In July 2003, the National Institute for Clinical Excellence (NICE) made a decision not to recommend anakinra therapy for use in rheumatoid arthritis (RA) in England and Wales [1]. The cost-effectiveness model used suggests that the additional health gains are simply not worth the additional costs [2]. This has stark implications. Many rheumatologists are currently anticipating a shift in clinical practice towards earlier and sequential use of etanercept, infliximab and adalimumab. In contrast, the anakinra analysis suggests that even the TNF-α inhibitors may not be cost-effective in comparison with traditional disease-modifying anti-rheumatic drugs (DMARDs) even in the patients with high disease activity for whom they are currently recommended. Rheumatologists must understand and engage in this economic evaluation debate, be aware of important criticisms of the modelling approach and also realise the influence that their own clinical practice may have on future NICE decisions.

It is widely understood that NICE uses economic evaluations to aid the health-care decision-making process in the UK. The principle is to maximize the health gain of a population within the constraints of available resources and equity concerns. Cost-effectiveness calculations are used to quantify the additional costs and benefits of a new intervention (e.g. biologics) versus existing treatments (e.g. DMARDs). The benefits are quantified using a generic measure, comparable and useable across all diseases and treatments, called the quality-adjusted life year (QALY) gained. For QALYs, health-related quality of life is measured on a scale from 1 (perfect health) to 0 (equivalent to death). An extra year of life in perfect health is 1 QALY gained, and two extra years of life in a severe disease state, say score = 0.2, is 0.4 QALYs gained. In RA, it is the improvements in Health Assessment Questionnaire (HAQ) disability score that are usually translated into the QALY measure. Thus, 2 years of a 0.6 HAQ improvement can be estimated to be 0.39 QALYs gained [1].

The way in which NICE uses the ratio of additional cost to additional benefit—the resulting incremental cost-effectiveness ratio (ICER)—to make decisions has recently been clarified [3]:

Below an ICER of £20,000/QALY, judgments about the acceptability of a technology . . . are based primarily on the cost-effectiveness estimate.

Above an ICER of £20,000/QALY, judgments . . . are more likely to make explicit reference to factors including the degree of uncertainty surrounding the calculation of ICERS, the innovative nature of the technology, the particular features of the condition and population receiving the technology, or the wider societal costs and benefits.

Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong.

The anakinra appraisal concludes ‘the cost per QALY of adding anakinra to the portfolio of therapies for RA was in excess of £69 000’ [1], leading NICE to exclude anakinra from its guidance. In a recently published report (Birmingham Rheumatoid Arthritis Model: BRAM), the same model has been used to analyse etanercept and infliximab giving £42 000 per QALY and £36 000 per QALY respectively [4]. If NICE were to use same model in the reappraisal, a continued positive judgement on both etanercept and infliximab would be in serious doubt. We believe that there are three issues which require further consideration.

The first issue is the level of response to be achieved for continuation. NICE guidance, following the British Society for Rheumatology (BSR) and the European League Against Rheumatism (EULAR) [5], suggests that a patient is deemed a responder after 3 months either if the DAS28 score improves by more than 1.2 or if the absolute DAS28 score is lower than 3.2, and that therapy for patients not achieving these criteria should be discontinued. In fact, the BRAM does not even explicitly include response, but rather focuses on time to withdrawal, using observational data for duration of therapy. The model predicts 6 to 9% of patients are withdrawn at 6 months. However, recent evaluation of 1589 patients in the BSR Biologic Registry (BSRBR) [6] suggests that 19% (i.e. double the rate in the model) had withdrawn by 6 months and 81% continued. Rheumatologists must be aware that their own clinical practice in this regard will influence future NICE decisions. The BSRBR data also show that only 62% of the 81% remaining on treatment actually achieved a EULAR moderate response criterion. Overall, therefore, 50% of the starting cohort are responding, which is actually close to data from randomized controlled trials (RCTs) used in previous calculations, the validity of which is discussed and resolved elsewhere [7, 8]. However, it also means that 30% of patients appear to remain on treatment outside the NICE guidance. To quantify the impact of this on the ICER results, we have used our own cost-effectiveness model for etanercept, which was submitted to and used by NICE in the initial appraisal [9]. Changing from 50% withdrawal at 6 months (our original assumption) to only 19%, the ICER result worsens from £16 660 per QALY to £24 550 per QALY, an increase of 47%.

A second issue is the level of HAQ improvement achieved by responders. This is linked to not explicitly distinguishing responders and non-responders in the model. The BRAM simply uses average improvement from clinical trials, a mixture of responders and non-responders (often around –0.5). In practice, patients who respond have higher HAQ improvements than those who do not. In our own modelling work, we used a HAQ improvement for ACR20 responders to estimate the level for etanercept and infliximab, which was submitted to and used by NICE in the initial appraisal [9]. Changing from 0.037 and 0.031 HAQ points per annum to +0.013 and +0.021, the ICER result worsens from £16 660 per QALY to £24 550 per QALY, an increase of 47%.

The final issue is the rate of disability progression over the long term. The BRAM assumes the same disability progression for all patients independent of duration, disease severity, level of response or indeed treatment, namely +0.031 HAQ points per annum. Thus a patient responding to etanercept or infliximab is assumed to have the same rate of HAQ progression as a patient who has failed all possible treatments and is now on palliation. At best this is implausible; in fact it is counter to the evidence. We have analysed patients with complete data from the 5 to 10-yr follow-up Early Rheumatoid Arthritis Study (ERAS) dataset (www.nwtrag.com/eras) [10]. The number of DMARDs patients had previously received can be a marker for differential progression. For patients moving from zero through to three previous DMARDs, average progression was +0.012, +0.021, +0.037 and +0.042 HAQ points per annum respectively (n = 887).
Secondly, we analysed differences between DAS28 moderate responders and non-responders. At some point in the 10-yr ERAS data, 620 patients (56%) had high disease activity (DAS28 > 5.1). In the non-responding group, HAQ progression worsened at +0.041 points per annum, while an actual improvement of −0.018 points was seen in the responding group. Again, we have quantified the impact of this on the ICER results, using our own model. Our original analysis used differential rates in HAQ progression dependent on treatment. We instead used the BRAM assumption that HAQ progression remains constant for the entire population. The ICER almost doubles from £16,660 to £32,450 per QALY. Thus, the BRAM may significantly over-estimate the ICER results.

When NICE reappraises the TNF-α inhibitors in 2005, new evidence will be incorporated into the cost-effectiveness calculations. Many rheumatologists believe that the focus of the appraisal will be on extending the patient group to patients with early disease, and to sequential biologic use. However, at face value, the recent NICE analyses suggest that perhaps even the original approval of etanercept and infliximab may be in doubt. Some of the initial results of the BSRBR suggest that rheumatologists’ clinical practice decisions regarding response and continuation may also have an impact on NICE’s calculations. This might be questionable, but it has been used in practice in the anakinra appraisal. A rigorous debate is required on the assumptions and use of evidence. Unless these issues are addressed, the current availability of biologics may be in question.

The authors have declared no conflicts of interest.

N. J. Bansback, A. Young1 and A. Brennan
Operational Research, School of Health and Related Research, Sheffield S1 4DA and 1Early Rheumatoid Arthritis Study (ERAS) Co-ordinator, St Albans Hospital, St Albans AL3 5PN, UK

Correspondence to: A. Brennan. E-mail: a.brennan@sheffield.ac.uk

References