



Critical appraisal of pharmacoeconomic studies comparing TNF- α antagonists for rheumatoid arthritis treatment

Marco Barbieri[†], Michael F Drummond, Jaume Puig Junoy, Miguel Angel Casado Gómez, F Javier Ballina García, Pilar Blasco Segura and José Luis Poveda Andrés

Clinical trials and economic models have showed that anti-TNF agents are effective and cost effective compared with standard therapies (mainly disease-modifying antirheumatic drugs) in patients with rheumatoid arthritis. However, no head-to-head clinical trials between these agents are available and the relative effectiveness and cost-effectiveness is uncertain. We have conducted a literature review in order to identify full economic evaluations that compared two or more TNF antagonists. A description of each study was given and key methodological issues identified. These included methods for evidence synthesis, model characteristics and methods to address uncertainty in model parameters. Important differences in methodological features and results have been found between studies. More attention in future studies should be given to methods for indirect comparisons between the biological agents.

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Rheumatoid arthritis (RA) is a chronic and progressive disease that affects approximately 0.5–1% of the adult population. The introduction of new TNF- α antagonists (infliximab, etanercept and adalimumab) has changed the clinical practice and the management of RA. Clinical trials [1–5] have proved the potential greater efficacy of treatment with TNF- α antagonists compared with standard therapies, including disease-modifying antirheumatic drugs (DMARDs). The substantial higher cost of these biological agents compared with more traditional strategies for the management of RA has raised questions about their cost-effectiveness. Several economic models [6–11] have been developed in order to estimate the value for money of infliximab, etanercept or adalimumab compared with DMARDs or placebo. In general, biological agents were associated with cost-effectiveness or cost-utility ratios below the thresholds commonly used to establish drug approval and reimbursement.

However, no head-to-head clinical trial comparing the anti-TNF medications has been performed to date, and no data on the relative effectiveness of these agents is available. Thus, some pharmacoeconomic studies have tried to assess their relative cost-effectiveness by synthesizing the clinical evidence from different sources, by means of decision models.

The objective of this paper is to critically appraise the pharmacoeconomic studies that compared two or three TNF antagonists in order to assess the quality of the methods and the data employed. In particular, we wanted to identify the main issues associated with the comparisons of the three biologic agents based on decision models, given the lack of head-to-head comparisons. Thus, a description of each study was given, highlighting the main drawbacks of each analysis. Finally, we focused on the methodological differences among studies and their impact on the final results in terms of cost-effectiveness.

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Affiliations

[†] Author for correspondence
 Universitat Pompeu Fabra, Balmes
 132, 08008 Barcelona, Spain
 Tel.: +39 515 873 445
 Fax: +39 515 873 445
marco.barbieri@upf.edu

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Methods

We performed a literature review in order to identify pharmacoeconomic studies comparing the TNF- α antagonists using both clinical databases (MedLine and Embase) and economic evaluation databases (National Health Service [NHS] Economic Evaluation Database [EED] and Office of Health Economics EED), until February 2007. Searches used index and text words encompassing RA, anti-TNF, adalimumab, etanercept and infliximab. In addition, the internet sites of the FDA and the NICE were checked.

The results of the search were screened by an investigator (MB) and articles were included if they met the following criteria:

- Publications in English or Spanish;
- Full economic evaluations (this includes cost–effectiveness analysis [CEA], cost–utility analysis [CUA], cost–benefit analysis [CBA], cost–minimization analysis [CMA] and cost–consequences analysis [CCA]);
- Comparison between two or three TNF- α antagonists (thus, economic evaluations comparing only one anti-TNF with other medications were excluded).

Full copies of the articles that met these inclusion criteria were then obtained and a detailed analysis of each study was performed in order to make a final decision on their eligibility.

A description of each article was given, focusing on some key features such as:

- Drugs compared and doses
- Form of economic analysis
- Model structure (if relevant)
- Time-horizon of the analysis
- Perspective of the analysis
- Source for efficacy and safety data
- Sources for utility weights (if relevant)
- Sources for economic data (resource use, unit costs and category of costs included)
- Cost–effectiveness results
- Results of sensitivity analysis

A critical appraisal of each article was also undertaken. We chose not to use a standard quality assessment checklist for economic evaluations (e.g., that developed by Drummond *et al.* [12]) because we wanted to focus our attention on some issues specific to RA, biological agents and methods for indirect comparisons that we felt were the most relevant factors for the economic evaluations analyzed. Thus, more than a general overview of the methodological characteristics of each study, this article highlights strengths and limitations of published economic evaluations on some specific issues such as model characteristics and assumptions, methods to synthesize efficacy evidence, assumptions on the progression of disease, methods to estimate costs associated to the disease and methods to handle uncertainty in model parameters. TABLES 1 & 2 provide a schematic view of the main characteristics and results of each study.

Results

Ten articles were initially thought to fulfill all the inclusion criteria. However, one study (Kobelt *et al.* [13]) was excluded because it considered the TNF- α inhibitors as a group without any comparison between them. Thus, nine studies were finally included. Three of these were conducted in the UK (Jobanputra *et al.* [14], Barton *et al.* [15] and Chen *et al.* [16]), two in the USA (Wailoo *et al.* [17] and Spalding *et al.* [18]), one in Spain (Hernandez-Cruz *et al.* [19]) one in Canada (Coyle *et al.* [101]), one in the Netherlands (Nuijten *et al.* [20]) and one in Sweden (Bansback *et al.* [11]). A review of methods and results of each of these articles will be given together with a critical appraisal focusing on key methodological issues previously described (limitations and strengths). Given that the work by Chen *et al.* was a revision of the Jobanputra and Barton studies with the attempt to overcome some of the previous limitations, we focused our analysis on the original.

Infliximab plus methotrexate versus etanercept

Five of the studies identified compared only etanercept as monotherapy with infliximab plus methotrexate (MTX). Two of these (Barton and Jobanputra) will not be described, since they were updated by the Chen analysis.

Hernandez-Cruz and colleagues carried out a CEA and CUA of infliximab plus MTX versus etanercept monotherapy for patients suffering from RA resistant to DMARDs in Spain [19]. A decision model was constructed in order to estimate the costs associated with the two strategies over 12 months. Patients who had failed at least one DMARD could receive etanercept at standard dose (25 mg twice weekly) or infliximab 3 mg/kg every 8 weeks plus MTX. Individuals who reached an American College of Rheumatology criteria (ACR)20 response with etanercept were assumed to continue this treatment, while patients who did not respond or suffered from severe toxicity were assumed to switch to infliximab (3 mg/kg) plus MTX. Individuals who reached an ACR20 response with infliximab 3mg/kg were assumed to continue this treatment, while patients who did not respond or suffered from severe toxicity were assumed to receive a higher infliximab dosage (5 or 10 mg/kg). ACR20 response with etanercept and infliximab was based on two published randomized controlled trials (RCTs) [1,3]. Data on toxicity were obtained from a RCT for etanercept [3] and from a Cochrane review for infliximab plus MTX [21]. Reduction in health assessment questionnaire (HAQ) score with etanercept and infliximab was also obtained from the two mentioned RCTs and directly converted to changes in quality-adjusted life years (QALYs) using a formula applied in Jobanputra *et al.*

In order to estimate resource use in the Spanish context, data were obtained from an observational study that followed 286 Spanish patients who had suffered from RA for over 1 year. The perspective of the analysis was that of the society, thus both direct (drug acquisition costs, personnel, hospitalizations, laboratory tests and treatment of side effects) and indirect costs were considered.

Table 1. Description of the main characteristics of the pharmacoeconomic studies included in the analysis .

Study	TNF inhibitors	Type of analysis	Country	Model structure	Perspective	Time-horizon	Sources for effectiveness data	Sources for safety data	Sources for resource use	Sources for utility weights	Analysis of uncertainty	Ref.
Nuijten <i>et al.</i> (2001)	ETA, INF	CMA	The Netherlands	Not relevant	Societal	1 year	Assumed equal efficacy	Assumed equal safety profiles	National databases, experts opinion and published study	Not relevant	Univariate SA	[20]
Hernandez-Cruz <i>et al.</i> (2004)	ETA, INF	CUA	Spain	Decision tree	Societal	1 year	One RCT for INF; one RCT for ETA	One RCT for ETA, one Ob study for INF	Spanish Ob study plus published studies	Association between HAQ and QALYs based on published studies	Univariate SA	[19]
Bansback <i>et al.</i> (2004)	ETA, ADA, INF	CUA	Sweden	Patient-level simulation	NHS	Lifetime	Three RCTs for ADA; two RCTs for ETA; one RCT for INF	One Ob study	Association between HAQ and costs based on published studies	Association between HAQ and QALYs based on published studies	Univariate SA and PSA	[11]
Chen <i>et al.</i> (2006)	ETA, INF, ADA	CUA	UK	Discrete-event simulation	NHS	Lifetime	RCTs or meta-analysis of RCTs for biological agents; RCTs or assumptions for DMARDs	One Ob study for ETA and INF; assumptions for ADA; a large UK database for other DMARDs	Based on published guidelines and experts opinion	Association between HAQ and QALYs measured by an equation based on a data set	Univariate SA and scenario analyses. Quasi-CIs around mean costs and benefits	[16]
Coyle (2006)	ETA, INF	CUA	Canada	Probabilistic Markov (cohort)	Payer	5 years	One RCT for ETA, one RCT for INF plus MTX; one RCT for gold	RCTs	RCTs, Canadian databases	HAQ changes multiplied by 0.2 to obtain QALYs change	Univariate SA and PSA	[101]

ADA: Adalimumab; CI: Confidence interval; CMA: Cost-minimization analysis; CUA: Cost-utility analysis; DMARDs: Disease-modifying antirheumatic drugs; EO: EuroQol; ETA: Etanercept; HAQ: Health assessment questionnaire; INF: Infliximab; NHS: National Health Service; Ob: Observational; QALY: Quality-adjusted life years; PSA: Probabilistic sensitivity analysis; RCT: Randomized controlled trial; SA: Sensitivity analysis; SF: Short form.

Table 1. Description of the main characteristics of the pharmacoeconomic studies included in the analysis (cont.).

Study	TNF inhibitors	Type of analysis	Country	Model structure	Perspective	Time-horizon	Sources for effectiveness data	Sources for safety data	Sources for resource use	Sources for utility weights	Analysis of uncertainty	Ref.
Spalding (2006)	ETA, ADA, INF	CUA	USA	Deterministic Markov model (cohort)	Payer	Lifetime	RCTs (one for each drug compared)	Reciprocal of duration on each agent taken from Barton (2004) [15]	RCTs, Jobanputra (2002) [14], function of HAQ score	HAQ scores converted to utilities by a published formula	Univariate SA	[18]
Wailoo <i>et al.</i> (2006)	ETA, ADA, INF	CUA	USA	Patient-level simulation	Medicare	Lifetime	Four RCTs for ETA; four RCTs for ADA; two RCTs for INF	One US registry	Mainly from US registry; costs associated to HAQ scores	EQ-5D and SF-36 from US registry; utilities associated to HAQ	Univariate SA and PSA	[17]

ADA: Adalimumab; CI: Confidence interval; CMA: Cost-minimization analysis; CUA: Cost-utility analysis; DMARDs: Disease-modifying antirheumatic drugs; EQ: EuroQol; ETA: Etanercept; HAQ: Health assessment questionnaire; INF: Infliximab; NHS: National Health Service; Ob: Observational; QALY: Quality-adjusted life years; PSA: Probabilistic sensitivity analysis; RCT: Randomized controlled trial; SA: Sensitivity analysis; SF: Short form.

In the base case, etanercept was associated with a higher ACR20 response compared with infliximab plus MTX (59 vs 50%) that led to higher QALYs (0.526 vs 0.478). Etanercept was also slightly less costly over a 1-year period than infliximab plus MTX (€14,926 vs €15,212 per patient). In univariate sensitivity analyses, etanercept was often the dominant strategy. However, important exceptions were found; for example, when it was assumed that patients who failed to reach an ACR20 response with infliximab were switched to etanercept (instead of receiving higher dosages of infliximab), the infliximab plus MTX strategy was substantially less costly than etanercept. When the lowest 95% confidence interval (CI) ACR20 response for etanercept and the highest 95% CI ACR20 response for infliximab found in the RCTs were used, infliximab plus MTX was the dominant strategy, in contradiction with the base case results.

Nuijten and colleagues instead carried out a CMA comparing etanercept at a standard dose with infliximab (3 mg/kg) plus MTX for patients with RA who failed at least two DMARDs in the Netherlands using a societal perspective [20]. The study was based on the assumption that the two TNF- α antagonists were equivalent in terms of efficacy and toxicity. Thus, all the analysis focused on total cost per patient over 1 year with the two strategies. It was assumed that no switching was possible even in the case of inadequate efficacy or adverse events. Resources used associated to direct medical

costs was mainly based on expert opinion, owing to the lack of published data at the time of the study, while for non-medical direct costs (transportation) and indirect costs they were derived from published studies.

In the base case, infliximab and etanercept acquisition costs were very similar (NLG31,526 vs NLG31,334 respectively). However, other direct medical costs were higher for infliximab, mainly owing to the concomitant use of MTX and the higher administration costs. Thus, the infliximab plus MTX strategy resulted more costly than etanercept (NLG45,115 vs NLG31,121). A few one-way sensitivity analyses were carried out and, in general, confirmed base case results. However, total costs with infliximab were strongly sensitive to changes in patient weight that was associated with the number of vials needed. Assuming two vials per infusion (weight <68 kg), the extra costs for infliximab plus MTX versus etanercept amounted to 22.7%, while assuming three vials per infusion (weight >68 kg and no storage of initiated vial), the extra cost with infliximab plus MTX raised to 62.6%.

Finally, in the technology assessment by Coyle and colleagues, costs and benefits of etanercept monotherapy and infliximab plus MTX were compared with standard DMARD sequences for patients that had failed MTX therapy from the perspective of the Canadian healthcare system [101]. Both etanercept and infliximab plus MTX were analyzed both as second-line (after MTX and before gold) and third-line treatments

Table 2. Cost-effectiveness results of the pharmacoeconomic studies included in the analysis.

Study	base case results		Sensitivity analyses	Ref.
	TNF inhibitors			
Nuijten <i>et al.</i> (2001)	ETA, INF	ETA less costly. Cost savings over 1 year: NLG12,444	ETA was cost-saving in all the univariate sensitivity analyses but difference depended on assumptions on INF doses	[20]
Hernandez-Cruz <i>et al.</i> (2004)	ETA, INF	ETA dominant: QALYs gained 0.048; cost savings: €286	ETA dominant in most scenarios, but INF more cost-effective when extreme values of CIs were used or when ETA was given to patients that initially failed INF	[19]
Bansback <i>et al.</i> (2004)	ETA, ADA, INF	ICERs between biologicals not estimated. Cost per QALY gained compared with DMARD: ETA: €36,927; ADA: €41,561; ADA plus MTX: €34,922; INF + MTX: €48,333	PSA performed only for the comparison between ADA plus MTX and ETA. At a willingness to pay of €44,000 per QALY, ADA plus MTX had a 83% probability to be cost effective compared with ETA alone.	[11]
Chen (2006)	ETA, ADA, INF	Incremental cost per QALY in late RA (early): ADA vs DMARDs: £141,000 (34,600); ADA plus MTX vs DMARDs: £64,400 (30,200); ETA vs DMARDs: £47,400 (30,400); ETA plus MTX vs DMARDs: £49,800 (28,500); INF plus MTX vs DMARDs: £139,000 (30,400); ETA plus MTX vs ADA plus MTX: £31,500 (24,900); ETA plus MTX vs INF plus MTX: £19,800 (24,600); ADA plus MTX vs INF plus MTX: £2560 (INF dominant)	Several analyses of scenario performed. base case results generally robust. When analyzed in late RA, ETA both as monotherapy and in combination with MTX was more cost effective than infliximab or ADA. When evaluated in early RA therapies, ETA or ADA alone provided the lowest cost-effectiveness ratios.	[16]
Coyle (2006)	ETA, INF	Incremental cost per QALY (second-line): ETA vs standard DMARDs: Can\$144,700; INF plus MTX vs standard DMARDs: Can\$113,000; Incremental cost per QALY (third-line): ETA vs standard DMARDs: Can\$125,700; INF plus MTX vs standard DMARDs: Can\$97,800	ICERs almost always higher than Can\$100,000; PSA: INF-based strategies are unlikely to be cost effective for willingness to pay lower than Can\$80,000, while ETA-based strategies are unlikely to be cost effective for values lower than Can\$100,000.	[101]
Spalding (2006)	ETA, ADA, INF	Incremental cost per QALY: ETA vs MTX: \$63,769; ADA vs MTX: \$89,772; ADA plus MTX vs MTX: \$194,589; INF plus MTX vs MTX: \$409,532	Univariate SA only for ETA vs MTX: sensitive to variation in HAQ reduction due to treatment effect, cost of ETA and withdrawal rate, ranging from ETA being dominant to a ICER higher than \$300,000/QALY	[18]
Wailoo <i>et al.</i> (2006)	ETA, ADA, INF	Total costs: INF: €94,029; ETA: €81,181; ADA: €79,535; Total QALYs: INF: 7.64; ETA: 7.66; ADA: 7.64; ICERs: ADA and ETA dominate INF; ICER ETA vs ADA: €92,058	When no drug wastage or no increase in dosage for INF was assumed, INF resulted significantly less costly. ICER for ETA and ADA vs INF over €600,000 per QALY	[17]

ADA: Adalimumab; CI: Confidence interval; DMARD: Disease-modifying antirheumatic drug; ETA: Etanercept; HAQ: Health assessment questionnaire; ICER: Incremental cost-effectiveness ratio; INF: Infliximab; MTX: Methotrexate; PSA: Probabilistic sensitivity analysis; QALY: Quality-adjusted life years; RA: Rheumatoid arthritis; SA: Sensitivity analysis.

(after MTX and gold). The economic analysis was based on a Markov model with a 6-month cycle length and 5-year time horizon. Patients could receive five different sequences of strategies that included or excluded biological agents. Patients could continue or withdraw their treatment on the basis of ACR response and severity of adverse events. Treatment response for biological agents were obtained from two separate RCTs [1,3]. Data on toxicities were obtained from the same trials and assumptions were made for long-term adverse events. The perspective of the analysis was that of payer, thus only direct costs were considered in the base case. In particular, only costs associated to RA medications were included, namely drug acquisition cost, monitoring costs and costs of managing adverse events. Resource use was mainly obtained from the two published trials.

The incremental QALYs with respect to standard DMARDs were 0.25 or 0.22 for infliximab plus MTX as second- or third-line therapy, respectively, and 0.27 or 0.25 for etanercept as second- or third-line therapy, respectively. Thus, etanercept was associated with slightly higher QALYs gained. Total costs over 5 years were Can\$9200 for standard DMARDs, Can\$37,900 for infliximab plus MTX second line, Can\$30,900 for infliximab plus MTX third line, Can\$48,400 for etanercept second line and Can\$41,200 for etanercept third line. Etanercept was thus more expensive than infliximab plus MTX both as second- or third-line treatment. These results generated a relatively high incremental cost per QALY gained for the biological agents (Can\$113,000 and \$97,800 for infliximab plus MTX as second- or third-line therapy, Can\$144,700 and \$125,700 for etanercept as second- or third-line therapy). Acceptability curves were presented and indicated that infliximab-based strategies are unlikely to be cost effective for a willingness to pay lower than Can\$80,000, while etanercept-based strategies are unlikely to be cost effective for values lower than Can\$100,000.

Infliximab plus MTX versus etanercept & adalimumab (monotherapy or with MTX)

There have been four pharmacoeconomic analyses that compared three anti-TNF agents. Bansback and colleagues estimated the costs and quality of life (QoL) associated with adalimumab monotherapy (40 mg every other week), adalimumab plus MTX, etanercept monotherapy, etanercept plus MTX and infliximab plus MTX in Sweden. All these strategies were also compared with DMARDs. The authors used a state-transition decision model based on individual patient simulations to estimate costs and benefits associated with a hypothetical cohort of patients with RA. Patients who entered the model could receive either one of the biological agents (as monotherapy or in combination with MTX) or a DMARD. On the basis of treatment response (ACR20 or ACR50), rate of adverse events and withdrawals, patients could continue the initial treatment or switch to other medications. The time horizon of the analysis was patient lifetime with a 6-month cycle length. Data on ACR20 and ACR50 response at 6 months for the biological agents were

taken from different RCTs (no head-to-head trial was available). The efficacy of DMARDs was instead taken from an observational study [22]. Adverse events and long-term withdrawals were also based on this observational study that included all the biological agents. The ACR20 and ACR50 responses were then converted to HAQ progression on the basis of clinical trial data. To estimate health utilities, a correlation between the Health Utility Index-3 and HAQ values was estimated (based on data from adalimumab trials) and converted to an algorithm. With regard to cost categories, only direct medical costs were considered, including drug acquisition and administration costs, monitoring and treatment of adverse events, personnel, hospitalizations and joint replacements. Resource use depended on patient pathways and expert opinion was used to assess those associated with the monitoring and treatment of adverse events and drug administration. The results of the analysis showed that relatively similar lifetime costs were found among the biological agents when the ACR50 was used as measure of effectiveness to drive the decision model, ranging from €90,058 for adalimumab monotherapy to €103,129 for etanercept plus MTX. In terms of QoL, adalimumab monotherapy was associated with the lowest QALY gain (1.65), but adalimumab plus MTX showed the highest gain (2.10). When the ACR20 was used as measure of effectiveness to drive the decision model, etanercept plus MTX was the most expensive strategy (€133,590) but also the most effective (2.95 QALYs gained), while the other strategies had similar lifetime costs. The authors did not perform any incremental analysis among the TNF- α antagonists, but they estimated the incremental cost per QALY for each strategy compared with the DMARD strategy. This ranged between €42,480 for etanercept monotherapy and €65,499 for adalimumab monotherapy when the ACR20 results were used, and between €34,922 for adalimumab plus MTX and €48,333 for infliximab plus MTX, when ACR50 results were used. A probabilistic sensitivity analysis (PSA) was carried out to estimate the uncertainty around model parameters. The authors concluded that, "on the basis of these findings, one cannot be certain about which TNF antagonist is the most cost effective".

Similarly, Spalding and colleagues compared adalimumab or etanercept as monotherapies, infliximab plus MTX and etanercept plus MTX, but as first-line therapies for early RA patients in the US context [18], since recent trials had shown that biologicals are also efficacious at onset of the disease [23,24]. Lifetime costs and benefits of the strategies compared were estimated through a Markov chain based on annual cycles. Patients entered the model at time of RA diagnosis and could immediately receive one of the biological agents. Patients remained on the study drug on the basis of its efficacy and tolerability. Sources for clinical data were different RCTs that provided HAQ reduction over the time horizon of the study. In the original trials, each biological agent was compared with MTX, thus direct comparison was feasible only for anti-TNF treatments versus MTX alone and not among biological agents. The transition probabilities for switching drugs was calculated by taking the reciprocal of the average duration that patients remain on

each drug (obtained from Barton *et al.* [15]). It was assumed that patients received the same benefits and costs from second-line therapies, independently from the treatment previously taken and duration of first-line treatment. HAQ scores were converted to utility weights by a published regression formula [14]. The base case analysis adopted the perspective of the payer, thus only direct costs were considered (RA medications, physician visits, monitoring and hospitalizations owing to adverse events). Data from clinical trials provided doses, frequency of administration for RA medications and rate of adverse events. Other resource use was estimated as a function of patients' HAQ scores based on published evidence. The results of the Markov model showed that the use of biological agents as first-line treatment produced an increase in QALYs between 2 and 10% with respect to MTX over patient lifetime, but at very high additional lifetime costs. The incremental cost per QALY compared with MTX was \$63,769 for etanercept monotherapy, \$89,772 for adalimumab monotherapy, \$194,589 for adalimumab plus MTX and \$409,532 for infliximab plus MTX. Incremental QALYs and costs for each agent were not provided, so it was not possible to directly compare cost-effectiveness results of biological agents. It was concluded that adalimumab and etanercept as monotherapies might be considered as cost effective strategies depending on the willingness to pay the threshold adopted.

In another study conducted in the USA, Wailoo and colleagues estimated the cost-effectiveness of etanercept and adalimumab as monotherapies in comparison with infliximab alone from the perspective of the Medicare program [17]. In addition, the study assessed the cost-effectiveness of using a second or third biologic drug in a sequence of treatment compared with infliximab alone. Recommended doses were used for etanercept and adalimumab while infliximab was initially given at 3 mg/kg every 8 weeks, but dose increase was assumed in the base case (4.5 mg/kg at 6 months and an increase of 0.4 mg/kg per year thereafter). In addition, drug wastage was assumed in the base case for infliximab and doses were rounded to full vials, this includes CEA, CUA, CBA, CMA and CCA.

A decision model based on individual patient simulations was developed where individual patients were followed from the time of starting treatment on a biologic until death, with changes calculated every 6 months. The primary sources for effectiveness data of the biologic drugs were randomized clinical trials (four for etanercept, two for infliximab and four for adalimumab). These studies provided data on the ACR20 and ACR50 response at 6 months for each biological agent. However, differences were found between studies in terms of comparator (placebo or MTX), patient characteristics, doses and timing regimes. Standard meta-analysis was considered as inadequate to synthesize all this evidence. Thus, the authors performed a meta-regression of the RCT data in order to estimate drug effectiveness by first calculating the probability of response on MTX alone and then applying the odds ratio for treatment response. Disease duration and baseline HAQ-Disability Index 1 were included as covariates in the meta-regression.

It was found that patients were expected to respond better to biological drugs the greater the time between diagnosis and treatment and if their baseline HAQ was lower.

The time to withdrawal for the biologic therapies was modeled using a Weibull survival curve based on a detailed disease registry comprising more than 17,000 US patients (the National Databank for Rheumatic Diseases [NDB]). It was found that for an average patient, duration on treatment was slightly higher for etanercept (33 months), followed by adalimumab (32 months) and infliximab (30 months). ACR20 and ACR50 biologic response, together with time of treatment, determined the HAQ score for the hypothetical patients for each anti-TNF or combination of anti-TNF. HAQ scores were then converted to health utilities by a multivariate regression based on the EuroQol (EQ)-5D results of the NDB 6-monthly assessments. Similarly, resource use was estimated as a function of patients' HAQ scores based on data from the NDB and generalized linear models were applied to estimate resource use over time. Cost categories reflected the Medicare perspective and included medications, outpatient visits, monitoring and hospitalizations.

The results of the probabilistic analysis based on individual patient simulations showed very similar lifetime health benefits associated with the three biological agents (7.64, 7.66 and 7.64, respectively). Etanercept and adalimumab were less costly (mean total costs US\$81,181 and US\$79,535) in the base case compared with infliximab (US\$94,029). Thus, infliximab was dominated by etanercept and of greater cost than adalimumab using base case assumptions. However, base case results were totally contradicted when no drug wastage for infliximab was assumed. In this case, where no rounding to full vials was considered, infliximab was less costly than adalimumab and etanercept, with associated incremental cost-effectiveness ratio (ICERs) higher than US\$500,000 per QALY. Similarly, in absence of dose increase (but with drug wastage) infliximab saved more than US\$13,000 compared with the other two biological agents, and the resultant cost-effectiveness ratios were extremely high (over US\$1 million per QALY for adalimumab and over US\$650,000 for etanercept as compared with infliximab).

Finally, the study by Chen and colleagues [16] was an updated version of Health Technology Assessment (HTA) by Barton *et al.* [15] and Jobanputra *et al.* [14] carried out in the UK. Several strategies for treatment of patients with early or late RA that include or exclude anti-TNF treatments were compared. Among biological agents, five alternative strategies were evaluated both as first-line treatments (early RA) or third-line options (late RA): adalimumab alone or in combination with MTX; etanercept alone or in combination with MTX; and infliximab (3 mg/kg every 8 weeks) in combination with MTX. A discrete event simulation model was used in order to estimate lifetime costs and QALYs associated with different sequences of treatments that might or might not include an anti-TNF agent (as first- or third-line option). Hypothetical patients were entered in the model and followed (individually) a sequence of

DMARDs chosen to reflect a typical clinical pathway for RA. Patients moved to the next treatment in the sequence because of lack of efficacy (increase in HAQ), adverse events or need for joint replacement. In addition, it was assumed that the sequences of treatments received might vary on the basis of reasons for discontinuation. Thus, costs and benefits associated with the different pathways were related to the length of each treatment period, which depended on treatment efficacy and safety. The initial HAQ reduction associated with the use of biological agents (when effective) was derived from RCTs or meta-analyses of RCTs both for early and late RA. Similarly, HAQ reduction on treatment for DMARDs were taken from clinical trials or based on authors' assumptions. Beta distributions were assigned to treatment effectiveness expressed as initial HAQ reduction. The time spent on each DMARD or on the TNF antagonists was estimated by means of a Weibull distribution and depended on data on safety and effectiveness. Data on toxicity were based on an observational study, while data for adalimumab were assumed to be the same as infliximab. Data for DMARDs were mainly taken from a large database representing UK clinical practice.

The relationship between QoL and HAQ was measured by an equation, based on a data set provided by Hurst *et al.* [25]. Only direct costs (drug acquisition and administration, monitoring and joint replacement) were considered, given that the perspective of the analysis was that of the NHS. Total costs for each treatment pathway depended on the time on each treatment, the HAQ reduction associated to each treatment and side effects.

When given as first-line strategy and compared with a sequence of DMARDs, adalimumab and etanercept alone showed the lowest ICERs (GBP£53,000 and 49,000 per QALY, respectively), while combination therapies were less cost effective (£78,000 per QALY for etanercept plus MTX, £170,000 per QALY for adalimumab plus MTX and up to £650,000 per QALY for infliximab plus MTX, mainly owing to low QALY gains). Etanercept and adalimumab alone dominated etanercept plus MTX and adalimumab plus MTX, respectively. The incremental cost per QALY for etanercept alone versus adalimumab alone was £43,100, while the incremental cost per QALY for etanercept or adalimumab in combination with MTX over infliximab plus MTX was £26,200 and £3830, respectively. When given as third-line strategy and compared with a sequence of DMARDs, etanercept alone or in combination and adalimumab in combination were associated with the lowest ICERs (approximately £50,000 per QALY), while infliximab or adalimumab plus MTX were less cost effective (£140,000 per QALY for both). The incremental cost per QALY for etanercept alone versus adalimumab alone was £18,300, while it was £31,500 for etanercept plus MTX versus adalimumab plus MTX. The incremental cost per QALY for etanercept or adalimumab in combination with MTX over infliximab plus MTX was £19,800 and £2560, respectively.

In general, when analyzed as third-line therapies, etanercept both as monotherapy and in combination with MTX was more cost effective than infliximab or adalimumab. When evaluated

as first-line therapies, etanercept or adalimumab alone provided the lowest cost–effectiveness ratios.

Expert commentary: critical appraisal of the published economic evaluations comparing anti-TNF treatments

The pharmacoeconomic studies described are characterized by important differences in terms of methodological features and data sources that explain the differences in cost–effectiveness results. The methodological quality of the analyses identified varies substantially and it is important to highlight strengths and limitations of each study.

The key issue in comparing different anti-TNF agents for the treatment of RA relates to the lack of head-to-head clinical trials. Concerns have been expressed over the use of indirect comparisons of treatments. For example, the Cochrane Collaboration's guidance to authors states that, "indirect comparisons are not randomized, but are observational studies across trials, and may suffer the biases of observational studies, for example confounding" [26].

Different approaches have been used in the published economic evaluations to address this issue. For example, Hernandez-Cruz and colleagues obtained clinical data directly from two different RCTs; one trial compared etanercept with placebo while the other trial compared infliximab plus MTX with MTX alone [19]. They stated that the patient populations of the two RCTs were relatively similar, but did not perform any statistical analysis to give a quantitative estimation of this homogeneity. A similar approach was taken by Coyle (for late RA) [101] and Spalding (early RA) [18]. Nuijten *et al.* instead adopted a cost–minimization approach, assuming that no difference in efficacy and toxicity between etanercept and infliximab could be proved, given the lack of direct comparisons [20]. Finally, in the UK HTA by Chen *et al.*, treatment effect was modeled through probabilistic distributions to take account for the uncertainty in clinical estimates, but these were mainly obtained from different trials [16].

All these approaches appear inappropriate. Although anti-TNF treatments have not been directly compared in a trial, they could be indirectly compared since both have been assessed against a common comparator. Statistical techniques are available to deal with the issue of a lack of head-to-head comparisons. For example, the use of a mixed treatment comparison (MTC) model [3] would enable a better estimation of the true relative effect of infliximab versus etanercept given the potential heterogeneity between trials [27,28]. In general terms, a MTC can be considered as an extension of a meta-analysis and consists of identifying a chain of evidence between treatments when head-to-head comparisons are not available. In the case of infliximab versus etanercept, a deviation from the standard MTC approach might also be necessary, because the medications given in the control arm of the two trials [1,3] are very different. Recently, Nixon and colleagues have developed a MTC model to compare the different biological agents in RA [29]. In particular, they performed a meta-regression in order to assess the impact of patients'

disease duration, and HAQ scores at baseline on the relative effectiveness of the biological agents versus placebo. The results of their analysis showed that the three TNF antagonists have comparable effectiveness in terms of ACR response. They also found that the relative effectiveness of biologic drugs versus the comparator is greater for studies with patients who have longer average disease duration while a study with higher average baseline HAQ is expected to show worse relative effectiveness. Given that in the etanercept pivotal trial [3] mean disease duration at baseline was higher than that in the infliximab trial (11 and 8.4 years, respectively) [1], and that mean HAQ score at baseline was lower in the etanercept trial than in the infliximab trial (1.6 vs 1.8), it is likely that the relative effectiveness of etanercept versus placebo is overestimated compared with the relative effectiveness of infliximab plus MTX versus MTX.

These statistical techniques were used only in the Wailoo study where a meta-regression was carried out to adjust for differences between original trials in terms of comparator (placebo or MTX), patient characteristics, doses and timing. They developed a MTC model with bivariate random effect, adding the meta-regression coefficients found for the disease duration and HAQ score at baseline. It should be acknowledged that these statistical techniques have only recently been developed and applied to pharmacoeconomic models. The issue of heterogeneity in the primary source of data was instead partially addressed in the study by Bansback and colleagues that adjusted the ACR20 and ACR50 trial results using a reference placebo [11], thus employing the relative treatment effect instead of the absolute effect in the analysis.

Specific issues are then associated with each of the studies analyzed. In particular, among studies that compared infliximab plus MTX and etanercept alone, several weaknesses were found.

In the study by Hernandez-Cruz *et al.*, mean ACR20 results (59% for etanercept vs 50% for infliximab) found in the trials were used as final measure of effectiveness, without taking into account the uncertainty around these mean values [19]. This appears particularly relevant given that the 95% CIs around the mean ACR20 results for etanercept and infliximab overlap (48–70% for etanercept and 39.4–60.6% for infliximab). Similarly, the reduction in HAQ scores obtained from the two RCTs was directly used in order to assess the gain in patients QoL and only mean estimates used, raising all the problems of indirect comparison and uncertainty we have previously mentioned. In addition to these key methodological issues, other points can be raised. The time horizon of the model was 1 year. This is inadequate to estimate the real costs and benefits of RA treatments that should be assessed over a long-time period given the progressive nature of the disease. As regards the cost analysis, details were given on unit costs and resource use for etanercept and infliximab that were appropriately taken from Spanish patients. However, no information was provided on average patient weight (which is fundamental for infliximab and irrelevant for etanercept) and on the number of vials per patient needed with infliximab.

Moreover, the cost analysis is driven by the ACR20 results obtained from the trials (given that toxicity was similar for etanercept and infliximab). This means that less patients in the infliximab branch of the model (50%) than in the etanercept branch (59%) reached a ACR20 improvement, and more patients in the infliximab arm had to change treatment (influximab dose increase in the base case). When etanercept was given to patients who failed to achieve ACR20 at 6 months with infliximab, the strategy of initial infliximab 3 mg/kg resulted in substantially lower costs (-€1137 per patient), contradicting base case results. Finally, the authors did not adequately address the issue of the uncertainty around cost parameters. Given that the cost results were relatively similar between the two strategies (etanercept was associated to a lower cost of €286 per patient, less than 2% of total costs of the two agents), a PSA would have provided information on the variability around mean values.

The main drawback of the study by Nuijten *et al.* is intrinsic in the form of economic evaluation performed. Concerns have been raised on the use of a cost-minimization analysis. For example, Briggs and O'Brien showed that a cost-minimization analysis is an appropriate method of analysis only under rare circumstances [30]. They argued that, "the analytic focus should be on the estimation of the joint density of cost and effect differences and the quantification of uncertainty surrounding the incremental cost-effectiveness ratio". Thus, if we are not only interested in mean values, but also on the uncertainty around these values, it is very rare that two medications are exactly equally effective.

With regard to the cost analysis, resource use for direct costs (which represent the higher category of costs of the analysis) were mainly obtained from expert opinion. The authors stated that etanercept and infliximab were not approved at the time of the study in The Netherlands and consequently not available for treatment in daily practice. Thus, some resource utilization was based on assumptions that might not reflect real clinical practice. Furthermore, no observational prospective study was available at the time of this work that could confirm the assumptions made. The authors reported a detailed breakdown of cost categories and of unit costs associated to each item. However, less transparency was found in reporting the quantities of resource use. As in the study by Hernandez-Cruz *et al.*, the time horizon of the model was 1 year [19]. Again, we believe this is inadequate to estimate the real costs of RA treatments and might overestimate the cost of infliximab because of the issue of the loading dose. In addition, the authors assumed an unrealistic scenario where all patients would continue the two biological agents over 1 year, without taking into account switching as a result of adverse events, lack of efficacy or mortality. Finally, the methods used to handle uncertainty in the cost analysis appear quite weak. The authors only reported mean values and performed few univariate sensitivity analyses. This approach does not provide enough information on the uncertainty around model parameters and around cost results, as previously stated.

The study by Coyle and colleagues presents some of the limitations already raised for Hernandez-Cruz. Specifically, the use of data directly obtained from no head-to-head clinical trials provided higher QALYs gained for etanercept compared with infliximab. This was partly overcome by the use of PSA to take account of the uncertainty in clinical estimates. However, results of the PSA were presented only for the comparisons between biological agents and DMARDs and not between etanercept and infliximab. Another limitation of the study was associated with methods used to estimate utility weights from HAQ changes. Specifically, the HAQ change was multiplied by a conversion factor of 0.2 to obtain QALY changes [14,15,19]. However, to assume a constant QALY gain for a given change in HAQ, independent of the degree of disease severity, does not appear to be clinically appropriate. Finally, only costs associated with RA medications were considered and it is not clear why RA-related hospitalizations, physician visits and surgeries were excluded. The exclusion of these costs might partly explain the high ICERs found for biological agents with respect to DMARDs, since benefits in terms of reduction of future costs were not included.

In the case of studies that compared all the anti-TNF options for RA, three of them [11,16,17] present several strengths. The study by Spalding is interesting because it compared biological agents in early RA [18], however, it did not provide details on incremental costs and QALYs for different options, but only final cost–effectiveness ratios. Thus, it is unclear whether study drawbacks (e.g., no methods used for indirect comparison, and assumptions on costs and benefits of second-line treatments) have favored any biological agent over another.

The technical quality of the paper by Bansback and colleagues is very high [11]. A probabilistic model based on individual patient-level simulations was used to take into account uncertainty in clinical estimates and heterogeneity in patient population. The use of a lifetime horizon permits the estimation of the impact of the different strategies on disease progression and the extrapolation of short-term trial results to a more appropriate time dimension. Utility values were taken from a large sample of RA patients (almost 2000) from a clinical trial. Both utility values and direct costs (excluding those of study drugs and side effects) were related to HAQ scores, which represents a standard approach in RA models [7,9]. Finally, the authors used a conservative approach for biological agents, assuming a ‘rebound’ effect when the anti-TNF agents were withdrawn. (They assumed a HAQ worsening at the point of withdrawal equal to the initial HAQ improvement).

The main problem with the analysis is related to the comparability of the ACR20 and ACR50 data used for the different strategies. The authors appropriately adjusted the ACR20 and ACR50 response rates found in the intervention arms (biological agents) of the different trials by the difference in response between trials in the placebo arms. This method is correct only if we assume that the patient populations in the different trials are completely homogenous. In fact, differences in the baseline characteristics of patient populations are likely to have an

impact on effectiveness results both in the placebo arms of the trials and possibly also on the relative effectiveness of an intervention with respect to placebo. In particular, as previously stated, in a recent paper by Nixon *et al.*, it has been proven that the relative effectiveness of biologic drugs versus the comparator is greater for studies with patients who have longer average disease duration at baseline, while a study with higher average baseline HAQ is expected to show worse relative effectiveness [29]. (We acknowledge that two of the authors of the Bansback *et al.* paper [NJ Bansback and A Brennan] are also coauthors of the Nixon *et al.* work.) In this case, the ACR20 and ACR50 data used to populate the Bansback model may be biased against some strategies. For example, in the Maini trial, patients had a HAQ score of 1.8 at baseline and a disease duration of 8.4 years, while patients in the Weinblatt *et al.* had an HAQ score of 1.55 and a disease duration of 12.2 years at baseline. The relative effectiveness of adalimumab plus MTX versus MTX alone (67 vs 15%) can therefore have been overestimated compared with the relative effectiveness of infliximab plus MTX versus MTX alone (50 vs 20%). For the same reasons the relative effectiveness of etanercept versus placebo might have been overestimated compared with the relative effectiveness of infliximab plus MTX versus MTX.

The outcome and cost results from the different strategies should thus be viewed with caution. The study by Chen and colleagues has some of the strengths identified in the work by Bansback *et al.* For example, they used discrete-event simulations to take account of patient heterogeneity and variability in clinical estimates over a lifetime horizon. Also, a rebound effect at treatment discontinuation was assumed. Furthermore, sequences of treatments were chosen in order to consider different possible pathways that reflected UK clinical practice. The analysis was conducted both for early and late RA patients and several scenarios were considered. Nevertheless, the sources used for some key parameters raise some doubts. This is particularly important in the case of some of the data used to populate the Weinbull distribution, given that the model is driven by the time spent on each treatment. Toxicity data were taken from an observational study performed in Sweden, and we cannot exclude potential confounding or selection bias in the primary study. The results of this study generated different parameters in the Weinbull distribution that led to a longer time on etanercept than infliximab. This appears to be the main reason for the higher QALYs and higher costs found for etanercept compared with infliximab. Similarly, assumptions were made for adalimumab toxicity. Finally, as acknowledged by the authors, costs associated with hospitalization (apart from those of surgery) or rheumatologist visits were excluded. It is unclear whether their exclusion has any impact on the comparison between the two biological agents, but they should have been included to have a full understanding of total RA costs with the different strategies.

The technology assessment by Wailoo and colleagues is of very high methodological quality. Both data sources and methods used to synthesize the effectiveness evidence appear appropriate,

as previously reported for indirect comparison statistical techniques. Disease progression and treatment withdrawal was estimated from a large US cohort of patients with a longer follow-up compared with RCTs. Appropriate methods and reliable sources were used to convert HAQ scores to health utilities, and two different instruments were adopted to obtain utility weights (EQ-5D and Short Form-36). The issue of the uncertainty in model parameters and variability in patients characteristics was addressed by the use of both individual patient simulations and PSA. Moreover, univariate sensitivity analyses were performed varying the assumptions on the lifetime progression of the disease that corroborate the robustness of the base case results. Thus, effectiveness results are highly supported by the quality of methods, data sources and the detailed description. It was found that the three biological agents are very similar in terms of QALYs gained, independently of the assumptions made, while sequential biological strategies provide only slightly higher health benefits.

The key question from this study is related to the costs associated with the biological agents. In particular, while lifetime costs with adalimumab and etanercept were relatively similar (adalimumab was approximately US\$2000 less costly in most of the analyses), lifetime costs with infliximab depended on the assumptions about its dosage. In general, it was found that the drug acquisition cost was the main element of total costs for each agent. Drug cost for infliximab varied substantially on the basis of patient's weight, assumption on dose increase and drug wastage. While the variability in patient's weight was investigated through the individual model simulations, different assumptions on drug wastage and dose increase were explored by univariate sensitivity analyses. These led to different results from the base case analysis, highlighting that infliximab would be less expensive than the other two biological agents when no drug wastage is assumed or when no dose increase is considered. While increases over time in infliximab doses reflects a common strategy when patients do not achieve the ACR20 or ACR50 targets, (but dose increase is likely to vary between locations and centre), it appears more unusual to lose uncompleted vials. In real life, more than one patient is likely to receive infliximab in each centre, and vials not fully used for a patient might be given to other patients, reducing drug wastage substantially. However, this needs further investigation.

In general, this work overcomes some of the weakness of previous models, particularly in terms of evidence synthesis, suggesting similar effectiveness between the biological agents and underlying the importance of the assumptions about drug doses and the associated costs.

Five-year view

The pharmacoeconomic studies published to date that compare TNF antagonists have not provided a clear answer about which should be considered the most cost-effective agent for RA patients resistant to DMARDs. For example, Hernandez-Cruz *et al.* or Nuijten *et al.* have found etanercept more cost effective

or dominant compared with infliximab, but with important limitations in methods and data sources, as previously reported. Similarly, the study by Chen *et al.* has suggested that etanercept might be more cost effective than infliximab plus MTX or adalimumab, but it appears that the results are strongly influenced by assumptions on drug toxicities. The two studies that have applied more sophisticated methods for indirect comparison of clinical estimates have instead showed that biological agents are likely to be very similar in terms of effectiveness results and that assumptions on drug dosage and wastage for infliximab can have a strong influence on cost-effectiveness results [11,17].

In order to overcome issues on the relative efficacy and safety, in the next years, ideally head-to-head trials of the various drugs should be available. If such trials have not been conducted, mixed treatment comparison models should be used in order to make the relevant comparison. It is also important that future studies consider all the relevant alternatives (including new products) and that alternative sequences of therapies are compared. Also, the positioning of the anti-TNF agent in a sequence of treatments can become important, since biological agents might show efficacy in different patient populations. However, we feel that the patient population chosen for the economic model should be based on that included in the pivotal trial for anti-TNF and its comparators, although there is a need to conduct subgroup analyses to assess the relative cost-effectiveness of biological agents in patients with different disease severity.

Future economic models are likely to be based on HAQ states, since HAQ is measured both in trials and long-term observational studies. HAQ states can also be assigned costs and QALYs. However, other important factors such as disease duration, sex, age or treatments previously received are important determinants of disease progression. It is likely that individual patient simulations will be preferred to the standard Markov model, especially when PSA becomes computably feasible for these types of models. Patient heterogeneity and its impact on disease progression is easier to model using micro-simulations. The possibility of a rebound effect on discontinuation of treatment with a TNF agent should be considered. Long-term progression (i.e., beyond the trial) should be modeled using a clinical database relevant to the setting(s) under study.

Another important feature that needs more investigation in the next few years is that of benefit measure. It is likely that CUA will be needed, and that utility weights estimates and their correlation with model health states can determine final results. Ideally, health utility data should be available from the clinical trial(s) of the drugs under investigation. If such data are not available, a free-standing study should be conducted in order to relate health utilities to HAQ states. Registries could also be used to collect utility data.

Published studies have shown that medication-related costs (acquisition, administration and the costs of dealing with adverse events) are the largest components of direct costs. Future studies should pay great attention when comparing

medication costs of drugs with a weight-based dosing regimen such as infliximab. Use of an average patient weight (e.g., 70 kg) is not sufficient to explore the relative cost-effectiveness of biological agents. Wastage of drug should also be considered in costing. However, it should be noticed that the drug price is always the main cost category, thus a reduction of these costs might dramatically increase the cost-effectiveness of the anti-TNF therapies. Finally, productivity losses owing to disease, and the gains from return to work, should be modeled, as these are relevant in several jurisdictions.

In general, we expect that future economic studies on anti-TNF will give special attention to the overall parameter uncertainty that can be explored using PSA. One way and multiway

sensitivity analyses can be used to explore how individual parameters affect study results and to assess the impact of the main structural assumptions in the model.

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Key issues

- Ten full economic evaluations comparing two or more anti-TNF agents in patients with RA have been published to date, all but one have estimated the impact of biologicals in patients who have failed previous disease-modifying antirheumatic drugs.
- Published studies are based on economic models (mainly cohort Markov models or individual patient simulations) and most have used a lifetime horizon to assess costs and benefits of therapies.
- The studies identified vary greatly in terms of methodological quality and data sources and critical appraisal of each study was needed to better interpret the reliability of study results.
- No head-to-head clinical trial is available for the three anti-TNF agents analyzed (adalimumab, infliximab and etanercept), so clinical data to populate the economic models were taken from separate studies. Different methods have been used to deal with this issue.
- In general, the studies that have used trial estimates to populate the economic model without any adjustment for potential differences in clinical studies have found etanercept to be more cost effective (or dominant) compared with infliximab plus methotrexate. This was owing to the slightly higher American College of Rheumatology criteria (ACR)20 and ACR50 response found in the pivotal trial for etanercept.
- Studies that have applied more appropriate statistical techniques for indirect comparisons (such as mixed treatment comparison models) have instead found similar effectiveness results between the biological agents and underlined the importance of the assumptions about drug doses and the associated costs.
- Patient weight, related doses and assumptions on drug wastage for infliximab appear to be a key determinant of relative cost compared with adalimumab and etanercept and need to be further investigated.
- If head-to-head trials of the various drugs are not conducted, mixed treatment comparison models should be used in future pharmacoeconomic studies. In addition, uncertainty in key model parameters need to be further explored and patient heterogeneity evaluated in subgroup analyses.

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Affiliations

- Marco Barbieri, MSc
 Universitat Pompeu Fabra, Balmes 132,
 08008 Barcelona, Spain
 Tel.: +39 515 873 445
 Fax: +39 515 873 445
marco.barbieri@upf.edu

Barbieri, Drummond, Puig Junoy et al.

- *Michael F Drummond, PhD*
University of York, Centre for Health Economics,
Heslington, York, YO10 5DD, UK
Tel.: +44 190 432 1401
Fax: +44 190 432 1402
md18@york.ac.uk
- *Jaume Puig Junoy, PhD*
Universitat Pompeu Fabra, Balmes 132,
08008 Barcelona, Spain
Tel.: +34 935 421 800
Fax: +34 935 421 808
jaume.puig@upf.edu
- *Miguel Angel Casado Gómez, Pharm PhD*
Pharmacoeconomics & Outcomes Research
Iberia, C/ Antonio Rodríguez 8, 28224 Pozuelo
de Alarcón, Madrid, Spain
Tel.: +34 917 156 565
Fax: +34 917 156 565
ma_casado@porib.com
- *F Javier Ballina García, PhD, MD*
Head of Unit of Rheumatology, University
Central Hospital of Asturias, C/Celestino
Villamil s/n, 33006 Oviedo, Spain
Tel.: +34 985 108 098
Fax: +34 985 274 780
jballina@telefonica.net
- *Pilar Blasco Segura, PhD*
Head of Pharmaceutical Service, Consorcio
Hospital General, Hospital General
Universitario de Valencia, Avda. Tres Cruces,
s/n, 46014 Valencia, Spain
Tel.: +34 961 972 141
Fax: +34 961 972 220
blasco_pil@gva.es
- *José Luis Poveda Andrés, PhD*
Hospital Universitario La Fe, Servicio de
Farmacia, Avda. Campanar 21, 46009
Valencia, Spain
Tel.: +34 961 973 133
Fax: +34 961 973 302
poveda_josand@gva.es