Cost-Effectiveness of Sequential Therapy with Tumor Necrosis Factor Antagonists in Early Rheumatoid Arthritis

ANDREW DAVIES, MARY A. CIFALDI, OSCAR G. SEGURADO, and MICHAEL H. WEISMAN

ABSTRACT. ***Objective.*** To estimate the comparative lifetime cost-effectiveness of sequenced therapy with tumor necrosis factor (TNF) antagonists as the initial therapeutic intervention for patients with early rheumatoid arthritis (RA).

Methods. Because patients with RA switch regimens many times throughout the course of disease, sequenced therapeutic interventions were modeled, continuing until the last effective agent failed or death occurred. The model used published clinical outcomes from short-term, randomized controlled trials. Direct treatment costs and costs of lost productivity were modeled for each of 5 alternative treatment sequences. Incremental cost-effectiveness ratios are expressed as quality-adjusted life-years (QALY) gained.

Results. Treatment sequences that included TNF antagonists produced a greater number of QALY than conventional disease modifying antirheumatic drug regimens alone. The cost-effectiveness of sequenced therapy initiated with adalimumab plus methotrexate (MTX) extendedly dominated both infliximab-plus-MTX–initiated and etanercept sequences. The cost of adalimumab plus MTX per QALY was US $47,157 excluding productivity losses, and $19,663 including productivity losses. A supplementary sequence that incorporated adalimumab-plus-MTX–initiated first-line therapy followed by another TNF antagonist as second-line therapy was modeled; this sequence resulted in additional QALY gained and extendedly dominated all single-TNF strategies.

Conclusion. Of the 3 single-TNF antagonist sequences, the adalimumab-plus-MTX–initiated sequence was cost-effective in producing the greatest number of QALY. Multiple TNF strategies, such as the supplementary sequence modeled in this analysis, may be cost-effective in producing even greater health gain. (First Release Dec 1 2008; J Rheumatol 2009;36:16–25; doi:10.3899/jrheum.080257)

Key Indexing Terms:
TUMOR NECROSIS FACTOR ANTAGONIST COST-EFFECTIVENESS ADALIMUMAB
QUALITY-ADJUSTED LIFE-YEARS RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic autoimmune disease that affects many body systems: musculoskeletal, nervous, respiratory, cardiovascular, renal, and hematologic, among others. RA prevalence is estimated to be 0.5% to 1% in diverse populations worldwide[1]. RA causes progressive joint damage, pain, disability, and premature mortality, particularly if not treated early and appropriately[1]. Throughout the disease course, patients with RA typically switch regimens many times as efficacy wanes, the patient becomes symptomatic again, or progression of disease continues[2]. Disease modifying antirheumatic drugs (DMARD) are often used as first-line therapy, in succession or in combination, along with other antiinflammatory agents, to relieve symptoms and control disease progression. Methotrexate (MTX), approved by the US Food and Drug Administration in 1985 for the treatment of RA, is the most widely used traditional DMARD and is the cornerstone of current treatment for RA[3]. Effective as this agent is, there are many patients who do not tolerate MTX or for whom MTX is insufficient to prevent progressive loss of function or joint damage. In addition, traditional DMARD therapy has often been difficult to sustain over time in some patients, partly because these agents have multiple toxicities[4].

Early and aggressive therapy for RA. More recently introduced biologic DMARD act more effectively than traditional DMARD on the underlying structural damage rather than

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only on alleviation of symptoms. These agents [adalimumab (Humira®; Abbott Laboratories, Abbott Park, IL, USA), etanercept (Enbrel®; Immunex Corp., Thousand Oaks, CA, USA), and infliximab (Remicade®; Centocor, Inc., Malvern, PA, USA)] target specific components of the dysregulated immune system, specifically, the cytokine tumor necrosis factor (TNF). Adalimumab is a fully human monoclonal antibody with high affinity and specificity for TNF. Adalimumab and other TNF antagonists have proved to be effective, not only in improving signs and symptoms of RA, but also in inhibiting the progression of joint damage and improving quality of life by inhibiting progression of disability[5-14].

Radiographic evidence of joint damage occurs early in patients with RA and, without treatment, joint damage is persistent and progressive, especially within the first 2 years[15-18]. Studies consistently find that early, effective treatment significantly reduces radiographic progression[19], and recent evidence shows that early and aggressive intervention in RA produces better clinical outcomes than late therapy[4,5,9,13,14,20-22]. The clinical effectiveness of TNF antagonists has raised expectations that early intervention with such agents may achieve better clinical outcomes and lengthen the time patients spend in remission and in lesser degrees of disability, which would positively affect both quality of life and the associated economic burden of disease[23-28].

Economic burden and disability. Considerable economic impact is seen early in disease progression. In the US, the average total direct cost of treatment for patients with RA, before the introduction of TNF antagonists, was estimated to be at least US $7,193 annually[25], with hospital admissions accounting for more than half of total direct costs[25,26]. The economic burden of RA intensifies with increasing degrees of disability; patients with RA in the highest quartile of functional disability were found to have direct costs 2.5 times greater than average and hospital costs 7 times greater than those patients at the lowest level of disability[26]. Societal costs of RA have also been correlated with the extent of disability, and significant socioeconomic impact (including the effect of lost productivity) has been noted as early as the first year after diagnosis[27-29]. Patients with RA have disability rates 1 to 5 times greater than disability rates in the general population, with work-related disability rates ranging from 30% to 40% at 5 years after initial diagnosis[28].

In a study of patients with early RA who were treated with conventional therapies (including DMARD)[28], 6% to 16% needed major adaptations or appliances that affected home and social life (e.g., wheelchairs, stair adaptations, major bathroom changes, and walking aids) within 5 years following diagnosis. Moreover, 10% to 28% required orthopedic surgeries (e.g., major joint replacement, excision arthroplasty or synovectomy, and other inpatient medical treatments for RA). Of the 48% of patients with early RA who were in paid employment at the time of their diagnoses, almost a quarter (22%) retired within 5 years because of RA symptoms and related disability.

Because biologic agents are considerably more expensive than traditional DMARD, evidence of the cost-effectiveness of TNF antagonist therapy in early RA is important. The use of cost-effectiveness evidence to aid in healthcare decision-making and reimbursement has increasingly been recognized as essential for ensuring value for money in allocating healthcare resources.

In chronic diseases such as RA, models that extrapolate from short-term efficacy measures in clinical trials to health outcomes over patients' lifetimes are necessary to identify the full influence of treatment in terms of costs and benefits.

The objective of the model reported here was to analyze the cost-effectiveness of TNF antagonist intervention in early RA, before extensive disease progression has occurred, compared with DMARD-only therapy. Little investigation into the cost-effectiveness of these agents in the early stages of RA has been done[30], and many cost-effectiveness models have not addressed therapy sequenced over the full course of disease. This model examines costs and clinical outcomes over a course of competing sequential regimens, rather than by comparing a single regimen against another. The analysis compared each TNF antagonist-initiated sequence with each of 3 other sequences (a DMARD-only sequence and 2 sequences initiated by the other TNF antagonists followed by DMARD use). A supplementary analysis modeled the potential cost-effectiveness gains obtainable by using 2 TNF antagonists (adalimumab plus MTX followed by etanercept monotherapy) before switching to traditional DMARD alone.

MATERIALS AND METHODS

Model overview. RA is a chronic disease characterized by periods of response to treatment followed by unpredictable loss of therapeutic effect and switches to alternative treatments[2,31]. The model, therefore, compared sequences of treatments rather than single agents. The individual patient simulation model follows a structure described by Bansback, *et al*[31], with individual patients' outcomes sampled at 6-month intervals (Figure 1). For the present analysis, 1000 patients were randomly simulated to experience several alternative sequences of therapies. Patients were entered into the model at a baseline degree of disability, represented by a score of 1.5 on the Health Assessment Questionnaire (HAQ) Disability Index, which was the mean baseline score of patients in the adalimumab PREMIER trial[14]. The PREMIER trial was the first head-to-head trial of a combination of a TNF antagonist plus MTX versus either agent alone in MTX-naïve patients with early RA (< 3 yrs). PREMIER evaluated a TNF antagonist plus MTX versus the TNF antagonist alone and versus MTX alone[14]. As patients progress through sequenced therapy, the HAQ score was modeled to deteriorate over time, with periods of response to treatment bringing the benefit of a slower rate of disease progression. At each initiation of a new therapy, patients who respond were modeled to also receive a one-time reduction in HAQ score, a benefit that was retained until loss of efficacy occurred.

HAQ profiles were used to calculate direct and indirect costs and quality of life (utility) through regression equations, with the HAQ score as the independent variable. Mortality was modeled using a Gompertz hazard-function derived from US life-table data[32], with relative risk adjustments for patients' prevailing HAQ scores.

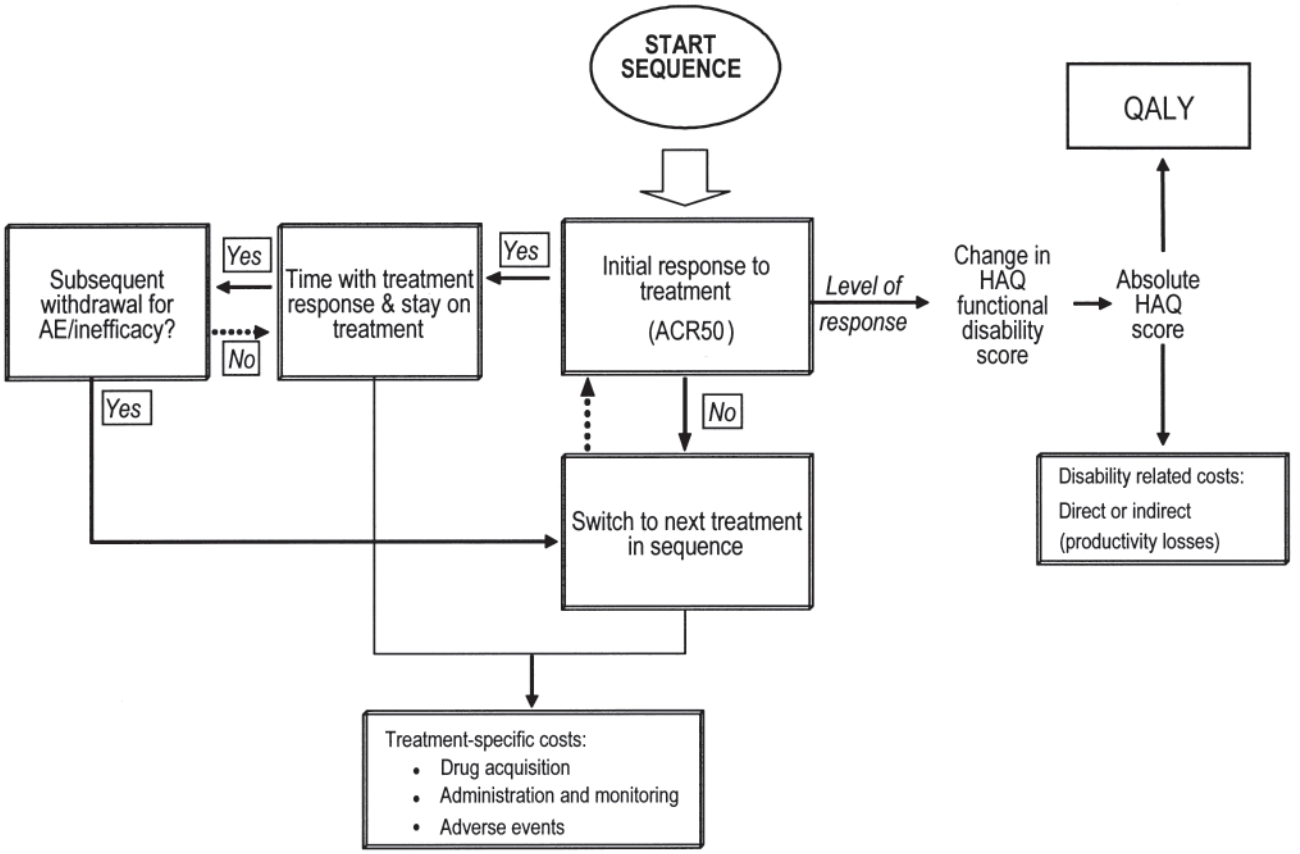

Figure 1. The sequences of model pathways; model design was based on 6-month cycles. ACR response was determined 6 months after each treatment was initiated, and subsequent withdrawals were determined at 6-month intervals. Following withdrawal from TNF antagonist therapy, patients were modeled to have switched to nonbiologic DMARD or rescue therapy. ACR: American College of Rheumatology, AE: adverse event, HAQ: Health Assessment Questionnaire, QALY: quality-adjusted life-years.

The model determined the effect of direct costs related to treatment of RA from a payer perspective, this being of most interest to organizations that reimburse healthcare costs in the US. Employer sponsors of health insurance are interested in economic effects on work productivity as well as direct costs of treatment, so the effect that chronic RA has on work productivity was also modeled. All costs and clinical outcomes were modeled over lifetimes, discounted at 3% per annum.

Modeled sequences. Response to therapies in the model was determined by the American College of Rheumatology (ACR) criteria[33]. Patients who did not achieve an ACR50 response level taking any therapy passed immediately to the next line of therapy at the end of the first 6-month interval. Patients passed through sequenced therapies, as shown in Table 1, until death or until the last scheduled DMARD failed. In practice, many alternative therapies are likely to be explored; however, for modeling purposes, a maximum of 3 effective DMARD regimens were assumed to follow the last biologic agent in each therapeutic sequence.

Five alternative treatment sequences were modeled. These included a reference sequence without biologic therapy, 3 sequences with a single biologic followed by traditional DMARD, and a dual biologic sequence in which treatment was initiated with adalimumab plus MTX followed by etanercept (Table 1).

Clinical inputs. The model extrapolated lifetime outcomes using short-term clinical trial data from trials comparing TNF antagonists with MTX in early RA. The randomized controlled trials used in this model were all conduct-

Table 1. Sequenced treatment regimens included in the model.

DMARD	ADA + MTX	ETN	IFX + MTX	ADA + MTX/ETN
MTX	ADA + MTX	ETN	IFX 3–5 mg + MTX	ADA + MTX
MTX + HCQ	MTX + HCQ	MTX + HCQ	MTX + HCQ	ETN
Leflunomide	Leflunomide	Leflunomide	Leflunomide	MTX + HCQ
Gold	Gold	Gold	Gold	Leflunomide
Palliative	Palliative	Palliative	Palliative	Palliative
Palliative	Palliative	Palliative	Palliative	Palliative
Palliative	Palliative	Palliative	Palliative	Palliative

ADA: adalimumab, ETN: etanercept, HCQ: hydroxychloroquine, IFX: infliximab, MTX: methotrexate, palliative: palliative maintenance therapy.

ed in early RA (< 3 yrs): PREMIER (adalimumab plus MTX vs either agent alone)[14], ASPIRE (infliximab plus MTX vs MTX)[34], and ERA (etanercept monotherapy only because combination therapy was not evaluated in the ERA trial)[9]. These are the only randomized controlled trials published that assess use of TNF antagonists in early RA. In all 3 studies, patients were MTX-naïve and had a disease duration of less than 3 years.

Clinical response criteria. Response to therapies according to ACR criteria was available from the 3 published trials for each biologic therapy compared in the model (Table 2). Initial response to the treatment sequence and subsequent clinical outcomes were driven by ACR responses, as categorized in 4 intervals (ACR0–20, ACR20–50, ACR50–70, and ACR70–100). The modeled probability of response falls (odds ratio 0.98 per year) as duration of RA increases[36].

Achieving at least an ACR50 response determined the acceptable response for continuation on therapy. Each level of response was associated with a given reduction (improvement) in the patient's HAQ score from baseline (Table 3: HAQ change), followed by a period of gradual increase until response was lost (Table 3: HAQ progression). Patients who withdrew from treatment because of an adverse event were excluded from receiving further TNF antagonist therapy (relevant only to the dual biologic sequences).

At the end of a treatment response period, a worsening of the patient's HAQ score equal to the original improvement was applied. At this point, however, patients retained the benefit of having experienced slower disease progression (modeled as HAQ change over time) than would have occurred without initial clinical response.

Adjusting response rates from different trials. Although MTX was the active control in each of the 3 TNF antagonist trials used to supply model inputs, the level of response among control patients varied (e.g., from 32% at ACR50 for etanercept and infliximab to 46% for adalimumab). Economic models of competing interventions frequently require adjustment for differing levels of response in patients receiving the control drug in different trials. An indirect comparison was performed for this analysis using an adjustment method applied by previous investigators in RA cost-effectiveness studies[31,43]. Adjustments for control-drug response were made as follows: adjusted response for biologic in trial B (Bio B) applied to MTX response in trial A (MTX A).

$$\text{Marginal response Bio B:} \quad \frac{\text{Response}_{\text{Bio B}} - \text{Response}_{\text{MTX B}}}{1 - \text{Response}_{\text{MTX B}}}$$

$$\text{Adjusted response: Response}_{\text{MTX A}} + \text{Marginal response}_{\text{Bio B}} \times [1 - \text{Response}_{\text{MTX A}}]$$

The ACR20, ACR50, and ACR70 rates used by the model for the 3 biologics and for MTX alone are presented in Table 2. To illustrate the adjustment, in the ERA trial, the ACR20 response rates for etanercept and MTX were 41% and 32%, respectively. This is equivalent to a marginal response for etanercept of about 13% in MTX nonresponders, which, when applied to the 46% control response in the PREMIER trial, improved the ACR50 response rate of etanercept in the model to an adjusted rate of 53%.

Adjustment equation example: (41% – 32%)/(100% – 32%) × (100% – 46%) + 46%

Modeling longterm outcomes. Patients experienced differing degrees of disease severity determined by their responses to successive therapies and the associated duration of periods of response. The duration of response for each simulated patient was determined by sampling the probability of withdrawal from therapy at each 6-month model interval. At each point that a patient discontinued a therapy, the ACR response to the next therapy in the sequence was determined with consequent changes in HAQ scores modeled as described above. Greater degrees of disease severity, as modeled by HAQ scores, were associated with greater mortality risk through a relative risk per HAQ point of 2.73 (Table 3) and lower health-related quality of life. This relative risk was used to adjust age-specific, all-cause mortality — modeled by fitting a Gompertz survival distribution to data from US life tables — according to the predicted HAQ score for the patient in each 6-month model interval.

Quality-adjusted life-years (QALY) combine estimates for patients' life expectancies with utility values that reflect differences in quality of life associated with different health states. Several studies have documented an association between HAQ scores and utility scores in RA[35,42,43]. HAQ scores during each 6-month interval were used to calculate utility values on a scale of 0 to 1 (death to perfect health) using a regression equation[40] derived from Health Utility Index Mark 3 (HUI-3) utility scores reported by 1990 patients whose HAQ scores ranged from 0 to 3 in 4 adalimumab trials (Table 3)[10,13,44,45]. The regression analysis used here is based on a cross-sectional model; the authors found that a repeated-measures mixed model produced similar results. Patients' utility scores are modeled to decline by 0.28 for each 1-unit increase in HAQ score.

Cost inputs. Drug costs per 6-month interval were calculated using AnalySource® (Table 4; Analysource, East Syracuse, NY, DMD America). Dosage escalation has been reported for infliximab[46-50]; therefore, infliximab costs were based on the assumption that 3 vials were used in the first 6 months of treatment and 4 vials were used in subsequent treatment periods.

The model also assigned drug monitoring and administration costs and the average costs of expected adverse events to each 6-month interval according to the drug with which patients were being treated based on physician fee schedules and diagnosis-related group codes (Table 4). Monitoring and administration costs were calculated based on clinicians' assessments of appropriate frequencies of healthcare contacts and diagnostic tests associated with treatment. Adverse event rates were based on the Geborek, *et al*[41] study of longterm treatment of RA. Other direct medical costs (e.g., physician visits, hospitalizations) vary with disease severity, and a regression equation based on HAQ scores[28] was used to model this effect of treatment; a 1-unit increase in HAQ score was associated with an additional US $2,313 per annum of healthcare resource. Where productivity costs were included in analyses, they were based on the proportion of annual average earnings lost associated with worsening HAQ scores.

Sensitivity analyses. The influences of several alternative assumptions regarding key parameter values in the model were examined through conventional sensitivity analyses. The results of these analyses are presented as a tornado diagram (Figure 2) depicting minimum and maximum values for

Table 2. Efficacy as measured by American College of Rheumatology (ACR) response rates from clinical trials Choi adjustment[35].

	PREMIER		ERA		ASPIRE		Model*	
	MTX	ADA**	MTX	ETN†	MTX	IFX** 3 mg	ETN	IFX 3 mg
ACR20, %	63	73	58	69	54	62	73	70
ACR50, %	46	62	32	41	32	46	53	57
ACR70, %	28	46	15	22	21	33	41	38

* Response rates adjusted to MTX rates in PREMIER[14]. ** Combination therapy with MTX. † Monotherapy from graphical presentation in ERA[9]. ADA: adalimumab, ETN: etanercept, IFX: infliximab, MTX: methotrexate.

Table 3. General model input data.

Parameter	Input Data	Probabilistic Distribution	Source
HAQ change			
ACR0–20	0.257 (0.144, 0.389)	Beta	Breedveld[14]
ACR020–50	0.541 (0.422, 0.658)		
ACR50–70	0.697 (0.604, 0.782)		
ACR70–100	0.800 (0.749, 0.847)		
HAQ progression			
During nonresponse	0.132 (0.100, 0.167)	Beta	Young[28]
During response	0.044 (0.430, 0.046)		Scott and Garrood[37]
RR for mortality*	2.73 (1.86, 4.02)	Log-normal	Sokka[38]
Direct costs (US $)**	1,553 (± 694) + 2,313 (± 483) × HAQ	Bivariate normal	Yelin and Wanke[26]
Productivity costs**	US $38,651 × 0.21 HAQ	NA	SSA[39]; Choi[35]
Utility†	0.76 (± 0.023) – 0.28 (± 0.003) × HAQ	Bivariate normal	Boggs[40]
DMARD response			
ACR20	0.37	Complementary log-log	Geborek[41]
ACR50	0.13		
ACR70	0		
Withdrawal rates			
DMARD	0.597 (0.501, 0.690)	Beta	Geborek[41]
ETN/ADA	0.132 (0.085, 0.187)		
IFX	0.158 (0.102, 0.225)		

Figures in parentheses are 95% confidence intervals or standard errors (±). * Per HAQ point. ** Per year. † For sensitivity analyses, the following alternative utility equations were applied: 0.77–0.17 × HAQ[42] and 0.956–0.299 × HAQ[35]. Costs are 2007 values. ACR: American College of Rheumatology, ADA: adalimumab, DMARD: disease modifying antirheumatic drug, ETN: etanercept, HAQ: Health Assessment Questionnaire, IFX: infliximab, MTX: methotrexate, NA: not applicable, SSA: US Social Security Administration.

Table 4. Summary of cost inputs (US $).

	Drug Costs*	Monitoring Costs**		Adverse Event Costs†
	Per 6-month Cycle	First 6 Months	Subsequent 6-month Cycles	Per 6-month Cycle
MTX	221.00	423.83	295.48	628.01
MTX + HCQ	73.00	423.83	295.48	628.01
LEF	330.00	423.83	295.48	628.01
Gold	1,707.00	423.83	295.48	628.01
ADA + MTX	8,802.56	423.83	295.48	709.06
ETN	8,756.54	423.83	295.48	709.06
IFX† 3 mg + MTX	8,935.10	1,371.78	855.91	1,033.71

* Drug costs were based on AnalySource®. ** Monitoring and adverse event costs were constructed from administration schedules and expert opinion, unit costs from the 2005 Medicare physician fee schedule, New York University Medical Center, and The DRG Handbook; drug unit costs were adjusted to 2007 values. † US $7,773.22 after first 6 months (infliximab costs were based on the assumption that 3 vials were used in the first 6 months of treatment and 4 vials were used in subsequent treatment periods). ADA: adalimumab, ETN: etanercept, HCQ: hydroxychloroquine, IFX: infliximab, LEF: leflunomide, MTX: methotrexate.

adalimumab cost-effectiveness ratios versus traditional DMARD for each varied parameter.

The uncertainty relating to which treatment sequences have the greatest likelihood of being cost-effective can more thoroughly be examined through probabilistic sensitivity analyses, in which model parameters are sampled at random from defined distributions. The model used beta, log-normal, and bivariate-normal distributions to represent uncertainty around proportions, relative risks, and regression inputs, respectively. For efficacy rates, the model adopted complementary log-log distributions (particularly suitable for small proportions), and sampled ACR50 and ACR70 efficacy rates conditional on ACR20 and ACR50 responses, respectively.

One thousand iterations of the model were performed, producing distributions of total costs and QALY resulting from each strategy. The cost-effectiveness of each strategy for any iteration can be expressed as a net monetary health benefit (NMHB). The NMHB will vary depending on the value decision-makers attach to each additional QALY; that is, their willingness to pay (WTP).

$$\text{NMHB} = (\text{QALY}_{\text{sequence}} - \text{QALY}_{\text{DMARD}}) \times \text{WTP} - (\text{COST}_{\text{sequence}} - \text{COST}_{\text{DMARD}})$$

For a given WTP, the probability that each strategy has of having the great-

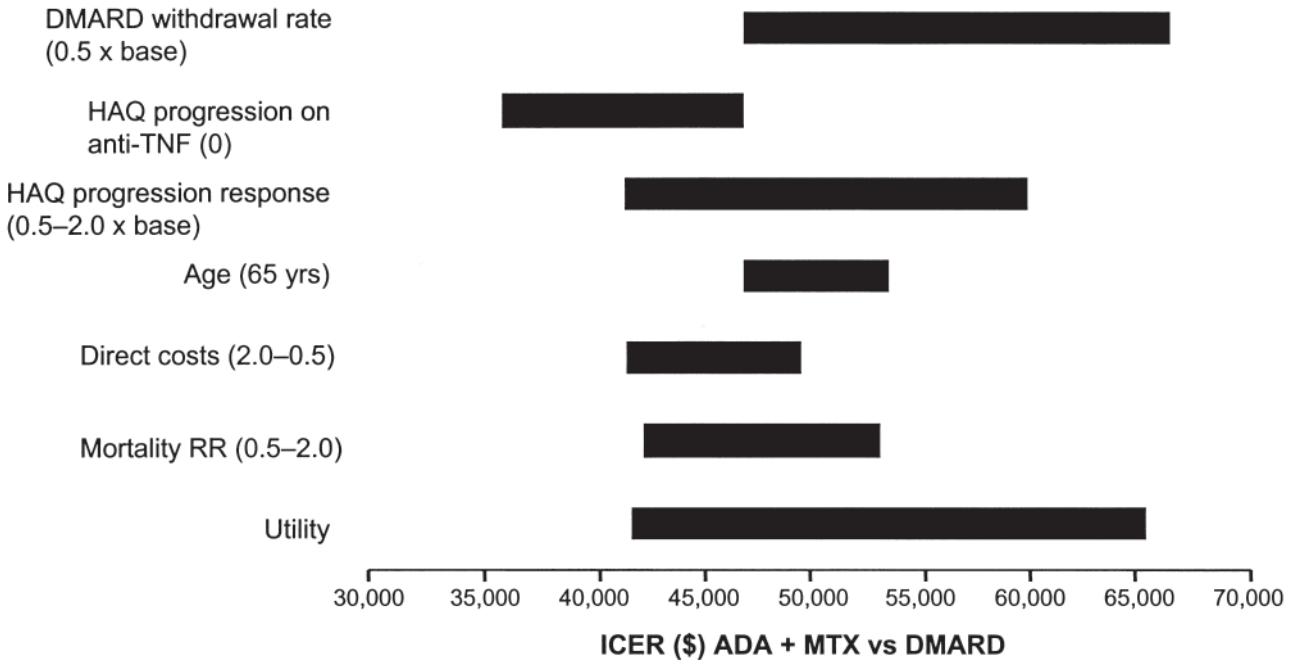

Figure 2. Univariate sensitivity analyses show minimum and maximum values for cost-effectiveness ratio of adalimumab versus traditional disease modifying antirheumatic drugs (DMARD) for each parameter. ADA: adalimumab, anti-TNF: TNF antagonist, HAQ: Health Assessment Questionnaire, ICER: incremental cost-effectiveness ratio, MTX: methotrexate, RR: relative risk.

est NMHB can be calculated by comparing the number of times each strategy had the greatest NMHB across all 1000 iterations. By plotting the results of this analysis of WTP values in a range from US $0 to US $100,000, cost-effectiveness acceptability curves were derived, which show the probability of a strategy being cost-effective at any WTP level within that range.

RESULTS

Table 5 presents a summary of modeled outcomes. Strong early response to therapy and the extended periods of response achieved by TNF antagonist therapies drove longer periods with slower progression of disability than could be achieved with a DMARD-only sequence. That advantage continued in the longer term because the underlying HAQ profile was better, resulting in greater QALY over the full TNF antagonist–initiated sequence — until palliative care, death, or failure of the last available agent.

Adalimumab use produced the greatest number of QALY over the course of disease, whether used as the only TNF

Table 5. Costs, quality-adjusted life-years (QALY), and lifetime cost-effectiveness ratios for 5 alternative treatment sequences.

		Sequence			
	DMARD	IFX + MTX	ETN	ADA + MTX	ADA + MTX/ETN
Drugs	6,762	52,181	61,468	70,502	110,623
Monitoring	7,534	11,445	7,627	7,606	7,744
Adverse events	3,553	16,401	14,570	14,717	15,639
Other direct costs	69,119	64,895	64,069	62,543	57,747
Total direct costs	96,967	144,922	147,735	155,367	191,753
Productivity costs	222,381	203,337	199,337	192,931	171,214
Total costs (including productivity)	319,348	348,259	347,072	348,298	362,967
Total QALY	2.001	2.896	3.005	3.240	4.220
Incremental (vs DMARD)					
Costs (excluding productivity)	NA	47,955	50,768	58,400	94,786
Costs (including productivity)	NA	28,911	27,724	28,950	43,619
QALY	NA	0.895	1.003	1.238	2.218
Incremental cost-effectiveness ratios (vs DMARD)					
US $/QALY (excluding productivity)	NA	Extendedly dominated	Extendedly dominated	47,157	42,727
US $/QALY (including productivity)	NA	Extendedly dominated	Extendedly dominated	23,377	19,663

ADA: adalimumab, DMARD: disease modifying antirheumatic agent, ETN: etanercept, IFX: infliximab, MTX: methotrexate, NA: not applicable, QALY: quality-adjusted life-years.

antagonist or as the second TNF antagonist in sequenced therapy. The adalimumab-plus-MTX–initiated sequence resulted in the greatest number of QALY (3.24), compared with 3.00 QALY in the etanercept sequence, 2.90 in the infliximab-plus-MTX sequence, and 2.00 in the DMARD-only sequence. When the adalimumab-plus-MTX–initiated sequence was followed by etanercept before switching to other DMARD, the number of QALY was increased by one-third over the course of therapy (4.22 QALY vs 3.24 QALY gained by adalimumab-plus-MTX–initiated sequence followed by DMARD).

Table 5 also presents the total direct costs incurred by each sequence modeled, as well as the total costs when the effect of lost productivity is added to the cost estimates. Incremental cost-effectiveness is expressed as the cost per QALY when comparing each sequence with the next most cost-effective sequence. A sequence that yields fewer QALY at greater cost than at least 1 other sequence is defined as dominated, and a sequence that has a greater incremental cost-effectiveness than a sequence that yields a greater number of QALY is defined as extendedly dominated when compared with a lesser sequence. Table 5 shows the cost per QALY for each sequence, on the basis of including both direct costs only and indirect costs of lost productivity.

While the etanercept sequence has a cost per QALY of US $25,856 compared with the infliximab-plus-MTX–initiated sequence, the cost per QALY of infliximab against DMARD is US $53,607, and both these sequences are extendedly dominated by the adalimumab-plus-MTX–initiated sequence (Figure 3). Comparing DMARD and single TNF sequences, the relevant comparator for the adalimumab-plus-MTX sequence is therefore DMARD, against which the adalimumab-plus-MTX sequence provided the greatest number of QALY at a cost per QALY of US $47,157. When productivity costs are added to direct costs, the infliximab-plus-MTX sequence is dominated by the etanercept sequence, although both remain extendedly dominated by the adalimumab-plus-MTX sequence for which the incremental cost-effectiveness ratio fell to approximately US $23,377 compared with the etanercept sequence.

The supplementary analysis showed that a strategy of treating with a second-line TNF antagonist (in this case, etanercept) subsequent to first-line adalimumab could yield an additional QALY when compared with adalimumab as the sole TNF antagonist in a sequenced strategy and extendedly dominate all single TNF strategies, at a cost of US $42,727 per QALY (US $19,663 including lost productivity).

Results of sensitivity analyses. Figure 2 presents the results of several one-way sensitivity analyses examining how the cost effectiveness of adalimumab versus DMARD changes with varying assumptions in the model. Applying a EuroQOL EQ-5D utility regression by Kobelt, *et al*[42] increased the cost per QALY of adalimumab to roughly US $65,000. When the HAQ progression was assumed to be twice that applied in the base case, or when the withdrawal rate from DMARD therapy was half that applied in the base case, cost per QALY was also between US $60,000 and US $70,000. Radiographic progression evidence suggests that TNF antagonists may arrest disease progression to the extent that the HAQ score remains stable during periods of continued response[5,9,11,13,14,34]. This scenario produced the lower incremental cost-effectiveness ratio for adalimumab of roughly US $36,000. Other sensitivity analyses produced cost per QALY for adalimumab versus etanercept of between US $42,000 and US $54,000.

Figure 4 plots the cost-effectiveness acceptability curves for each sequence. At any value of WTP per QALY, up to nearly US $50,000, an all-DMARD sequence had the great-

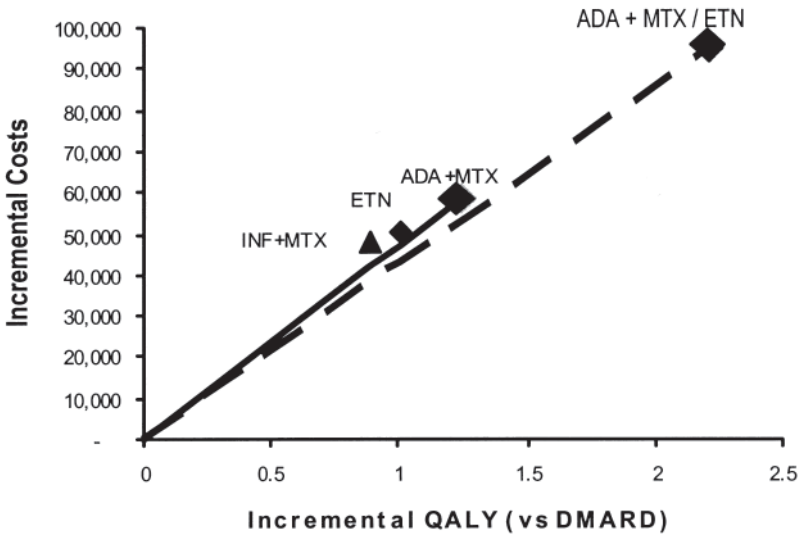

Figure 3. Cost-utility plane. MTX: methotrexate, ADA: adalimumab, ETN: etanercept, INF: infliximab, DMARD: disease modifying antirheumatic drug, QALY: quality-adjusted life-years.

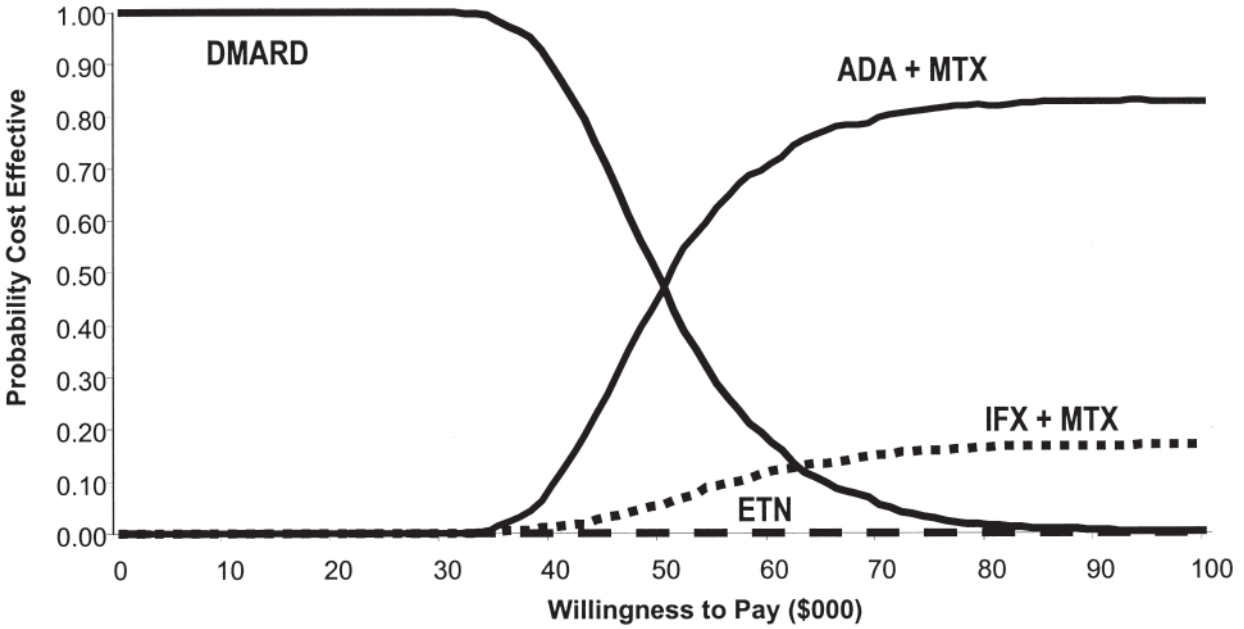

Figure 4. Cost-effectiveness acceptability curves (excluding productivity costs). ADA: adalimumab, DMARD: disease modifying antirheumatic drug, ETN: etanercept, IFX: infliximab, MTX: methotrexate.

est probability of being cost-effective. This is consistent with the base case analysis. At this level of WTP, the adalimumab-plus-MTX sequence produces the greatest number of QALY and is cost-effective compared with other single TNF sequences.

DISCUSSION

The modeled treatment strategy of first-line TNF antagonist use reflects a potential approach to the management of patients with early RA requiring aggressive therapy. In light of recent evidence, sequential therapeutic approaches to RA have changed, with the most effective therapies being used earlier in treatment, even in combination, rather than being deferred until disability and symptoms have worsened. In addition, recent clinical trials have demonstrated that TNF antagonist use may provide greater effectiveness when used in combination with traditional DMARD, particularly MTX[7,8,10-14], rather than being used as monotherapy. This treatment pattern is reflected in the model.

An international consensus statement on the use of biologic agents in the treatment of RA, released in 2006, supported an early role for TNF antagonists in sequential therapy[51]. TNF antagonists were recommended as monotherapy or as combination therapy with an effective traditional DMARD, such as MTX, and were also judged (on the basis of published evidence) to be effective in MTX-naïve patients.

In this model, TNF antagonists were used as first-line therapy for treatment of early RA versus initial treatment with a traditional DMARD alone, such as MTX monotherapy, which has often been the first-line treatment choice after diagnosis. Whereas trials of biologics in patients with longstanding disease enrolled patients with incomplete continued response to MTX or other traditional DMARD, studies in early RA compare biologics to MTX at a disease stage in which treatments have not yet failed. MTX, therefore, produced greater ACR response rates than those observed in trials of patients with longer-duration, potentially more severe RA. As a consequence, the clinical trial data cannot credibly support analyses of sequences in which TNF antagonists follow MTX failure in early RA. However, observational evidence may accumulate as treatment of early RA with TNF antagonists becomes more widespread; this evidence may inform an assessment of such a strategy. This also places a greater burden on TNF antagonists in early RA trials than in later disease settings, in which MTX responses would tend to be poorer, and the marginal benefits of TNF antagonists more readily apparent. Despite this, first-line treatment with adalimumab plus MTX resulted in a cost per QALY of US $47,157; often, payers in the US consider US $50,000 per QALY to be a minimum cost-effectiveness threshold[52], at which point adalimumab-plus-MTX therapy was found to have a 70% probability of being cost-effective.

All patients in the model continued to have disease progression whether responding to treatment or not, although the disease progressed at a slower rate for responders. Initiation of TNF antagonist therapy in patients with early RA may produce radiographic outcomes that are dramatically better than outcomes attainable in later stages of RA, possibly even arresting all radiographic progression and leading to healing. Incorporating such benefits would improve the cost-effectiveness of TNF antagonist therapy in

patients with early RA if inhibition of radiographic progression was sustained even after patients ultimately withdrew from TNF antagonist therapy. As an illustration of the potential for inhibition of radiographic progression to improve cost-effectiveness, our sensitivity analyses included a scenario in which HAQ progression with successful TNF-antagonist therapy was zero.

The model adjusted the response rates for TNF antagonists, accounting for different placebo response rates across the relevant trials, using the method employed by Choi, *et al*[35] to allow comparisons of each TNF antagonist against a common response rate for MTX. Adalimumab plus MTX combination therapy and etanercept monotherapy each have an adjusted rate for an ACR20 response rate of approximately 73%; however, adalimumab-plus-MTX therapy had marginally stronger ACR50 and ACR70 response rates. These differences explain the greater cost-effectiveness of adalimumab versus etanercept.

This analysis had 3 primary limitations. First, ERA trial data were used to model responses to etanercept monotherapy because combination therapy with MTX was not studied in the ERA and thus could not be evaluated in our model. The TEMPO trial[12] studied combination therapy using etanercept plus MTX versus etanercept alone and versus MTX alone, but the TEMPO inclusion criteria differed substantially from the inclusion criteria of PREMIER and ASPIRE. The TEMPO trial did not exclude patients with long-standing RA, and patients with disease duration up to 20 years were included (average duration of disease of TEMPO patients was 6.8 years). Also, TEMPO patients were not required to be MTX-naïve, and those with inadequate MTX response could be excluded from the trial. These criteria are inconsistent with the stricter inclusion criteria used in the PREMIER, ASPIRE, and ERA studies, which included only MTX-naïve patients with early RA. For sequential TNF antagonist use, clinicians may question the likely efficacy of a second TNF antagonist in patients who have either failed to respond to the first agent or whose response has been lost over time. We addressed a treatment sequence of adalimumab plus MTX followed by etanercept (the next-best option in this analysis as measured by both QALY and cost-effectiveness); however, the cost-effectiveness of this sequence may depend on response to etanercept in adalimumab-experienced patients. In the model, we assumed that etanercept efficacy in adalimumab-treated patients would be equivalent to etanercept efficacy in TNF antagonist–naive patients (i.e., as demonstrated in the ERA trial). However, in practice, etanercept, as well as adalimumab and infliximab, would be prescribed in combination with MTX. The dual sequence results suggest that, even with lesser efficacy of second-line etanercept therapy, this sequence could remain a cost-effective option.

Second, this model did not consider the influence of delays in treatment initiation for early RA. For example, initiation of TNF antagonist therapy after an MTX failure would likely exaggerate the benefits of the TNF antagonist by setting the comparison against post-MTX DMARD, which are likely to be less effective. Treatment delay would also increase the likelihood that patients would have already progressed to greater disability (i.e., a greater HAQ score) before beginning TNF antagonist therapy. These patients, therefore, would have been less likely to achieve radiographic inhibition. As the effect of radiographic progression becomes better quantified through clinical investigations, the ability to model the specific question of treatment delays will improve.

Finally, our study suffers from a paucity of evidence on the effectiveness of traditional DMARD. Our analysis assumed that all DMARD could be characterized by their effectiveness on the basis of longer-term efficacy (as in the report by Geborek, *et al*[41]). There is some evidence to support the equivalence of many traditional DMARD therapies. However, greater response rates applied to all DMARD could negatively affect the cost-effectiveness of TNF antagonists, as demonstrated by our sensitivity analyses. The model followed the approach of other published studies in adjusting for differing response rates in patients in control arms of different trials by independently adjusting ACR20, ACR50, and ACR70 response rates.

Modeled comparisons of sequenced therapy in early RA showed that early intervention with any of the 3 available TNF antagonists cost-effectively produced superior lifetime outcomes compared with traditional DMARD treatment alone. Of the 3 TNF antagonists, adalimumab had the most favorable cost-effectiveness, whether used as initial therapy followed by DMARD or followed sequentially by another TNF antagonist. Unfortunately, no data exist for etanercept combination therapy for comparable patients with early RA. Consequently, an etanercept-plus-MTX–initiated sequence could not be evaluated in this study.

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