

# Cost-Effectiveness of Biologic Agents for Treatment of Autoimmune Disorders: Structured Review of the Literature

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**ABSTRACT** *Objective.* Four new biologic treatments have been approved for several autoimmune disorders. Economic evaluations have been used to model their cost-effectiveness.

*Methods.* We conducted a structured literature review in Embase and PubMed to identify all relevant cost-effectiveness models investigating one or more of these 4 drugs in autoimmune disorders.

*Results.* Fifteen full economic evaluations were identified [13 for rheumatoid arthritis (RA), 2 for Crohn's disease (CD), and 1 for ankylosing spondylitis (AS)]. While several studies found adalimumab, etanercept, and infliximab to be cost-effective (using a threshold around \$50,000/quality-adjusted life-year) for treatment of severe RA, not all studies concurred, and there was significant variation in the range of cost-effectiveness ratios reported. Neither study in CD found treatment with infliximab to be cost-effective. Only one study was identified in AS: treatment with infliximab was found to be cost-effective.

*Conclusion.* Modeling treatment strategies in chronic relapsing diseases such as RA, CD, and AS presents particular challenges, as reflected in the variation in cost-effectiveness results reported. A reference case for economic evaluations, such as that suggested by the OMERACT (Outcome Measures in Rheumatology) Health Economics Working Group will facilitate comparison and interpretation of results. (J Rheumatol 2006;33:2124–31)

*Key Indexing Terms:*

RHEUMATOID ARTHRITIS  
MODELS

ECONOMICS

SYSTEMATIC REVIEW  
BIOLOGIC DRUGS

Economic evaluations of healthcare interventions are increasingly required by regulatory authorities in order to inform decisions about reimbursement<sup>1</sup>. The Pharmaceutical Benefit Scheme in Australia, followed by the province of Ontario, Canada, were the first institutions to require evidence of cost-effectiveness as part of the submission process of a new drug. In 1999, the National Institute of Clinical Excellence (NICE) was set up in the UK with the mandate to provide guidance on the use of new and existing medicines and treatments. NICE requires an economic evaluation as part of its submission procedures for the appraisal of new technologies. In the USA, the Academy for Managed Care Pharmacy (AMCP) has devel-

oped formulary submission guidelines for managed care formulary committees that recommend inclusion of cost-effectiveness evidence of new treatments<sup>2</sup>.

In recent years, new biologic agents have been approved for the treatment of several autoimmune disorders. Adalimumab, etanercept, and infliximab inhibit activities of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Anakinra is a recombinant, nonglycosylated form of the human interleukin 1 antagonist (IL-1Ra)<sup>3</sup>. In the USA, adalimumab, anakinra, etanercept, and infliximab have been approved for the treatment of rheumatoid arthritis (RA). Adalimumab, etanercept, and infliximab have been approved for psoriatic arthritis; and etanercept and infliximab for ankylosing spondylitis (AS). In addition, etanercept is indicated for plaque psoriasis and juvenile rheumatoid arthritis, while infliximab has been approved for Crohn's disease (CD), and more recently, for ulcerative colitis. These agents have been shown to be effective in several clinical trials<sup>4–10</sup>. In addition, there have been reports in the clinical literature of investigations in several other conditions such as Wegener's granulomatosis, reflecting interest in using these drugs for other autoimmune disorders<sup>11,12</sup>.

While these biologic agents constitute a new opportunity to provide effective treatment for chronic and sometimes debilitating diseases, their acquisition cost remains significantly higher than standard treatments. In situations such as these, where there is a clear clinical benefit but at a possibly signif-

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icant additional cost to the health system, cost-effectiveness evaluations provide valuable information to clinicians and decision-makers about whether the provision of the treatment is the most efficient and fair way to allocate scarce health resources in order to provide the best overall health for the population that is being served.

In practice, cost-effectiveness analyses investigate the ratio of the incremental costs and the incremental benefits of the treatment of interest to the next best option. This ratio is called an incremental cost-effectiveness ratio (ICER). In the context of unavoidably limited budgets for healthcare (whether in privately or publicly funded health systems), it is impossible to fund all available health technologies. In theory, cost-effectiveness analyses should help decision-makers make the best use of scarce resources, by estimating the value of additional benefits provided by treatments and focusing on those that bring the most benefits for each dollar spent. Unfortunately, in practice, cost-effectiveness analyses are often perceived as methods for rationing resources, so it needs to be emphasized that their purpose is to ensure that the available resources are spent in the most efficient and fair way possible.

One commonly used approach in cost-effectiveness analyses is to calculate ICER in the form of cost per quality-adjusted life-years (QALY). QALY are an index of survival that is weighted or adjusted by the patient's quality of life during the survival period. QALY are particularly useful because they allow for comparisons between interventions across different conditions. For example, the cost-effectiveness of a treatment for RA can be compared with one for AS.

In order to provide estimates of ICER, economic modeling is often necessary. While general methodological guidelines exist offering good modeling principles, evaluating treatments for autoimmune disorders is associated with a number of specific challenges<sup>13-15</sup>. The objective of our study was to conduct a structured review of the literature to identify cost-effectiveness evaluations involving at least one of 4 biologic treatments, adalimumab, anakinra, etanercept, and infliximab, in autoimmune disorders, in order to identify specific challenges that arise from such conditions and draw implications for future cost-effectiveness modeling in this field.

## MATERIALS AND METHODS

We conducted a literature search using the scientific literature databases PubMed and Embase up to February 15, 2005. We used different combinations of the following search terms: "biologics," "cost effectiveness," "cost-utility," "economics," "model," "anakinra," "adalimumab," "etanercept," and "infliximab." Both authors conducted the initial searches independently and then combined the results of their search in one reference database and removed duplicates. This initial search yielded 917 abstracts. A list of abstracts was then compiled and manually evaluated by one reviewer using the predefined inclusion and exclusion criteria that are listed in Table 1.

The manual review yielded 19 potential abstracts, the full articles of which were reviewed so that they could be assessed for inclusion. Of these 19, one study was excluded because it did not report cost-effectiveness ratios<sup>16</sup>. A second was excluded because it was a review article<sup>17</sup>. Finally, 2 Health Technology Assessment (HTA) reports were excluded because they reported models developed by industry for their submission to NICE but were

not deemed to be reported in sufficient detail to qualify for inclusion in this structured review<sup>18,19</sup>. The final number of studies included was 15. The stages of the literature search are shown in Figure 1. We used a predefined evidence table to extract relevant data from the identified studies. These included information on the country, population, comparator, perspective, time horizon, discount rates, methods, measures of resource use, measure of costs, price year, measure of health outcome, results, and authors' stated conclusions. Data extraction was then independently checked. All costs were converted into US dollars using the exchange rate of \$1 = £0.561 = €0.818 (January 2006 rates).

## RESULTS

Fifteen full economic evaluations investigating at least one of the 4 biologic drugs adalimumab, anakinra, etanercept, and infliximab were identified<sup>20-34</sup>. There were 12 for RA, 2 for CD, and one for AS. There were no cost-effectiveness studies in other disease areas. There were 5 studies in the UK, 4 in the USA, 2 studies in Sweden, one joint study in Sweden and in the UK, one study in France, one study in The Netherlands, and one study in Spain.

In the field of RA, most studies investigated the cost-effectiveness of treatments in patients with severe disease. For example, several studies investigated patients who had already failed a disease modifying antirheumatic drug (DMARD). However, one study investigated infliximab with MTX versus leflunomide in patients with early RA; while another investigated infliximab in methotrexate (MTX) naïve patients<sup>25,32</sup>.

One difficulty in using the results of economic evaluations is that there is no agreed-upon cutoff number that establishes whether an intervention is cost-effective. In fact the cost-effectiveness of an intervention depends on what is termed the decision-maker's ceiling ratio. This ceiling ratio can be inferred from the amount that decision-makers are willing to pay for health interventions. For example, if the incremental cost of treatment A is \$50,000 per QALY compared to treatment B and the decision-maker recommends it, then we can infer that the ceiling ratio is at least \$50,000 per QALY. Although there is no set figure for this ceiling ratio, a study of the decisions made by NICE in the UK showed that interventions seemed to be recommended for values at or below £30,000 (\$53,490) per QALY. In the US, the figure of \$50,000 is often used as an acceptable cutoff point.

The cost-effectiveness results of the studies identified varied considerably. Several studies in RA and AS found favorable results for adalimumab, etanercept, and infliximab, defined as cost-effectiveness ratios around or below \$50,000/QALY. Detailed results are reported in Table 2. For example, Bansback, *et al*<sup>21</sup> concluded that adalimumab, etanercept, and infliximab were cost-effective in patients in the UK with moderate to severe RA who had failed at least 2 traditional DMARD. Brennan, *et al*<sup>23</sup> investigated the use of etanercept combined with DMARD versus DMARD alone in the United Kingdom. Results were favorable to etanercept in patients who had failed 2 DMARD.

Kobelt, *et al*<sup>31</sup> investigated patients with advanced RA in

Table 1. Inclusion and exclusion criteria for the review.

Inclusion	Exclusion
<ul style="list-style-type: none"> <li>• The following autoimmune disorders: rheumatoid arthritis, juvenile arthritis, lupus, psoriatic arthritis, psoriasis, ankylosing spondylitis, Wegener's granulomatosis, Crohn's disease, ulcerative colitis, Sjögren's syndrome</li> <li>• Interventions included anakinra, adalimumab, etanercept, or infliximab</li> <li>• Study design was a cost-effectiveness evaluation comparing treatments</li> </ul>	<ul style="list-style-type: none"> <li>• Burden of disease, cost of illness studies, cost studies</li> <li>• Languages other than English or French</li> <li>• Publications before 1995</li> </ul>

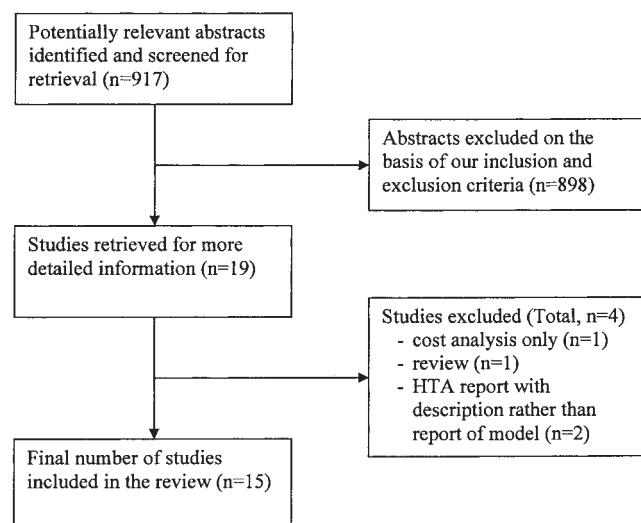


Figure 1. Stages in our search of the literature.

Sweden and in the UK comparing infliximab with MTX to MTX alone using 2 Markov models. The cost-utility ratios were favorable to infliximab. Kobelt, *et al*<sup>30</sup> investigated etanercept and infliximab in patients with RA who had failed 2 DMARD including MTX in Sweden. Cost-utility ratios were favorable to the biologics. Wong, *et al*<sup>34</sup> investigated patients with active refractory RA and compared infliximab combined with MTX to placebo with MTX using a lifetime Markov model. Results were favorable for the biologic treatment. Rubio-Terres and Dominguez<sup>32</sup> investigated infliximab with MTX compared to leflunomide in patients with early RA in Spain. The incremental cost of the infliximab with MTX compared to leflunomide treatment was \$16,798. In the disease area of AS, Kobelt, *et al*<sup>29</sup> investigated patients with active unremitting disease taking infliximab compared to standard care. Results were favorable to infliximab, particularly in the 30-year model.

A number of economic studies demonstrated less favorable results for biologic treatments. In the preliminary version of the Birmingham Rheumatoid Arthritis Model (BRAM), Jobanputra, *et al*<sup>28</sup> found ICER for etanercept and infliximab

used in the treatment sequence of DMARD to be higher than acceptable levels of cost-utility ratios in the UK. Using an updated version of the BRAM, Barton, *et al* found that etanercept and infliximab as part of the treatment sequence of DMARD had high cost effectiveness ratios compared to treatment sequences of DMARD without these biologic agents. Welsing, *et al*<sup>33</sup> investigated the cost-effectiveness of various treatment combinations and sequences of leflunomide and etanercept in patients with RA in The Netherlands. The cost-utility of etanercept was found to be above the acceptable threshold.

In patients who were MTX-resistant, Choi, *et al*<sup>24</sup> found that etanercept incurred much higher incremental costs to meet American College of Rheumatology response criteria ACR 20 or ACR 70 weighted over a 6-month period. In MTX-naïve patients, Choi, *et al*<sup>25</sup> compared etanercept, leflunomide, MTX, sulfasalazine, and no second-line treatment. Etanercept, although the most efficacious option, incurred higher costs. It should be noted that the last 2 studies did not report results in cost/QALY, so it is difficult to draw firm conclusions concerning the cost-effectiveness of the treatments.

Only one study investigated the cost-effectiveness of anakinra in patients in the UK. Anakinra as part of treatment sequences of DMARD was not found to be within acceptable limits of cost-effectiveness ratios, although the question remains whether it may be cost-effective in patients who are treatment-resistant to infliximab and etanercept<sup>26</sup>.

In CD, biologic treatments were not cost-effective in the treatment of perianal fistulae, or for maintenance therapy in patients with moderate to severe active disease. Due to the high cost of these treatments, cost-effectiveness ratios were less favorable for maintenance therapy across diseases. Arseneau, *et al*<sup>20</sup> investigated an adult population in the US with symptomatic perianal fistulae and compared infliximab with standard treatment of 6-mercaptopurine-metronidazole for one year and from a third-party payer perspective. They found that the cost-utility for infliximab was above acceptable levels. Jaisson-Hot, *et al*<sup>27</sup> investigated infliximab in patients with CD resistant to conventional therapy in France. Infliximab could be cost-effective in the case of relapsing retreatment after the first infusion, but maintenance infusions

Table 2. Cost-effectiveness studies in the treatment of autoimmune disorders.

Reference/Country	Population	Type of Analysis	Drugs	Results
RA				
Bansback et al. (2005)	Patients with moderate to severe RA who had failed at least 2 DMARD	Patient based state transition model	Adalimumab, etanercept and infliximab with and without MTX compared to DMARD	Etanercept + MTX and adalimumab had similar cost/QALY results (range from €35,000 (\$42,882)/QALY to €52,000 (\$63,710)/QALY.
Sweden				
Barton et al. (2004)	Hypothetical cohort of patients with RA	Discrete event simulation model	Sequences of DMARD with and without the inclusion of etanercept and infliximab.	Etanercept and infliximab in the DMARD sequence had a lifetime ICER of £50,442 (\$61,801)/QALY and £68,591 (\$84,037)/QALY respectively.
UK				
Brennan et al. (2004)	Adults with RA previously failing 2 DMARD	Patient level simulation model	DMARD sequence with and without etanercept	Etanercept in the DMARD sequence had a lifetime ICER of £16,330 (\$20,007)/QALY
UK				
Choi et al. (2000)	MTX resistant patients with RA	Decision-analytic model	Etanercept with and without MTX compared with various DMARD sequences and no second line treatment	Both etanercept strategies incurred higher cost per ACR20 than hydroxychloroquine, sulfasalazine and MTX. Etanercept and MTX had an ICER of \$42,600 per patient with ACR 20 response
USA				
Choi et al. (2002)	MTX- naive patients	Decision-analytic model	Etanercept compared to leflunomide, MTX, sulfasalazine or no 2nd line treatment.	The cost per ACR20 and ACR70WR was lower for sulfasalazine and MTX compared to etanercept.
USA				
Clark et al. (2004)	Hypothetical cohorts of patients with RA	Discrete event simulation model	DMARD sequences (same as Barton 2004) with and without anakinra	Estimate of the ICER of anakinra was £106,000 (\$129,871)/QALY to £604,000 (\$740,020)/QALY
UK				
Jobanputra et al. (2004)	Hypothetical cohort of patients with RA	Discrete event simulation model	Etanercept or infliximab used either as 3rd DMARD in a sequence of DMARD or separately as last resort therapy.	The ICER for etanercept and infliximab used as 3rd sequence DMARD were £83,000 (\$148,354) and £115,000 (\$205,551)/QALY respectively. Used as last in the sequence of DMARD, the ICER were £72,000 (\$128,692) and £95,000 (\$169,803)/QALY respectively
UK				
Kobelt et al. (2003)	Patients with advanced RA disease	2 Markov models based on epidemiological cohorts followed for up to 15 yrs in Sweden and the UK.	Infliximab with MTX compared to MTX alone	ICER gained was SEK 32,000 (\$4,215) in Sweden and GBP 21,600 (\$38,608) in the UK for one-year treatment and SEK 150,000 (\$19,726) and GBP 29,900 (\$59,055) in the UK for 2-year treatment
Sweden, UK				
Kobelt et al. (2004)	Patients with RA having failed 2 DMARD including MTX.	Analysis cohort of 160 patients initiating infliximab or etanercept in rheumatology units in Sweden.	Etanercept and infliximab	The ICER was €43,500 (\$53,296)/QALY if improvement occurred after 3 mo treatment and €36,900 (\$45,210)/QALY if the improvement occurred after 6 wks.
Sweden				
Rubio-Terres et al. (2001)	Patients with early RA	Cost-minimization model.	Infliximab with MTX compared to leflunomide	The cost per patient of a yearly treatment was estimated at 315,023 Ptas (\$2,319) for leflunomide compared to 2,596,286 Ptas (\$19,118) with infliximab and MTX
Spain				
Welsing et al. (2004)	RA patients with advanced disease, treated unsuccessfully with $\geq 2$ DMARD, including MTX.	Markov model	Switches between usual treatment, leflunomide, and etanercept when treatment was failing	The option leflunomide with switch to etanercept and then switch to usual treatment had the most favorable ICER of the treatment strategies that included etanercept: €163,556 (\$200,389)/QALY compared with usual treatment.
The Netherlands				
Wong et al. (2002)	Patients with active RA refractory to MTX	Markov model	Infliximab with MTX compared to placebo with MTX	Including direct costs only, the lifetime ICER was \$30,500/QALY (direct costs only) and \$9,100/QALY (indirect costs included).
USA				
Ankylosing spondylitis				
Kobelt et al. (2004)	Patients with active AS with unremitting disease	Non parametric model using patient level data for the 2 year model. Markov model for the extension to 30 yrs.	Infliximab compared to standard care	Results for the 2 year model show an ICER of £6,214 (\$11,107)/QALY. The long-term cost-effectiveness model leads to a cost per QALY of £9,600 (\$17,159).
UK				
Crohn's disease				
Arseneau et al. (2001)	CD patients with symptomatic perianal fistulae.	Markov model	Three infliximab strategies were compared to 6MP/metronidazole	The cost per QALY for infliximab compared to standard treatment ranged from \$355,450/QALY to \$377,000/QALY.
USA				
Jaisson-Hot et al. (2004)	Patients with active, moderate- to severe-CD resistant to conventional therapy	Markov model	Surgery followed by conventional therapy compared to (a) infliximab retreatment when patients relapse or do not respond (b) Infliximab maintenance infusions every 8 weeks	The ICER ranged from €63,700 (\$78,045)/QALY to €762,245 (\$933,902)/QALY.
France				

ACR20 : American College of Rheumatology 20, ACR70WR : American College of Rheumatology 70 Weighted Response;  
DMARD: disease modifying anti-rheumatic drugs, ICER: incremental cost-effectiveness ratio, QALY : quality adjusted life year,  
Exchange rate used: \$1= £0.561= €0.818

every 8 weeks were not cost-effective using the \$50,000/QALY threshold.

## DISCUSSION

This structured review of the literature identified 15 cost-effectiveness studies evaluating the use of biologic agents for the treatment of autoimmune disorders. While several studies

found biologic agents to be cost-effective (using a threshold around \$50,000/QALY) for the treatment of severe RA, not all studies concurred, and there was significant variation in the range of cost-effectiveness ratios reported. Neither study in CD found treatment with infliximab to be cost-effective. Only one study was identified in AS: treatment with infliximab was found to be cost-effective.



Restricting our search to the 4 biologics adalimumab, anakinra, etanercept, and infliximab, we searched for cost-effectiveness studies across a range of diseases. The rationale of these inclusion criteria was to include disease areas where the small number of publications would not allow for a structured review in itself. For example, with only one study for AS and 2 studies in CD, a review would not be possible for these specific disease areas<sup>20,27,29</sup>. With the search strategy used in our review, implications can be drawn for the design of cost-effectiveness of models for autoimmune disorders, although evidently unique characteristics that surround the clinical context of specific diseases will remain. The variation in results obtained can be explained in part by a number of different ways researchers have modeled the disease and treatment strategies. We explore 3 areas in more depth in this discussion: the sequential nature of treatments, the choice of health outcome measures used in the economic evaluation, and the inclusion of productivity costs.

*Sequential nature of treatments.* The conditions included in this review are chronic conditions that require a range of therapeutic agents that may be given in sequence over the long term. In addition, the biologic agents investigated have so far been approved for patients with severe and often refractory forms of the disease, where these agents are indicated after a number of other treatments have failed, or where the patient has stopped responding. Thus modeling in this area will involve investigating complex sequences of treatments rather than just one therapeutic agent, and will therefore also require evidence of current treatment patterns in the patient populations concerned. The sequential nature of the treatments is apparent in the majority of the RA models<sup>22,24,25,28,33,34</sup>. For example, the treatment sequences used in the BRAM model were based on a review of the literature as well as a postal survey of British rheumatologists, and included 12 possible DMARD<sup>22</sup>. The complexity of models being developed in these disease areas highlights the need for the models to remain transparent and explicit in their methods. The models developed for CD also reflect the complexity of treatment for this disease. For example, Arseneau, *et al*<sup>20</sup> investigate 3 possible sequences of treatments including infliximab and a combination treatment of 6 mercaptopurine-metronidazole. Jaisson-Hot, *et al*<sup>27</sup> investigated retreatment with infliximab when patients relapse or do not respond, as well as maintenance infusions every 8 weeks compared to surgery and conventional treatment.

The sequential nature of treatments in these diseases has been addressed in a number of the economic evaluations, although not in all. The challenge for the analyst investigating this issue is to adequately represent the nature of the disease and the treatment pathways while keeping the model explicit and transparent.

*Health outcome measures.* All economic evaluations require a measure of health outcome as well as costs. A widely used measure of health outcome is the QALY, which combines

measures of both quantity and quality of life. QALY are calculated by estimating the total number of life-years gained from treatment and weighting each year with a quality of life score, or utility, to reflect the quality of life in that year. A simplified example is of a patient living for 10 years with a quality of life of 0.7 on a scale of 0 to 1 (with 0 as death and 1 as perfect health), corresponding to  $(0.7 \times 10)$  7 QALY. There are a number of methods available to elicit valid preference-based utilities for different health states. The use of a common measure such as QALY is necessary for decision-makers to make reimbursement decisions because they allow for the comparison of cost-effectiveness ratios across disease areas.

The majority of the models identified in our review use the QALY as a measure of the health outcome in the economic evaluation, thereby providing results in terms of cost per QALY gained. The difficulty in not using QALY is apparent when the results of a model are reported using a different metric; for example, Choi, *et al*<sup>24,25</sup> provide results using a cost per ACR 70-weighted response. Although this may be a useful measure, it limits the comparability with other model results in the disease area, as well as the comparability of interventions across disease areas. Reporting the cost per QALY of infliximab for RA and CD will provide comparative value lost when a common metric is not used.

The models identified also used a number of methods to calculate utilities to derive QALY. For example, Kobelt, *et al*<sup>30,31,33</sup> used the EQ-5D, a generic health state questionnaire that converts the results into utilities for health states by using pre-scaled responses obtained by time trade-off, from a relevant reference group. Bansback, *et al*<sup>21</sup> derived utilities from a relationship between the Health Assessment Questionnaire (HAQ) disability index (DI) and Health Utility Index-3 (HUI-3) from clinical trial results. Barton, *et al*<sup>22</sup>, Jobanputra *et al*<sup>28</sup>, Clark, *et al*<sup>26</sup>, and Brennan, *et al*<sup>23</sup> derived utilities from HAQ scores. In the AS model, Kobelt, *et al*<sup>29</sup> derived utilities from 2 disease-specific quality of life instruments: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI). Wong, *et al*<sup>34</sup> used utilities derived from a self-reported global health questionnaire using a visual analog scale. Arseneau, *et al*<sup>20</sup> and Jaisson-Hot, *et al*<sup>27</sup> in their respective CD models both used utilities derived using standard-gamble techniques.

The OMERACT Health Economics Working Group makes the recommendation that patients' values be used for clinical choices, and the general population's values be used for health policy decisions<sup>15</sup>. The variety of techniques used to obtain the health state utilities in the reviewed studies highlights the importance of continuing to explore this issue. For example, future studies should assess how comparable different methods are, and how much using utilities derived in different ways for the same health states affects the overall cost-effectiveness results.

*Productivity costs.* The chronic and recurring nature of

autoimmune disorders makes the inclusion of productivity a necessary issue for modelers to address. There is evidence of productivity losses associated with a range of these conditions<sup>35-40</sup>. Productivity costs as defined by the US Panel on Cost Effectiveness and Medicine refer to “the costs associated with lost or impaired ability to work or engage in leisure activities due to morbidity and lost economic productivity due to death”<sup>41</sup>.

Nine of the 15 studies include some measure of productivity costs<sup>23-25,29-34</sup>. For example, Choi assumed a relationship between the HAQ score and work loss and calculated productivity losses using the average wage for working adults<sup>24,25</sup>. In their study of patients with AS, Kobelt, *et al*<sup>42</sup> included short-term sick leave, reductions in working time due to AS, and early retirement; they also evaluated the costs using the human capital approach, one of several methods proposed in the literature. In their study of RA patients in Sweden, Kobelt, *et al*<sup>30</sup> used collected data on work capacity to evaluate the cost of short- and longterm absence from work. Again, estimation of costs was done using the human capital approach. In their study of infliximab for patients with RA in Sweden and the UK, Kobelt, *et al*<sup>31</sup> assumed that work loss was dependent on disease severity as established by the corresponding HAQ score. Rubio-Terres and Dominguez<sup>32</sup> used the number of hours spent in hospital to estimate productivity losses and estimated costs using Spanish hourly wage. Welsing, *et al*<sup>33</sup> estimated indirect costs from absence from paid labor using patient diary and questionnaires recorded during the clinical trial. In the study by Wong, *et al*<sup>34</sup>, indirect costs were based on employed patients during the clinical trial (ATTRACT). Beyond one year, indirect costs were assumed to be one or 3 times direct costs. Six of the evaluations include no productivity costs at all<sup>20-22,26-28</sup>. Interestingly, neither of the 2 studies on CD (one of which more specifically addresses fistulizing CD) deals with the issue of lost productivity<sup>20,27</sup>. However, studies have shown that inflammatory bowel disease is associated with reduced employment and productivity losses, and such issues should be considered for inclusion in models of these diseases<sup>35,36</sup>.

The ways in which productivity costs are evaluated and included in economic evaluations remain a matter of debate. The OMERACT Health Economics Working Group makes the broad recommendation to include all associated medical and nonmedical direct costs in the costs, but to report indirect costs (i.e., productivity losses) separately<sup>15</sup>. The US Panel on Cost Effectiveness and Medicine has argued that these losses of productivity may best be evaluated using a preference-based measure (or utility) of health related quality of life. However, not all quality of life instruments such as the EQ-5D explicitly question respondents on these issues. The uncertainty with regard to how to best approach this issue is reflected in the variety of ways this question has been addressed by analysts<sup>42</sup>. The human capital approach may overestimate productivity costs in economic evaluations, because there is a risk of double-counting when changes in life expectancy and

health related life expectancy have already been incorporated in measures of health such as the QALY. Friction cost methods, which focus on the valuation of lost time from paid work as a result of illness, are becoming a more acceptable methodology among health economists to evaluate lost production<sup>42</sup>.

Although we have highlighted 3 particular issues for which there is no consensus in economic modeling, the themes identified in our review are not exhaustive. Other important issues concern the absence of head to-head trials between relevant comparators and how to model clinical effectiveness when what is available to the analyst are indirect comparisons between the different biologic agents. Also of importance is the choice of the time horizon, particularly how long patients are assumed to stay on treatment in different models. Short-term evaluations (1 to 2 year time horizon) will produce different results than lifetime models. There are other areas that need to be addressed in economic evaluations: the use of clinical outcome measures, inclusion of adverse events and mortality, the modeling of clinical effectiveness after discontinuation of therapy, and the stratification of the population of the study by risk. These elements have been highlighted in the OMERACT 6 Health Economics Working Group report that suggests a reference case for economic evaluation in RA<sup>14,15</sup>.

We did not identify other systematic reviews of cost-effectiveness models that were not disease-specific. The other reviews on cost-effectiveness of biologics are in the field of RA. For example, Maetzel<sup>14</sup>, Wong<sup>17</sup>, and Emery<sup>43</sup> provide reviews of the cost-effectiveness of new biologic interventions for RA.

Our study is not a full systematic review. In order to qualify as such, it would have been necessary to also conduct an appraisal of the quality of these studies in a systematic manner based on established criteria<sup>44</sup>. Nevertheless, our structured review used established and accepted methods for conducting our search and extracting data. Future work should focus on appraising the quality of these studies.

Our review identified cost-effectiveness models evaluating biologics in autoimmune disorders. The themes we have explored are common to these biologic treatments and they cut across the diseases identified. Knowledge of the issues and how they are addressed will be useful to researchers developing these models and to decision-makers appraising their validity. For disease areas where there are relatively few or no economic evaluations available, future models can draw on the experience and issues that surround existing models. In particular, there are a number of economic models in RA that can inform development of models in other diseases where there are far fewer models. The resolution of these methodological issues will benefit models irrespective of the disease they target.

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