necessary information for the model, despite not being head-to-head comparisons of the options. In the absence of efficacy data on children with Crohn's disease, the authors used data from adult patients with Crohn's disease and the results were very sensitive to variations in this parameter. The authors suggested that these trials were the only available evidence, but they did not support this claim with a review of the literature, which makes it impossible to assess its validity. The utility values were measured in patients with Crohn’s disease and using expert...
opinion, and the methods and health states were clearly reported. These utility estimates were from adult patients, which increases the uncertainty in the estimates.

Costs:
The direct medical costs were analysed and they appear to have been appropriate to the perspective. The resource types, their valuations, and the unit costs were provided and further information was available in their source publications. The resource use following surgery was estimated by a panel of UK gastroenterologists, using the Delphi method, but the size of this panel was not reported. The same panel provided the health state utility for the non-responding active state, which was not available from the literature.

Analysis and results:
The model type and structure were clearly presented, with a diagram and all the probability transitions. The authors acknowledged a number of limitations to their study, including assumptions for the duration of disease efficacy, the reliance on data extrapolated from adult patients, and the uncertainty in the cost and utility estimates. They evaluated the impact of data variability in thorough sensitivity analyses and presented the results comprehensively. Despite being well reported, the uncertainty remains high due to the use of adult data as a proxy for the paediatric population and the other assumptions which were required for the model.

Concluding remarks:
Despite some limitations with availability of data estimates, the methods appear to have been appropriate and comprehensive. The conclusions reached by the authors are uncertain, but were reported to have been based on the best available evidence.

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