The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis

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Executive summary

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Background

Using effectiveness data from trials where the comparator does not reflect current clinical practice may give a misleading impression of the incremental cost-effectiveness of the new technology in question. This is likely to be a particular problem for treatments for chronic diseases, where the clinical pathway is often complex, and for which appropriate comparative data tend to be limited. The focus for this report was to evaluate two new drugs, etanercept and infliximab [antibodies against tumour necrosis factor (anti-TNFs)], for use in the treatment of rheumatoid arthritis (RA). The comparators in the trials of anti-TNFs tend to be placebo and so do not reflect clinical practice. Earlier work by the authors resulted in the development of a preliminary model that was used to overcome the limitations of the trial data. That work showed that decision analytic models based on estimates of the effectiveness of the drug directly derived from the trial data were inadequate representations of real-life clinical practice and potentially resulted in misleading estimates of the incremental cost-effectiveness. This report takes forward this work by exploring ways of avoiding the use of inappropriate comparators through the use of suitably flexible modelling techniques. The modelling approach described here is potentially applicable to other conditions, especially those where a sequential approach to therapeutic options exists.

Objectives

The main objective of the research reported here was to overcome some of the identified limitations of the Birmingham Preliminary Model (BPM). Thus, the study sought to address the structural issues relating to mortality and quality of life (QoL) effects and to identify data on the general pattern of QoL of RA patients. The aim was to restructure the model so that different sequences of treatment could be considered, and to determine the sequence that best represents current clinical practice in the UK. An additional aim was to demonstrate the flexibility inherent in using a modelling approach to consider these health policy questions.

Methods

The preliminary model used in the earlier review, the BPM, was developed further in the work reported here. The Birmingham Rheumatoid Arthritis Model (BRAM) is essentially a substantially revised and extended version of the BPM. Some of the most significant changes from the BPM are listed below.

- The BRAM describes the current state of a patient in terms of Health Assessment Questionnaire (HAQ) score, rather than quality of life more generally.
- Mortality is allowed to depend on HAQ score.
- The BRAM also includes provision for the average rate of increase in HAQ to vary according to treatment.
- There is provision for joint replacement to be included in the analysis; the risk of this again depends on HAQ. However, the model may also be run without consideration of joint replacement.

The newly developed BRAM model is also used to investigate further the limitations of the methods that use clinically inappropriate comparators.

Like the BPM, the BRAM operates as an individual sampling model. This type of model is a form of discrete event simulation in which only one individual is considered at a time. The intention behind this type of model is to produce a realistic set of virtual patient histories, from which estimates of population mean costs and mean effects (e.g. quality-adjusted life-years) can be estimated. This requires consideration of individual variation at all relevant points in the model. Such variation has been incorporated wherever practicable within the limitations of the available data.

To ensure that the model truly reflected modern clinical practice a systematic review of drug use in the treatment of RA and a survey of current practice by rheumatologists in the UK were also undertaken.

Results

The results from the survey of rheumatologists highlighted the fact that RA has different
manifestations and responds to different agents in different patients, all of which makes any summary of practice difficult to achieve and open to the criticism of being an oversimplification. However, the findings generally agree with other surveys and trends observed, such as the increasing acceptance of methotrexate as first line drug of choice in patients with RA, especially if the disease is of an aggressive nature. The newer anti-TNF agents have also begun to be incorporated into use.

One of the central issues explored in this project is the importance of specifying the correct comparison in the analysis being undertaken. This was investigated using two separate analyses: the situation of comparing anti-TNFs with placebo, and the comparison of a sequence using anti-TNFs with a sequence that represents current practice in the UK.

The incremental cost-effectiveness ratios resulting from the use of an inappropriate comparator of placebo were consistently lower than in the base case where appropriate comparator drugs sequences were used. The focus of the BRAM on a drug sequence helped to avoid the incremental cost-effectiveness of new treatments appearing lower than they really are when inappropriate comparators are used. To test the effect on the analysis results of using the disease-modifying antirheumatic sequence that represents current UK practice, the BRAM were run for the strategies representing current UK practice. The results were not very different from the base-case results.

As with any health technology assessment exercise, there remain some potentially important uncertainties in this evaluation work. A major benefit associated with the adoption of a modelling approach is that the importance of some of the uncertainties can readily be explored. The BRAM was used to demonstrate how the sensitivity of the analysis results to variation in key assumptions and data-based estimates can be explored. The issues investigated include: the effect of joint replacement on HAQ, the assumptions concerning rate of change in HAQ, and the proportions of patients who reach palliation.

Conclusions

The main achievement of this work was to bring about a more realistic modelling of real-life clinical pathways and events, as it has developed from the BPM to the BRAM. This has been brought about by overcoming structural and data limitations. In addition, the modelling approach reflected in the BRAM is applicable to other chronic conditions, especially those where a sequential approach to therapeutic options exists. The model has been successfully restructured so that different sequences of treatment can readily be considered, including the sequence that best represents current clinical practice in the UK. In addition, the flexibility inherent in using a modelling approach to consider these health policy questions has been demonstrated. One of the key uncertainties that can now be explored concerns the impact of new drugs on disease progression. Current evidence on this is weak, but should new agents demonstrate such a benefit then the BRAM may be a suitable vehicle through which to investigate the costs and full effects.

Inevitably, there remain problems and limitations with the BRAM, but these are almost entirely data limitations. As data on these issues become available the BRAM provides a convenient tool through which reanalysis might be undertaken.

Publication

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