A Cost Effectiveness Analysis of Treatment Options for Methotrexate-Naive Rheumatoid Arthritis

HYON K. CHOI, JOHN D. SEEGER, and KAREN M. KUNTZ

ABSTRACT. ***Objective***. New treatment options for patients with methotrexate (MTX)-naive rheumatoid arthritis (RA) have become available. Given wide variability in efficacy and cost among different treatment options, we sought to determine their relative cost effectiveness to help guide policy in different cost constrained settings.

Methods. We performed a cost effectiveness analysis comparing 5 monotherapy options for patients with MTX-naive RA: (1) etanercept, (2) leflunomide, (3) MTX (up to 15 mg weekly), (4) sulfasalazine (SSZ), and (5) no second line agent. A decision analysis model was used with a time horizon of 6 months. We employed 2 measures of effectiveness based on published clinical trial data: American College of Rheumatology (ACR) 20% response proportion (ACR 20) and a weighted average of proportions achieving ACR 70, ACR 50, and ACR 20 (ACR 70 weighted response, ACR 70WR). Incremental cost effectiveness ratios were calculated as additional cost per patient achieving either outcome, compared with the next most expensive option.

Results. In both base case analyses employing ACR 20 and ACR 70WR as effectiveness measures, MTX and SSZ both cost less and were more effective (i.e., cost saving) than no second line agent. Leflunomide cost more and was less efficacious than SSZ (dominated) in analyses using either outcome. The most efficacious option, etanercept, cost US $41,900 per ACR 20 and $40,800 per ACR 70 WR compared with SSZ and MTX, respectively. When we included only direct costs in analyses, the least expensive non-dominated option was SSZ with incremental cost effectiveness ratios of US $900 per ACR 20 and $1500 per ACR 70WR compared with no second line agent. Overall, relative cost effectiveness between MTX and SSZ was sensitive to variation in relevant variables in sensitivity analyses. Otherwise, our extensive sensitivity analyses did not substantially affect the base case results.

Conclusion. MTX is cost effective (cost saving vs the no second line agent option) for MTX-naive RA in achieving ACR 20 or ACR 70WR over a 6 month period. Based on available data, the relative cost effectiveness between SSZ and MTX cannot be determined with reasonable certainty and SSZ therapy appears to be as cost effective as MTX (cost saving) in achieving ACR outcomes over a 6 month period. The most efficacious option, etanercept, incurs much higher incremental costs per ACR 20 or ACR 70WR than other options analyzed. Whether etanercept compared with MTX is cost effective depends on whether > $40,000 per ACR 20 or ACR 70WR over a 6 month period is considered acceptable. (J Rheumatol 2002;29:1156–65)

Key Indexing Terms:
RHEUMATOID ARTHRITIS METHOTREXATE-NAIVE COST EFFECTIVENESS

Disease modifying antirheumatic drugs (DMARD) have been used to slow the progression of rheumatoid arthritis (RA) and minimize its consequences. Among these drugs, methotrexate (MTX) has become the dominant choice of therapy to treat patients with RA for the past decade because of its superior efficacy and tolerability[1]. In recent years, clinical trials evaluating RA treatments have recruited participants on the basis of MTX treatment history: MTX-naive[2-4] or MTX resistant[5,6]. MTX-naive patients tend to be those with early RA[4] and MTX resistant patients tend to be those with later stages of RA[5,6].

Recently, a number of new RA treatment options have been shown to be safe and effective specifically in patients with MTX-naive RA[2-4]. Given the wide variability in cost among these new options and conventional ones, their relative cost effectiveness (CE) has become an important issue. Recently, we reported on the CE of treatment options for patients with MTX resistant RA[7]. In the current study, we sought to determine the CE of new and conventional treatment options for MTX-naive RA to help guide policy in different cost constrained settings.

MATERIALS AND METHODS

Model for comparison of treatment options. We compared 5 treatment options

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for MTX-naive RA: (1) etanercept, (2) leflunomide, (3) MTX, (4) sulfasalazine (SSZ), and (5) no second line agent. We used 2 RA-specific measures of effectiveness. The first was the American College of Rheumatology (ACR) 20 response criteria, which represent improvement by at least 20% in tender and swollen joint count and by at least 20% in 3 of 5 other core set measures (patient global assessment, physician global assessment, physical disability score, acute phase reactant, and patient pain assessment)[8]. As the second measure of effectiveness, we used a weighted outcome measure of ACR responses relative to a full weight of ACR 70 response (ACR 70 weighted response, ACR 70WR) by calculating a weighted average of proportions achieving ACR 70, ACR 50, and ACR 20. A weight of 1 was assigned to ACR 70, a weight of 50/70 to ACR 50, and a weight of 20/70 to ACR 20. The formula used to calculate ACR 70WR is:

ACR 70WR = proportion achieving ACR 70 + (proportion achieving ACR 50 – proportion achieving ACR 70)•50/70 + (proportion achieving ACR 20 – proportion achieving ACR 50)•20/70.

We constructed a decision tree that models the potential events that may occur within 6 months of initiation of therapy (Figure 1). In Figure 1, squares and circles represent decision nodes and chance nodes, respectively. Decision tree outcomes were based on the occurrence of toxicity related to each therapy as well as ACR response. The initial branch models the chance that patients receiving each agent may experience drug toxicity. Patients without drug toxicity may achieve either clinical response meeting ACR improvement criteria (ACR 20 or ACR 70WR) or not. Drug toxicity could be either minor or major. Patients with minor drug toxicity were assumed to have the same clinical outcomes as those experiencing no drug toxicity, whereas patients with major drug toxicity were assumed to require discontinuation of therapy and to fail to achieve ACR response[9]. The decision tree was constructed and analyzed using DATA software (Version 3.5, TreeAge Software Inc., Williamstown, MA, USA).

We took a societal perspective in the estimation of costs in the base case analysis. The total cost of therapy with each agent was composed of direct costs (cost directly to health care system) associated with treating MTX-naive RA patients, combined with indirect costs incurred of lost productivity due to morbidity. We repeated the analysis including only direct costs. The time horizon for this analysis was 6 months, which represents the usual duration of most clinical trials of RA. This time horizon also reflects the longest period during which a particular DMARD option can be continued without clinical benefit before switching to a different therapy.

Alternatives that were both more costly and less effective than another option were eliminated from consideration through simple dominance. Incremental CE ratios were calculated as the additional cost per patient achieving ACR 20 improvement or achieving ACR 70WR, compared with the next most expensive option. Alternatives that had a higher incremental CE ratio than a more expensive and effective option were eliminated through weak dominance. All costs were converted to 1999 US dollars using the medical care component of the Consumer Price Index from the Bureau of Labor Statistics (www.bls.gov). All cost estimates were rounded to the nearest dollar and all incremental CE ratios were rounded to the nearest $100. No discounting was performed because the time horizon was 6 months.

Data and assumptions. ACR response data for all considered treatment options were taken from source clinical trials[2-4,10]. The efficacy (net drug effect after adjusting for the placebo effect in each trial) represents the probability of achieving ACR response on each drug subtracting the effect of placebo among those who would not have improved on placebo (Table 1). For example, the European placebo-controlled leflunomide trial reported that the probabilities of achieving ACR 20 response were 0.568 and 0.29 in the SSZ and placebo group, respectively[2]. Therefore, the efficacy of SSZ was calculated to be (0.568 – 0.29)/(1 – 0.29) = 0.39. Employing the same calculation, 2 trials provided the efficacy estimation for leflunomide as 0.37 and 0.39[2,3]. We used a weighted average of these 2 efficacy estimates (0.38) for the base case analysis. Our base case estimate of ACR response for MTX was based on (1) the US leflunomide trial[3], (2) the trial comparing leflunomide and MTX[10], and (3) the early RA trial comparing etanercept and MTX[4]. The first trial suggested the efficacy of leflunomide was higher than that of MTX (up to 15 mg weekly)[3], while the second trial reported the opposite[10]. The third trial found the efficacy of MTX (up to 20 mg weekly) is close to that of etanercept[4]. Thus, for our base case estimate of ACR response for MTX, we assumed that the efficacy of MTX (15 mg weekly) is the same as that of leflunomide. Our base case estimate of etanercept was estimated based on the etanercept trial for early RA (0.56)[4].

The base case estimate of the probability of achieving ACR response given no second line therapy was from the placebo group in the US leflunomide trial (0.27)[11]. The base case estimate for the probability of achieving ACR improvement for other therapeutic options considered in our analysis was calculated from efficacy estimate of each component using the formula:

$$\text{Probability of achieving ACR response} = P_{placebo} + (1 - P_{placebo}) \bullet E_{drug}$$

where $P_{placebo}$ = the proportion achieving ACR response without second line agent (0.27) and E_{drug} = the efficacy of the drug option. For example, when treated with leflunomide, the estimated proportion of patients achieving ACR 20 is 0.27 + (1 – 0.27)•0.38 = 0.55 (Table 1). Of note, the proportion of patients achieving ACR 20 response with etanercept therapy was estimated to be 0.27 + (1 – 0.27)•0.56 = 0.68, which is larger than the actually reported ACR response proportion by 3 percentage points (0.65)[4]. Sensitivity analysis was performed in each final outcome estimate.

The definition and probability of major and minor adverse effects to MTX therapy and the relative proportion of the 2 were based on a published estimate of these events[9]. The authors defined major adverse effects to be those requiring hospitalization or extended outpatient diagnostic and therapeutic intervention, while minor adverse reactions were those requiring minimal diagnostic or therapeutic intervention as an outpatient[9]. The frequency of

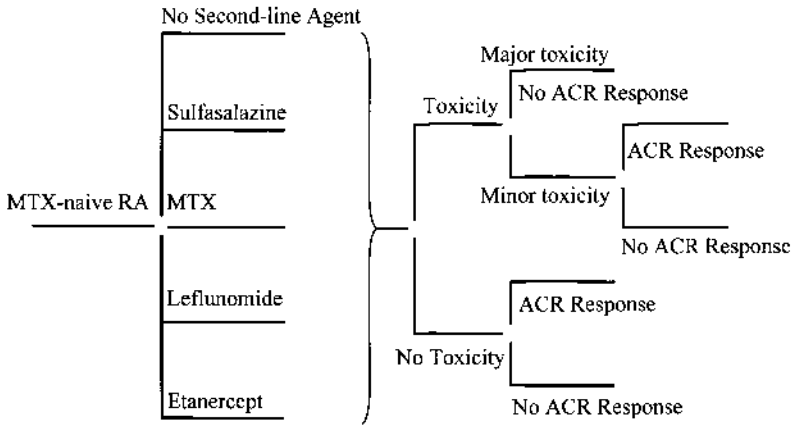

Figure 1. Overview of a decision tree. Squares represent decision nodes; circles represent chance nodes.

Table 1. Base case estimates and their ranges for sensitivity analyses over a time horizon of 6 months.

Variable[Ref]	Baseline Estimate (Range) ACR 20, %	ACR 70WR, %
Efficacy of individual drug		
SSZ[2]	39 (31–47)	19 (15–23)
MTX[2,3,10]	38 (30–46)	21 (17–25)
Leflunomide[2,3]	38 (30–46)	21 (17–25)
Etanercept[4]	56 (45–67)	36 (29–43)
Probability of achieving ACR response		
No second line agent[2]	27 (22–32)	15 (12–18)
SSZ[2]	56 (44–67)	31 (25–38)
MTX[2,3,10]	55 (44–66)	33 (26–39)
Leflunomide[2,3]	55 (44–66)	33 (26–39)
Etanercept[4]	68 (54–81)	46 (36–55)
Adverse effect		
Probability of toxicity to no second line agent	0	
Probability of toxicity to SSZ	0.2 (0.1–0.3)	
Proportion with SSZ major toxicity[9†]	0.1 (0.02–0.18)	
Probability of toxicity to MTX[9]	0.2 (0.1–0.3)	
Proportion with MTX major toxicity[9]	0.1 (0.02–0.18)	
Probability of toxicity to leflunomide[2,3,10†]	0	
Probability of toxicity to etanercept[4,5†]	0	
Direct costs (6 months), $		
Medication costs		
No second line agent	0	
SSZ, 2 g daily[12]	109	
MTX, 15 mg weekly[12]	504	
Leflunomide, 20 mg daily[12]	1469 (1108–2418)	
Etanercept, 25 mg twice/week[12]	6600 (1650–6600)	
Monitoring costs/toxicity costs, $/$		
Costs for no second line agent[13–15‡]	513 (257–1026)/0	
Costs for MTX[13]	799 (400–1598)/263 (62-527)	
Excess costs for SSZ over no second line agent[13–15‡]	106 (53–212)/0	
Excess costs for leflunomide over no second line agent[13-15‡]	76 (38–151)/0	
Excess costs for etanercept monotherapy over no second line agent[4,5†]	0/0	
Surgery costs, $		
Average annual surgery costs for a HAQ of 1.23 (mean from reference[17]), $	2913 (2797–3496)	
Ratio of surgery costs between best and worst quartiles of HAQ (mean HAQ of 0.31 vs 2.15)[§17]	6.97 (5.58–7.66)	
Estimated surgery costs using exponential regression and ranges		
No second line agent[17‡]	1132 (1048–1520)	
SSZ[17‡]	907 (886–1285)	
MTX[17‡]	779 (758–1013)	
Leflunomide[17‡]	779 (758–1013)	
Etanercept	710 (690–928)	
Indirect costs (6 months), $		
Slope of linear regression between HAQ and working capacity[18]	–0.2096 (–0.2515– –0.1677)	
Average income for working age (18–64) persons for 6 months[19]	13,421 (10,737–26,841)	
Estimated indirect costs using the linear regression and ranges		
No second line agent[18,19‡]	9712 (7769–11,654)	
SSZ[18,19‡]	9112 (7289–10,934)	
MTX[18,19‡]	8643 (6914–10,371)	
Leflunomide[18,19‡]	8643 (6914–10,371)	
Etanercept[18,19‡]	8324 (6659–9989)	

ACR20: American College of Rheumatology 20% response criteria; ACR 70WR: weighted average of ACR responses relative to a full weight of ACR 70 response (ACR 70 weighted response); MTX: methotrexate; HAQ: Health Assessment Questionnaire.

† Assumed based on the reference(s); ‡ Estimated based on the reference(s); § The equation for the regression equation between the surgery assignment (y) and the HAQ score (x) was $y = 635.64e^{1.0936x}$. Equation based on the estimated average surgery costs for a HAQ of 1.23 and the ratio of surgery costs between the best:worst quartiles of HAQ score of 6.97.

adverse effects to MTX was estimated at 20% and of these, 90% were minor[9]. In our base case analysis we assumed toxicity probabilities for SSZ were the same as those for MTX (which may bias against SSZ). We assumed that the adverse effects associated with leflunomide or etanercept are negligible as suggested by their respective clinical trials[3,4,11].

Costs

Direct costs. The direct cost of each therapeutic option for MTX-naive RA patients included medication costs, costs of monitoring therapy, costs of toxicity arising from therapy, and costs of surgery that can be potentially reduced with effective treatment (Table 1). We assumed that discontinuation of a given treatment option due to major side effects occurred 8 weeks after its initiation and the option incurred only monitoring costs of no second line agent for the remainder of the 6 months. Medication costs were average wholesale prices obtained from the 1999 Red Book[12]. Monitoring costs were based on published estimates[13] or, where published estimated costs were not available, by summing costs of each monitoring component recommended by ACR for each DMARD[14], or by monitoring guidelines in the package insert of leflunomide (Arava® package insert, Hoechst Marion Roussel, 1998). The cost of each laboratory monitoring component was based on the 1999 Clinical Diagnostic Laboratory Fee Schedule of Health Care Financing Administration and the cost of an ophthalmologic monitoring visit for hydroxychloroquine was based on the 1999 Resource-Based Relative Value Scale physician payment system data [15]. The monitoring costs for the no second line agent option were calculated by subtracting the ophthalmologic monitoring cost (once over the 6 mo period) from the monitoring cost of hydroxychloroquine, the least expensive among DMARD monitoring costs[13]. We assumed the monitoring costs for etanercept were the same as those of no second line agent. The toxicity cost associated with MTX therapy was based on a study of hospital charges[9] in which $440 (1992 dollars) was estimated for the toxicity cost per patient taking MTX therapy for 6 months ($517 in 1999 dollars). We converted this charge estimate to costs ($259 in 1999 dollars) by applying a region-specific cost-to-charge ratio of 0.509[16]. The toxicity cost associated with SSZ was assumed to be the same as that associated with MTX. We assumed no toxicity costs for leflunomide or etanercept.

Inpatient surgical costs were included to capture the potential savings associated with improvement of RA from each option. Recently, Yelin, *et al* reported that 51.7% of the direct cost of RA was due to hospital admissions, of which 95.2% was from surgical admissions[17]. In addition, that study found that functional status measured by Health Assessment Questionnaire (HAQ) was the only consistent and strong predictor for the total direct RA costs. Patients with RA in the worst quartile of function experienced total annual direct costs that were 2.55 times greater and total hospital costs that were 6.97 times greater than those in the best quartile. Using these data, we developed an exponential relationship between HAQ score and inpatient surgery costs. Using the HAQ improvements reported from the clinical trials, we then estimated surgery related costs for each treatment related strategy (Table 1).

Medical admission costs were assumed to be largely due to the toxicity of DMARD treatments, and these costs were included in the toxicity cost estimation. We did not consider the costs of medical admission for the diagnosis and management of RA, since by and large admission for diagnosis is almost never done and flares of RA are managed in the ambulatory setting.

Indirect costs. Indirect costs were included to capture the potential savings associated with improvement of RA from each option. We used a HAQ-based indirect cost assignment using the same HAQ efficacy estimates used for estimating for surgery costs. We assumed a linear relationship between work capacity and HAQ score based on a recent CE analysis in a Swedish RA population[18] to infer the indirect cost savings associated with HAQ improvement. Average wage for working age 18–64 persons was estimated at $13,421 per 6 months in 1999 dollars[19]. This average wage was multiplied by work capacity achieved by each option to estimate the cost of lost work capacity (indirect cost) (Table 1).

Sensitivity analyses. Sensitivity analyses were performed to determine the robustness of the base case results to variations in baseline estimates. The ranges used for each variable in the analyses are shown in Tables 1 and 4.

Three way sensitivity analyses were performed to determine the robustness of the base case results to variation of more than one key variable, including our main variable of MTX efficacy. Different levels of incremental CE ratios per either outcome are employed to represent different budgetary CE thresholds in different medicoeconomic settings. The results are graphically presented (Figures 2 and 3).

Source of support for the study. There was no specific financial support for this study. None of the authors was supported by any of the companies that produce the evaluated medications or any other DMARD potentially competing with the evaluated medications.

RESULTS

Base case analyses. Using baseline estimates shown in Table 1, effectiveness, costs, and incremental CE ratios per patient achieving ACR 20 and ACR 70WR are shown in Tables 2 and 3, respectively. The MTX option was the least expensive ($10,926 for 6 mo) and the etanercept option was the most expensive ($16,165 for 6 mo). For the SSZ and MTX options, medication costs accounted for 6% and 22% of the direct costs, respectively, whereas for leflunomide and etanercept monotherapy, the medication costs accounted for 52% and 84% of their direct costs, respectively.

In the base case analysis using either ACR 20 or ACR 70WR as the effectiveness outcome for MTX-naive RA patients, MTX cost less and was more efficacious than the no second line agent option. Therefore, MTX was cost saving compared with no second line agent. The next more expensive option, SSZ, also cost less and was more efficacious than the no second line agent option. SSZ increased the probability of achieving ACR 20 by 1 percentage point and increased total costs by $101 compared with the MTX option, resulting in an incremental CE ratio of $11,500 per patient with ACR 20 response over a 6 month period. Using the outcome of ACR 70WR, SSZ cost more but was less efficacious than MTX therapy (i.e., ruled out by simple dominance). Leflunomide was also dominated by MTX under base case assumptions.

The most effective therapy, etanercept, increased the probability of achieving ACR 20 by 12 percentage points and increased total costs by $5138 compared with SSZ, resulting in an incremental CE ratio of $41,900 per patient with ACR 20 response over a 6 month period. Similarly, etanercept increased the probability of achieving ACR 70WR by 13 percentage points and increased total costs by $5138 compared with MTX, resulting in an incremental CE ratio of $40,800 per patient with ACR 70WR over a 6 month period.

Analyses with only direct costs. In the analyses including only direct costs, the least expensive non-dominated option was SSZ, with incremental CE ratios of $900 per ACR 20 and $1500 per ACR 70WR compared with no second line agent (Tables 2 and 3). Leflunomide remained dominated in analysis using either ACR outcome. The incremental CE ratio for etanercept was $48,300 per ACR 20 and $42,900 per ACR 70WR compared with SSZ and MTX, respectively. These incremental CE ratios for etanercept were close to those in the analyses where total costs were considered (Tables 2 and 3).

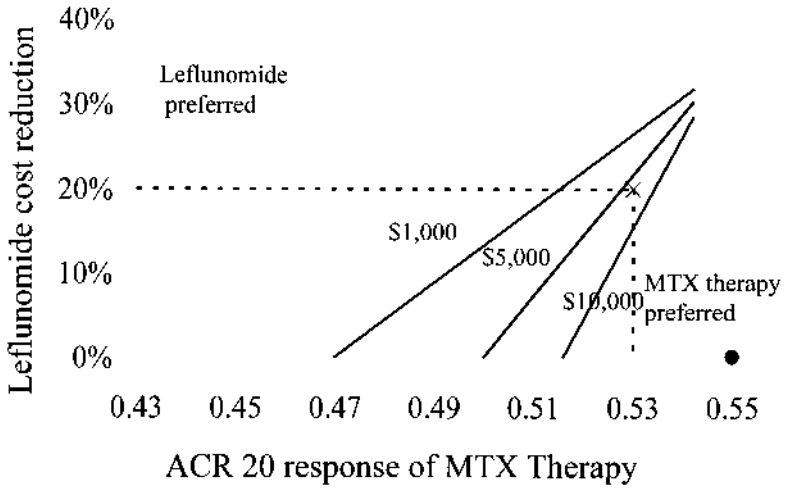

Figure 2. Three-way sensitivity analysis of ACR 20 estimate of MTX therapy (*x* axis) and leflunomide cost reduction (*y* axis) with acceptable cost effectiveness threshold for the choice of MTX or leflunomide. The lines indicate the incremental cost effectiveness thresholds per ACR 20 necessary over 6 months to use leflunomide over MTX: $1000, $5000, and $10,000 per ACR 20. For a particular cost effectiveness threshold, points to the upper left of the line indicate that leflunomide is preferred; points to the lower right of the line indicate that MTX is preferred. Closed circle: base case. For example, "x" denotes a setting where MTX outcome was reduced by 2 percentage points (ACR 20 response: from 55 to 53) and leflunomide cost was reduced by 20%. The mark is between the $5000 threshold line and $10,000 threshold line. Therefore, the preferred option in this setting is leflunomide if the allowed budgetary cost effectiveness threshold is $10,000 per ACR 20, whereas the preferred option is still MTX if the cost effectiveness threshold is $5000 per ACR 20.

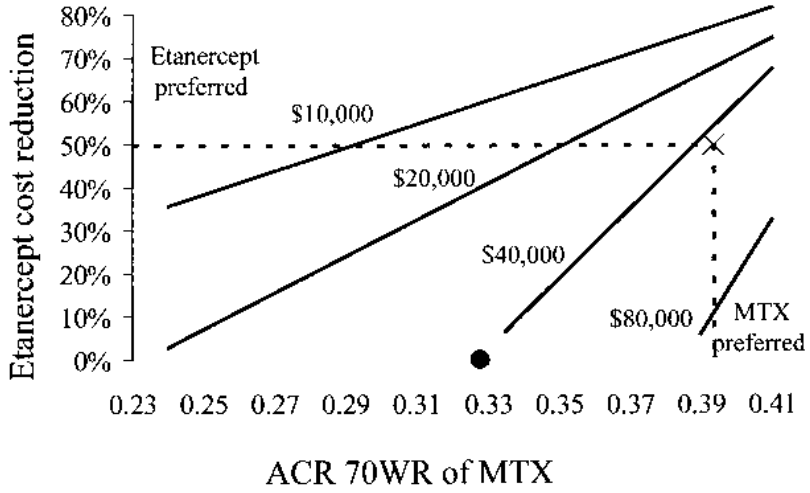

Figure 3. Three-way sensitivity analysis of ACR 70WR estimate of MTX therapy (*x* axis) and etanercept cost reduction (*y* axis) with acceptable cost effectiveness threshold for the choice of MTX or etanercept. The lines indicate the incremental cost effectiveness thresholds per ACR 20 necessary over 6 months to use leflunomide over MTX: $1000, $5000, $10,000, and $20,000 per ACR 20. For a particular cost effectiveness threshold, points to the upper left of the line indicate that etanercept is preferred; points to the lower right of the line indicate that MTX is preferred. Closed circle: base case. For example, "x" denotes a setting where MTX therapy outcome was increased by 20% (ACR 70WR: from 33 to 39) and etanercept cost was reduced by 50%. The mark is between the $40,000 threshold line and $80,000 threshold line. Therefore, the preferred option in this setting is etanercept if the allowed budgetary cost effectiveness threshold is $80,000 per ACR 20, whereas the preferred option is still MTX if the cost effectiveness threshold is $40,000 per ACR 20.

Sensitivity analyses

One way sensitivity analyses, ACR 20. The sensitivity analyses with ACR 20 outcome are summarized in Tables 4 and 5. The dominance status between SSZ and MTX reversed over the tested ranges of ACR 20 response, monitoring costs, and toxicity costs. Leflunomide remained dominated over the

Table 2. Base case effectiveness, direct costs, total costs, and cost effectiveness (CE) of different strategies for MTX-naive RA with ACR 20 outcome over a time horizon of 6 months.

Treatment Options	Probability of Achieving ACR 20	Direct Costs, $	Incremental CE Ratio†, $ (Direct Costs)/ACR 20	Total Costs, $	Incremental CE Ratio†, $ (Total Costs)/ACR 20
No second line agent	0.27	1640	—	11,379	—
SSZ	0.56	1888	900	11,027	11,500
MTX	0.55	2312	D	10,926	CS
Leflunomide	0.55	2814	D	11,428	D
Etanercept	0.68	7812	48,300	16,165	41,900

† The difference in cost divided by the difference in the probabilities of achieving ACR 20 for each strategy compared with the next-best non-dominated strategy. * Weak dominance. CS: cost-saving; D: dominated.

Table 3. Base case effectiveness, direct costs, total costs, and cost effectiveness (CE) of different strategies for MTX-naive RA with ACR 70WR outcome over a time horizon of 6 months.

Treatment Options	Probability of Achieving ACR 70WR	Direct Costs, $	Incremental CE Ratio†, $ (Direct Costs)/ACR 70WR	Total Costs, $	Incremental CE Ratio†, $ (Total Costs)/ACR 70WR
No second line agent	0.15	1640	—	11,379	—
SSZ	0.31	1888	1500	11,027	D
MTX	0.33	2312	29,300	10,926	CS
Leflunomide	0.33	2814	D	11,428	D
Etanercept	0.46	7812	42,900	16,165	40,800

† The difference in cost divided by the difference in the probabilities of achieving ACR 70WR for each strategy compared with the next-best non-dominated strategy, rounded to the nearest $100. * Weak dominance. CS: cost-saving; D: dominated.

ranges of all variables except when there was a substantial increase in leflunomide ACR 20 response (from 55% to 64%) or substantial decrease in leflunomide cost (> 30% reduction). The incremental CE ratio per patient achieving ACR 20 improvement for etanercept was greater than $39,000 unless the cost of etanercept was reduced or the probability of achieving ACR 20 response increased. When the cost of etanercept was reduced by 25%, and 50% of the baseline cost, the incremental CE ratio over MTX was $28,400 and $15,000 per ACR 20, respectively (Table 4). When we increased the ACR 20 estimate of MTX closer to that of etanercept (from 55% to 66%) and increased the cost of MTX to that of 20 mg weekly (from that of 15 mg weekly) to reflect the result of the recent head-to-head trial of the 2 agents[4], the incremental CE ratio of etanercept compared with MTX therapy was $258,500 per patient with ACR 20 response.

One way sensitivity analyses, ACR 70WR. The sensitivity analyses with ACR70WR outcome are shown in Tables 4 and 5. The dominance status between SSZ and MTX was sensitive to more variables than in the analyses with ACR 20. These variables included ACR 70WR response, monitoring costs, toxicity costs, and indirect costs. Leflunomide remained dominated over the range of all variables except when there was an increase in the leflunomide ACR 70WR response, decrease in the ACR 70WR response of MTX, or decrease in leflunomide cost (> 30% reduction). When the ACR 70WR response of leflunomide was increased from 33% at baseline to 36%, the incremental CE ratio of this option compared with MTX became $7500 per patient with ACR 70WR response. The incremental CE ratios per patient achieving ACR 70WR improvement for etanercept was greater than $36,000 unless the cost of etanercept was reduced or the probability of achieving ACR 20 response increased. When the cost of etanercept was reduced by 25% and 50% from the baseline cost, the incremental CE ratio over MTX was $28,000 and $15,100 per ACR 70WR, respectively (Table 4). When we increased the ACR 70WR response of MTX closer to that of etanercept (43% for MTX and 46% for etanercept) and based the cost of MTX on 20 mg weekly instead of on 15 mg weekly to reflect the result of the recent head-to-head trial of the 2 agents[4], the incremental CE ratio of etanercept over MTX therapy became $193,900 per patient achieving ACR 70WR response.

Three way sensitivity analyses. Figure 2 shows a 3 way sensitivity analysis varying the ACR 20 response of MTX (x axis) and the cost reduction of leflunomide (y axis) with incremental CE ratios of $1000, $5000, and $10,000 per ACR 20 (3 lines in Figure 2). In this analysis, leflunomide was dominated unless the efficacy of MTX therapy was lower than that of leflunomide. Therefore, the range in the graph covers the MTX outcome only below its baseline level. This sensitivity analysis indicates that a substantial reduction in leflunomide cost is necessary, even with the MTX therapy outcome esti-

Table 4. Summary of one way sensitivity analyses on drug efficacy and cost estimates[§].

Variable[†]	Incremental CE Ratio[††], $/ACR 20			Incremental CE Ratio[††], $/ACR 70WR		
	SSZ	MTX	Etanercept	SSZ	MTX	Etanercept
Base case	11,500	CS	41,900	D	CS	40,800
Probability achieving ACR response						
No second line agent						
20% > baseline	12,500	CS	45,200	D	CS	42,300
20% < baseline	10,800	CS	39,000	D	CS	39,400
SSZ						
20% > baseline	CS	D	476,200	CS	D	67,500
20% < baseline	D	CS	39,900	D	CS	40,800
MTX						
20% > baseline	D	CS	266,100	D	CS	91,500
20% < baseline	CS	D	41,900	CS	D	36,900
Leflunomide						
20% > baseline	D	D	243,100	D	D	83,500
20% < baseline	11,500	CS	41,900	D	CS	40,800
Etanercept						
20% > baseline	11,500	CS	17,700	D	CS	21,700
20% < baseline	11,500	CS	D	D	CS	154,400
Cost of SSZ						
50% > baseline	17,700	CS	41,500	D	CS	40,800
Using enteric coated tablet price	25,200	CS	41,500	D	CS	40,800
Cost of leflunomide						
30% < baseline	11,500	CS	41,900	D	CS	40,800
50% < baseline	38,100	D	41,900	D	D	42,600
Cost of etanercept						
25% < baseline	11,500	CS	28,400	D	CS	28,000
50% < baseline	11,500	CS	15,000	D	CS	15,100
75% < baseline	D*	CS	2200	D	CS	2200

D: dominated; CS: cost-saving; CE: cost effectiveness.
[§] Leflunomide was dominated except for a few ranges described in the text in detail and its data are not shown in this table.
[†] The range of each variable by percentage corresponds to that of the actual values in Table 1.
[††] The difference in cost ÷ the difference in the probabilities of achieving ACR 20 or ACR 70WR for each strategy vs the next-best non-dominated strategy, rounded to the nearest $100.
* Weak dominance.

mate below its baseline, for leflunomide to become a preferred option over MTX with incremental CE thresholds of $1000, $5000, or $10,000 per ACR 20. Figure 3 shows a 3 way sensitivity analysis varying the ACR 70WR response of MTX (*x* axis) and the cost reduction of etanercept (*y* axis) with incremental CE ratios of $10,000, $20,000, $40,000, and $80,000 per ACR 70WR (4 lines in Figure 3). The preference of MTX therapy over etanercept was apparent over the tested range of assumptions. Substantial reduction in etanercept cost was necessary to achieve an incremental CE ratio of $10,000, $20,000, $40,000, and $80,000 per ACR 70WR.

DISCUSSION

Our objective was to provide clinicians and policy makers information about the incremental benefits in terms of ACR response and costs of choosing one treatment option over another among the options available for MTX-naive RA patients. We compared 5 treatment options using both ACR 20 and ACR 70WR over a 6 month period as outcome measurements. We found that MTX was a cost saving option in achieving ACR 20 and ACR 70WR over a 6 month period compared with no second line agent.

SSZ was also more effective and less costly than no second line agent and the total costs and efficacy estimates associated with SSZ were close to those of MTX over a 6 month period ($11,027 and $10,926 in total costs, respectively). Thus, with minor changes in relevant variables, the MTX option became dominated by SSZ (Tables 4 and 5). The sensitivity of the relative dominance between MTX and SSZ indicates uncertainty about the incremental CE between the 2 agents and strongly argues for the close similarity in the CE between them. This argument is also supported by the results of analyses including only direct costs, where the least expensive non-dominated option was SSZ, which dominated MTX in ACR 20 analysis. Thus, we conclude that based on currently available data, the relative CE between SSZ and MTX cannot be determined with reasonable certainty and SSZ may well be as cost effective an option as MTX in achieving ACR outcomes over a 6 month period. Leflunomide cost more but was not more efficacious than the next option (dominated). This result

Table 5. Summary of one way sensitivity analyses on other variables.

Variable†	Incremental CE Ratio††, $/ACR 20			Incremental CE Ratio††, $/ACR 70WR		
	SSZ	MTX	Etanercept	SSZ	MTX	Etanercept
Base case	11,500	CS	41,900	D	CS	40,800
Monitoring costs for no second line agent						
20% > baseline	23,100	CS	41,900	D	CS	41,600
20% < baseline	CS	D	41,900	CS	0	40,000
Monitoring costs for MTX						
20% > baseline	CS	D	41,900	CS	3900	39,600
20% < baseline	29,600	CS	41,900	D	CS	42,000
Excess monitoring costs of SSZ over no second-line agent						
100% > baseline	23,500	CS	41,000	D	CS	40,800
50% < baseline	5600	CS	42,300	D	CS	40,800
Monitoring costs for leflunomide						
100% > baseline	11,500	CS	41,900	D	CS	40,800
50% < baseline	11,500	CS	41,900	D	CS	40,800
Probability of toxicity to MTX						
50% > baseline	CS	D	41,900	CS	1730	39,800
50% < baseline	26,000	CS	41,900	D	CS	41,800
Proportion with major toxicity to MTX						
80% > baseline	CS	D	41,900	CS	6300	39,300
80% < baseline	33,500	CS	41,900	D	CS	42,300
Probability of toxicity to SSZ						
50% > baseline	26,410	CS	40,800	D	CS	40,800
50% < baseline	CS	D	43,000	CS	2000	40,800
Proportion with major toxicity to SSZ						
80% > baseline	34,200	CS	40,300	D	CS	40,800
80% < baseline	CS	D	43,500	CS	6800	40,800
Probability of toxicity to leflunomide						
Same as MTX	D	CS	41,900	D	CS	40,800
Exclusion of surgery costs	1700	D	49,900	CS	2900	41,300
Average income for working age (18–64) persons for 6 months						
100% > baseline	D*	CS	37,900	D	CS	38,800
20% < baseline	CS	D	43,200	CS	300	41,200
Slope of linear regression between HAQ and working capacity						
20% steeper than baseline	23,500	CS	40,600	D	CS	40,400
20% less steep than baseline	CS	D	43,200	CS	300	41,200

D: dominated; CS: cost-saving; CE: cost effectiveness.

§ Leflunomide was dominated except for a few ranges described in the text in detail and its data are not shown in this table.

† The range of each variable by percentage corresponds to that of the actual values in Table 1.

†† The difference in cost ÷ the difference in the probabilities of achieving ACR 20 or ACR 70WR for each strategy vs the next-best non-dominated strategy, rounded to the nearest $100.

* Weak dominance.

remained the same in analyses including direct costs only. Therefore, this option is not cost effective. The dominated status of leflunomide persisted with variation of relevant variables in sensitivity analyses, except when the efficacy of leflunomide was substantially better than that of MTX or the cost of leflunomide was reduced by at least 30%.

The most efficacious option, etanercept, cost $41,900 per ACR 20 and $40,800 per ACR 70WR compared with SSZ and MTX, respectively. These incremental CE ratios of etanercept were close to those from the analyses including only direct costs. These incremental CE ratios did not decrease substantially in sensitivity analyses, except with a reduction in etanercept cost or an increase in etanercept ACR response. When we increased the ACR outcome of MTX closer to that of etanercept and increased the cost of MTX to 20 mg weekly to reflect the recent head-to-head trial of the 2 agents[4], the incremental CE ratio of etanercept notably increased (to $258,500 per ACR 20 and $193,900 per ACR 70WR).

Because we used RA-specific outcomes, the incremental CE ratios presented in our analyses need to be interpreted differently for the specific cost constrained heath care setting in which these options would be considered. For example, whether the combination of etanercept is cost effective depends on whether $41,900 per patient with ACR 20 or $40,800 per patient with ACR 70WR over a 6 month period is considered acceptable in a given medicoeconomic setting.

Our analysis implicitly assumes that all options are equally available and clinically acceptable. In settings where MTX

and SSZ are clinically unacceptable, choosing between leflunomide and etanercept can be helped by estimating their relative CE. To simulate this clinical setting, we eliminated MTX and SSZ from our decision tree and repeated the analyses. The incremental CE ratio of leflunomide was $200 per ACR 20 and $300 per ACR 70WR over a 6 month period compared with no second line therapy. In contrast, the incremental CE ratios for etanercept compared with leflunomide remained high ($36,000 per ACR 20 and $36,900 per ACR 70WR). These analyses suggest that when MTX and SSZ are clinically unacceptable, the choice of leflunomide incurs small costs per ACR outcomes compared with no second line agent. These analyses also indicate that the most efficacious option, etanercept, incurs much higher incremental costs per ACR 20 or ACR 70WR than the other options included in our analyses.

An advantage of using ACR outcomes in CE analysis is their direct availability in publications of recent trials. Additionally, the analysis can be readily expanded with additional options in the future. We chose ACR 20 response criteria as one of our outcome measures because it is the most widely used among recent arthritis trials. In a recent publication evaluating the utility of different ACR response criteria, ACR 20 was recommended as the primary measure of efficacy in RA trials[20,21]. However, because the ACR 20 improvement index does not optimally reflect the degree of improvement beyond ACR 20, a CE analysis employing only ACR 20 is likely to bias against more efficacious therapeutic options that can achieve more than 20% improvement. Thus, a weighted outcome measure of ACR responses relative to a full weight of ACR 70 (ACR 70WR) was adopted in our analysis to help overcome this potential shortcoming of ACR 20. We feel that since ACR 70WR provides more information, including incorporation of the degree of improvement with each treatment option, the results obtained using ACR 70WR provide a more comprehensive assessment of the CE than those using ACR 20.

There are caveats and limitations in our analysis. Although our base case analysis estimated efficacy of each option based on 4 randomized trials[2-4,10] comparing head-to-head one option to the other, it is the general view that only through the randomization of all treatments together in one trial could one expect absolute comparability. Presently, such data are not available and it appears doubtful that such a comprehensive randomized trial evaluating all the options will be performed in the future. Another relevant issue might be the generalizability of our efficacy estimates because they are based on a limited number of trials due to the absence of additional, relevant trials. Additionally, since our source studies are all randomized trials, potential concerns about their generalizability to the general RA population should extend to our study. Although these efficacy data are based on all available relevant trials and are employed in efficacy comparisons in expert review and discussion, the potential impact of different efficacy estimates from the future studies or even from current opinions of readers should refer to the results of our extensive sensitivity analyses. For example, if one believes that the efficacy of etanercept monotherapy is as much as 20% higher than its baseline estimate (ACR 20 = 81%), the incremental CE ratio for etanercept over MTX was $17,700 per ACR 20 and still substantially higher than the incremental CE ratio of the rest of considered options discussed above. Although one would expect a significant association between HAQ and indirect costs similar to our source article based on the Swedish health care system[18], the magnitude of its association or the average income level may vary substantially among different countries. Our sensitivity analyses suggested a minimal impact from these potential differences (Table 5). Similarly, our results were robust in the sensitivity analysis varying surgery cost variables (the coefficient of the association between HAQ and the cost and the mean surgery cost). Additionally, when we entirely removed the surgery costs from our model, the results remain similar, especially for the incremental CE ratios for leflunomide and etanercept (Table 5).

Although RA-specific outcomes (ACR 20 and ACR 70WR) employed in the current analysis still allow comparisons of interventions within RA, we cannot make absolute statements about whether a given option is cost effective compared to other widely accepted cost effective interventions in medicine. To overcome this limitation, a generic measure of effectiveness such as quality-adjusted life year would be necessary. The time horizon for this analysis was 6 months, which represented the usual duration of most clinical trials of RA patients. Thus, our analysis could not incorporate the possibility that variable duration of efficacy in strategies may affect CE over a longer time horizon. Because RA patients usually continue a given DMARD indefinitely as long as the selected agent is effective without side effects, costs and benefits will accumulate over a longer time horizon. There have been recent reports of remarkable efficacy in preventing radiologic progress with anti-tumor necrosis factor agents[4,22,23]. It remains to be seen how much differential clinical benefit (effectiveness) this radiologic benefit can bring into CE analysis compared with more conventional, less expensive options over longer time horizons.

In conclusion, our analysis indicates that MTX is cost effective for MTX-naive RA in achieving ACR 20 or ACR 70WR over a 6 month period. Based on currently available data, the relative CE between SSZ and MTX cannot be determined with reasonable certainty and SSZ therapy appears to be as cost effective as MTX (cost saving compared with no second line agent) in achieving ACR outcomes over a 6 month period. The most efficacious option, etanercept, incurs much higher incremental costs per ACR 20 or ACR 70WR than the other options considered in our analysis. Whether etanercept compared with MTX is cost effective depends on whether > $40,000 per ACR 20 or ACR 70WR over a 6 month period is considered acceptable.

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