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ORIGINAL ARTICLE

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Modeling and cost-effectiveness analysis of etanercept in adults with rheumatoid arthritis in Japan: a preliminary analysis

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Abstract The tumor necrosis factor (TNF) antagonist etanercept is an antirheumatic agent which was approved by Japanese regulatory authorities in January 2005. In Japan, the cost-effectiveness of this therapy for patients with rheumatoid arthritis (RA) has not previously been evaluated. This study models the cost-utility of etanercept in comparison with standard therapy with disease-modifying antirheumatic drugs (DMARDs) among adult Japanese RA patients who have failed a previous course of the DMARD bucillamine. A Markov model with 6-month cycles was constructed to compare two therapeutic strategies: etanercept versus standard therapy. For each cycle, one of three options was possible: a patient could (i) remain on current therapy if American College of Rheumatology criteria for 20% clinical improvement (ACR20) were achieved, (ii) switch to another drug in the therapeutic pathway if ACR20 was not achieved or if side effects severe enough to cause treatment discontinuation occurred, or (iii) they could die. The therapeutic pathway for the etanercept strategy was etanercept, methotrexate (MTX), sulfasalazine (SSZ), combination therapy (MTX + SSZ) and, finally, no DMARD. The pathway for standard therapy was identical except the initial therapy was MTX (etanercept was excluded). Results from clinical trials in U.S. and European patient populations were used to derive model probabilities for disease progression, response to drug therapy, and relationships between ACR20 response and functional improvement as measured by the Health Assessment Questionnaire (HAQ) disability index. An equation was developed to predict utility from HAQ scores of Japanese patients. Costs for drugs and medical services in Japan were obtained for April 2003. Analysis was conducted from a societal perspective, including lost productivity costs due to RA disability and premature mortality. Costs were discounted at 6% annually, and quality-adjusted life years (QALYs) at 1.5% annually. Model parameters were varied by 20% above and below base-case values in sensitivity analyses. Compared to standard therapy, the etanercept strategy was ¥6.39 million more costly per patient but yielded an additional 2.56 QALYs. The incremental cost-utility ratio was ¥2.50 million/QALY. Sensitivity analyses revealed that cost-utility was most strongly influenced by the acquisition cost of etanercept and the percentage of etanercept recipients who achieved ACR20. Using commonly applied thresholds for acceptable cost-effectiveness in the United States ($50000 = ¥5.5 million/QALY) and the United Kingdom (£30000 = ¥5.7 million/QALY), etanercept therapy in Japan can be considered cost-effective. Cost-utility ratios did not exceed these thresholds in any sensitivity analysis. Further analyses should be conducted once clinical and epidemiologic data for Japanese patients become available.

Key words Anti-tumor necrosis factor (TNF)-α · Cost-effectiveness analysis · Disease-modifying antirheumatic drug (DMARD) · Etanercept · Japan · Rheumatoid arthritis (RA)

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Introduction

In Japan, the reported prevalence of rheumatoid arthritis (RA) in the general population is 0.2%, with an annual incidence of approximately 0.01%.[1] Rheumatoid arthritis is

more common in Europe and North America, where its prevalence is between 0.5% and 1.0% and its annual incidence approximately 0.03%.[2,3] Nevertheless, RA imposes a significant economic burden on the Japanese health care system. The average direct medical cost for treating a Japanese RA patient is estimated to be ¥417134 annually (unless otherwise specified, all costs are in Japanese Yen).[4] Medications comprise 55.4% of this amount.

Clinical practice guidelines for RA recommend pharmacologic treatment with disease-modifying antirheumatic drugs (DMARDs).[5] Unlike non-steroidal anti-inflammatory drugs (NSAIDs), which provide only symptomatic relief, DMARDs have the potential to retard joint damage and preserve function. Beyond improving patient outcomes, there is an economic rationale for drugs that can slow or halt the progression of RA, because the cost of therapy correlates strongly with disability. Among Japanese patients, after adjusting for age, sex, disease duration and body mass index, direct medical costs for RA treatment increase by more than 33% for every unit increase in disability score on the Japanese version of the Stanford Health Assessment Questionnaire (HAQ; range 0 to 3).[6]

Etanercept is a recombinant biologic response modifier that binds tumor necrosis factor (TNF), thereby reducing the synthesis of pro-inflammatory cytokines.[7] Etanercept has been demonstrated to yield significantly greater improvement in RA symptoms than standard therapy with the DMARD methotrexate (MTX).[8,9] Most adverse effects of etanercept are mild or moderate.[8–12]

This study models the pharmacoeconomics of etanercept therapy for Japanese RA patients. Japan does not have formal guidelines for conducting pharmacoeconomic analyses,[13] and is not as advanced as North America, Europe and Australia in the economic assessment of new drugs.[14] Due to growing medical costs, however, there is increasing interest in pharmacoeconomic analysis in Japan. Markov models were employed to evaluate the cost-utility of etanercept in comparison with standard pharmacologic care.

Methods

Prescribing strategies

As shown in Fig. 1, two prescribing strategies were compared, one based on standard therapy in Japan, the other incorporating etanercept. Prior to beginning either strategy, patients were required to have failed first-line therapy with bucillamine, a cysteine derivative frequently prescribed for RA in Japan.[15] This criterion reflects the restriction of the late phase II clinical trial of etanercept in Japan to patients who had failed prior therapy with one or more DMARDs. Based on this, eligibility requirements such as inadequate patient response to prior DMARD therapy have been imposed on prescribing.

After failure to respond to bucillamine, patients in the etanercept group initially received etanercept 25 mg administered twice-weekly as subcutaneous injection. Patients who had an inadequate response after 6 months or severe side effects with etanercept were switched to MTX monotherapy at 6 mg/week, the standard dosage in Japan. Inadequate response to therapy was defined as failure to achieve American College of Rheumatology criteria for 20% clinical improvement (ACR20).[5] Patients who subsequently responded inadequately or experienced severe side effects with MTX were switched to sulfasalazine (SSZ) at the standard dosage in Japan of 1000 mg/day. Those who had an inadequate response or severe side effects with SSZ monotherapy were switched to combination therapy with MTX and SSZ (MTX + SSZ). Patients who failed all of

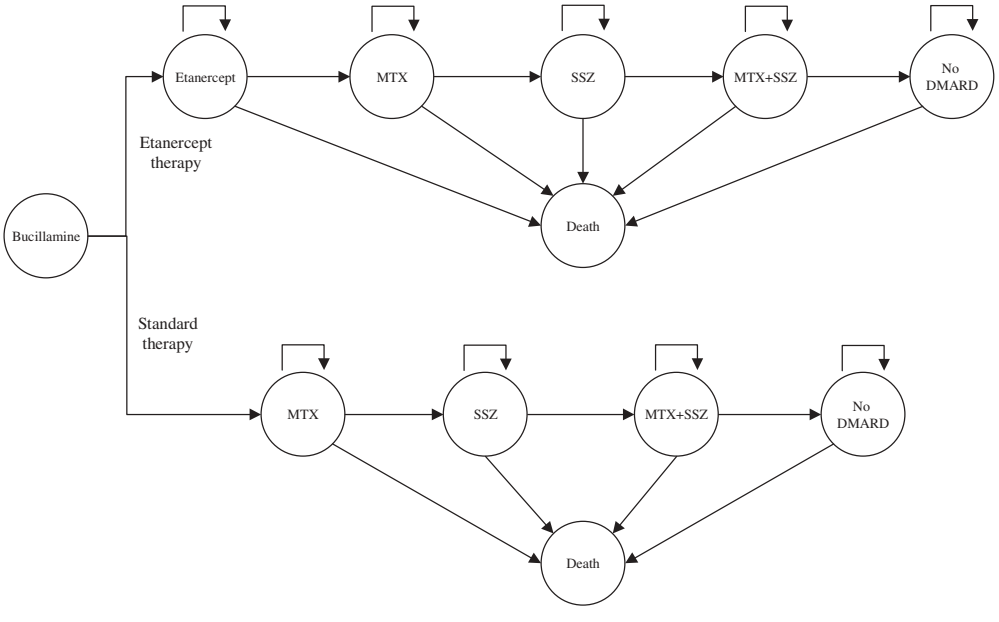

Fig. 1. Structure of the Markov model used to compare cost-utility of etanercept versus standard therapy. After failure to respond to bucillamine therapy, a patient enters one of two therapeutic pathways: etanercept therapy or standard therapy. At each 6-month time step, patients may remain on their current therapy, switch to the next therapy in the pathway if response to current therapy was inadequate, or die. *MTX*, methotrexate; *SSZ*, sulfasalazine

these treatments were taken off DMARD therapy. The therapeutic pathway for patients in the standard therapy group differed only by exclusion of etanercept as initial therapy.

Model structure

The etanercept and standard therapy strategies were compared using the Markov model depicted in Fig. 1. Each cycle of the model had a 6-month duration, since RA therapy is commonly re-evaluated on a 6-month basis in Japan. At the start of each cycle, patients could remain on their current therapy, switch to the next therapy in the pathway if they failed to achieve ACR20 with current therapy, or die. Patients could not switch from current medication to an earlier treatment in the therapeutic pathway. Death was an absorbing state. The time horizon was the lifetime of the cohort. Monte Carlo simulation was used to generate 10000 trials of the model.

Clinical trial data

The population in this analysis was modeled after the characteristics of patients included in the phase III clinical trial in the United States.[10] Patients had chronic RA, an average age of 53 years and a female to male ratio of 4:1. The ratio of female to male RA patients in Japan is also 4:1.[16] Transition probabilities used in the Markov model are summarized in Table 1.

Probabilities of achieving ACR20 for the different therapies were derived from clinical trial results. The ACR20 probability for etanercept therapy was set at 59%, the ACR20 response rate at 6 months among patients receiving 25 mg etanercept in the U.S. phase III trial.[10] Six-month ACR20 probabilities for MTX and SSZ were estimated as 42.3% and 37.1%, respectively, based on results reported by Kawai et al.[17] where ACR20 score was calculated as 70% of General Improvement score, an evaluation method used in Japan. The 6-month ACR20 probability for MTX + SSZ combination therapy was assumed to be the same as for SSZ monotherapy (37.1%).

Probabilities of side effects severe enough to require treatment discontinuation were estimated from dropout rates due to adverse events in clinical trials. For etanercept, the 6-month probability of discontinuation due to side effects and lack of efficacy was set at 2.4%, based on results from a long-term open label extension of short-term clinical trials.[12] For MTX and SSZ, the 6-month probabilities of treatment discontinuation were 5.6% and 7.2%, respectively, based on results of a long-term study with both agents.[18]

Utilities

The unit of utility in this analysis was the quality-adjusted life year (QALY). Utilities were calculated from HAQ disability index scores using the following equation:

$$\text{Utility} = 0.74 - 0.17 \times \text{HAQ}$$
$$\left(R^2 = 0.48, \quad F = 75.1, \quad P < 0.001\right)$$

This equation was obtained from a survey of 307 Japanese RA patients. Both HAQ and EuroQol (EQ-5D) were measured in this survey.[19]

HAQ response and progression

HAQ score in patients who achieved ACR20 with etanercept therapy was assumed to change by a factor of 0.53 over 6 months, based on results for patients receiving 25 mg etanercept in U.S. clinical trials.[20] For example, a patient with an initial HAQ score of 2.0 who achieved ACR20 would be predicted to have a HAQ score of 1.06 after 6 months ($2.0 \times 0.53 = 1.06$). HAQ score was assumed not to decrease in patients who did not achieve ACR20 or who discontinued therapy due to side effects.

Rate of HAQ score change for ACR20 responders receiving MTX or SSZ is not available from the literature because only mean HAQ score change has been reported for these agents; results stratified by ACR20 response have not been. Strand et al.[21] reported a mean HAQ score decrease of 0.2 over 12 months for patients receiving MTX, and Smolen et al.[22] reported a mean HAQ score decrease of 0.29 over 24 weeks for patients receiving SSZ. These values were adjusted to account for ACR20 response. Brennan et al.[20] estimated that HAQ score change for ACR20 responders is 2.28 times the change for non-responders, based on results for subjects in the etanercept

Table 1. Values of variables included in the Markov model

	Etanercept	MTX	SSZ	MTX + SSZ
Probabilities				
ACR20 achievement rate (%)	59	42.3	37.1	37.1
HAQ change factor when ACR20 is achieved	0.53	0.80	0.71	0.71
6-month discontinuation rate (%)	2.4	5.6	7.2	7.2
HAQ progress rate (HAQ units/year)	0	0.0673	0.0673	0.0673
Costs (¥)				
Annual drug acquisition costs	1478016	58421	62712	121133

MTX, methotrexate; SSZ, sulfasalazine; ACR20, American College of Rheumatology criteria for 20% clinical improvement; HAQ, Health Assessment Questionnaire

group. The following equation of Brennan et al. was used to estimate HAQ score change for ACR20 responders receiving MTX and SSZ:

$$\text{HAQ change for ACR20 responders} = \frac{\text{Mean HAQ change}}{\%\ \text{ACR20 responders} + \dfrac{\%\ \text{ACR20 nonresponders}}{2.28}}$$

For the base-case analysis, the ACR20 response rates used in this equation were 46% and 56% for MTX and SSZ, respectively.[21,22] This yielded HAQ score change factors of 0.8 for MTX recipients who achieved ACR20 and 0.71 for SSZ recipients who achieved ACR20. Because there is no study of HAQ score change with MTX + SSZ combination therapy, patients receiving MTX + SSZ who achieved ACR20 were assumed to have the same HAQ score factor as those receiving SSZ monotherapy (0.71).

For patients receiving MTX, SSZ, or MTX + SSZ therapy, and for those in the final therapeutic state in the Markov model (No DMARD therapy), HAQ score was assumed to increase at the low background rate of 0.0673 per 6 months, based on findings by Brennan et al.[20] This increase was applied independently of any change in HAQ score due to ACR20 response. The HAQ score was assumed not to increase during etanercept therapy, even for patients who did not achieve ACR20, based on results from the long-term open label study.[12]

Costs

Direct medical costs

The costs of ambulatory care for both treatment strategies were estimated using medical treatment fees and average drug prices for April 2005. While patients in the standard therapy group were assumed to make one outpatient visit per month, patients in the etanercept group were assumed to make two outpatient visits per month because of the restriction on self-injection in Japan by the Ministry of Health, Labor and Welfare.

The approval NHI price of etanercept is ¥15396 per 25-mg vial. Additional costs for basic outpatient fee, guidance and management of home self-injection, and needles amounted to ¥70200 over 6 months. Including these costs, the 6-month cost of etanercept 25mg twice weekly was ¥809208. Because there is an increased risk of tuberculosis while taking etanercept or other anti-TNF agents,[23] costs of an annual tuberculin skin test and lung computed tomography scan were also included (¥13489/year). The total 6-month medical costs for patients receiving etanercept were ¥815952.5.

The drug acquisition costs for MTX and SSZ shown in Table 1 are based on dosages of 6mg/week and 1000mg/day, respectively. In addition, costs of treating gastrointestinal (GI) side effects of MTX or SSZ were included. Gastrointestinal side effects were assumed to occur at a 6-month incidence rate of 16.2% and 11.5% for MTX and SSZ recipients, respectively, based on results of studies by Kashiwazaki et al.[24] and Nishioka et al.[25] Frequency of GI side effects among MTX + SSZ recipients was assumed to be the same as for MTX recipients (16.2%). Patients experiencing GI side effects were prescribed an eight-week course of the proton pump inhibitor lansoprazole at a cost of ¥13720. Although interstitial pneumonia has been associated with MTX therapy,[26] no cases of interstitial pneumonia occurred among MTX recipients receiving 6mg/week in the study by Kashiwazaki et al.[24] Costs of treating interstitial pneumonia were therefore not included in this model.

Table 2. Predicted annual costs of hospitalization for rheumatoid arthritis (RA), stratified by patient HAQ score

HAQ score	Annual hospitalization rate	Predicted annual hospitalization costs[a] (¥)
0.0–0.5	0.0567	110162
>0.5–1.0	0.1481	287645
>1.0–1.5	0.1860	361229
>1.5–2.0	0.1389	269667
>2.0–2.5	0.2273	441274
>2.5–3.0	0.4286	832116

[a] Average cost per RA hospitalization = ¥1941604

Table 3. Retirement rates for Japanese RA patients, stratified by HAQ score

HAQ score	Retirement rate
0.0–0.5	0.289
>0.5–1.0	0.500
>1.0–1.5	0.619
>1.5–2.0	0.667
>2.0–2.5	0.800
>2.5–3.0	0.750

Analysis of medical records at the Nippon Medical School hospital yielded an average cost of a single hospitalization for RA of ¥1941604 per patient. College records were analyzed to obtain annual hospitalization rates for HAQ score categories at intervals of 0.5, as shown in Table 2. Annual RA-related hospitalization rates were multiplied by the average cost per RA-related hospitalization to obtain predicted annual hospitalization cost within each HAQ score category. These predicted costs and midpoints of the HAQ score categories were used to derive the following linear regression equation that predicted annual hospital inpatient costs from RA patient HAQ scores:

$$\text{Predicted annual hospital costs} = ¥227377 \times \text{HAQ} + ¥42617$$

Indirect costs

Indirect costs included lost productivity caused by inability to work. Data collected at the Nippon Medical School were analyzed to obtain retirement rates for RA patients by HAQ score category, as shown in Table 3. Rates were not stratified by sex because few men were included in the sample (26 men, 133 women). These retirement rates and midpoints of the HAQ score categories were used to derive

Table 4. Incremental cost-utility of etanercept compared to standard therapy for Japanese RA patients (base-case analysis)

Therapeutic strategy	Cost (million ¥)	QALYs	Cost-utility (million ¥/QALY)
Standard	17.60	6.80	
Etanercept	23.99	9.36	2.50

QALY, quality-adjusted life years

the following regression equation that predicted job retirement on the basis of RA patient HAQ score:

$$\text{Retirement rate} = 0.2077\ln(\text{HAQ}) + 0.572$$

The cost of lost productivity due to inability to work stratified by age, gender and HAQ score was calculated by multiplying retirement rate by age- and gender-adjusted employment rates and wages estimated from the 2001 wage census[27] and the 2001 report of the labor force survey,[28] as follows:

$$\text{Cost of lost productivity}_{\text{age,sex,HAQ}} = \text{Retirement rate}_{\text{HAQ}} \times \text{Adjusted}^{*}\ \text{6-month wage}_{\text{age,sex}}$$

Mortality

Excess mortality due to RA was calculated by subtracting the age- and gender-specific mortality rates of the Japanese general population[29] from mortality rates of RA patients matched by age and sex. Probability of death for RA patients in any time cycle was calculated using the following exponential equation incorporating age, sex and HAQ score:

$$D_{\text{RA}} = D_{\text{normal}} \times \exp(0.57\text{HAQ} + 0.96G)$$

where D_{RA} is mortality among RA patients, by age; D_{normal} is mortality in healthy adults, by age; HAQ is HAQ score; and G is sex (female = 0, male = 1). The coefficients in this equation were derived from a Cox proportional hazards model used by Wolfe et al.[30] to predict mortality in a cohort of 400 RA patients in Kansas.

The cost of lost productivity due to excess mortality was then calculated from the age- and sex-specific employment rate and the total average wages that would have been earned from age at death until age 60 years (normal retirement age in Japan) had the patient not died prematurely due to RA.

Discounting

Costs and QALYs were discounted annually at 6% and 1.5%, respectively, in accordance with United Kingdom guidelines for pharmacoeconomic analysis from the National Institute for Clinical Excellence (NICE).[31]

Sensitivity analyses

Sensitivity of the results to variation in model parameters was assessed for the following variables: percentage of patients achieving ACR20 with etanercept, MTX and SSZ; rate of HAQ score change for each therapy; and costs of etanercept, MTX and SSZ. Each variable was varied within a range of 20% above and below its base-case value.

Results

Table 4 reports the costs and QALYs for the etanercept and standard therapy strategies for Japanese RA patients in the base-case analysis. Considering total direct medical and indirect costs, the etanercept strategy was ¥6.39 million more costly per patient than the standard therapy strategy. Compared to patients in the standard therapy group, those in the etanercept group achieved an additional 2.56 QALYs. The incremental cost-utility ratio was therefore ¥2.50 million per QALY.

Figure 2 depicts the results of the sensitivity analyses as a tornado diagram; cost-utility is most sensitive to the variables with the widest bars in this figure. The cost of etanercept has the greatest influence on cost-utility, which ranges from ¥1.88 million per QALY in the scenario in which etanercept costs 80% of the base-case value to ¥3.12 million per QALY in the scenario in which it costs 120% of the base-case value. The model is also highly sensitive to the rate of decrease in HAQ score among ACR20 responders receiving etanercept, with cost-utility ranging from ¥2.09 million to ¥2.97 million per QALY. The model was least sensitive to the cost of DMARDs, with cost-utility ranging from ¥2.49 million to ¥2.51 million per QALY.

Discussion

A recent review of economic analyses of anti-TNF agents concluded that these medications are reasonably cost-effective for patients with active RA who fail to respond to standard DMARD therapy.[32] Among RA patients in Japan who have had inadequate response to bucillamine, a therapeutic strategy using etanercept as initial pharmacologic treatment would be more expensive than standard therapy without etanercept, but would result in an incremental gain of QALYs. Compared to standard therapy, the cost-utility

* Adjusted for age- and gender-specific employment rate

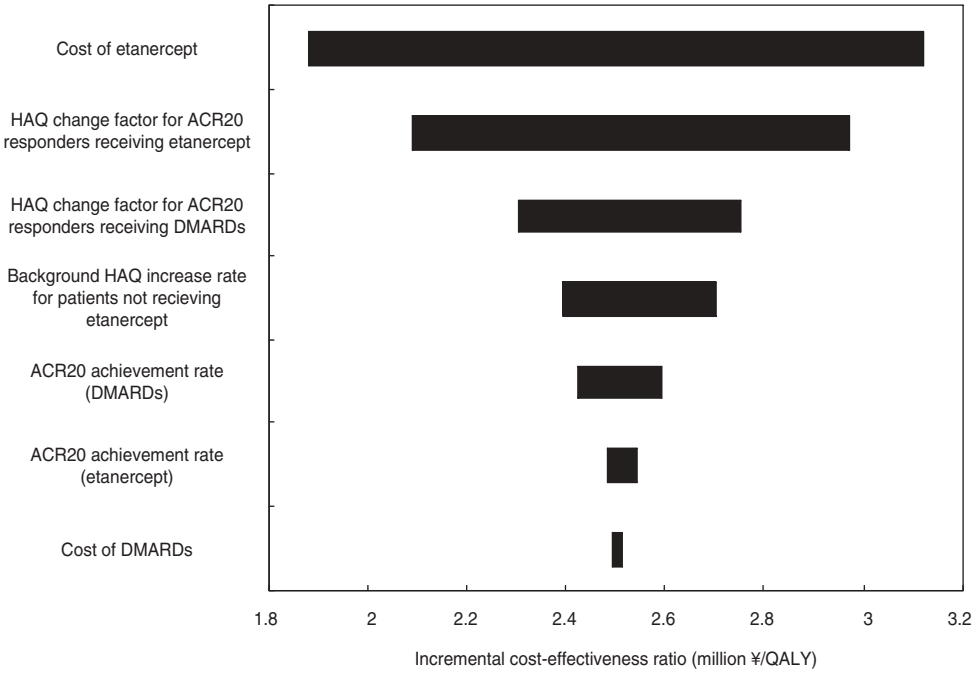

Fig. 2. Results of sensitivity analyses with model parameters varied over a range 20% above and below their values in the base-case analysis

ratio for etanercept would be ¥2.50 million per QALY. No threshold value of acceptable cost-utility has yet been established in Japan. In the U.S., $50000 (¥5.5 million) per QALY is the threshold below which medical technologies are informally but widely considered to be acceptably cost-effective.[33] Although the U.K. does not have a fixed threshold below which medical technologies are automatically judged cost-effective, NICE cautions that a technology with incremental costs greater than £30000 (¥5.7 million at £1 = ¥190) per QALY would require strong arguments to be accepted.[34] Thus, etanercept therapy in Japan can be considered acceptably cost-effective by U.S. and U.K. standards. Furthermore, in no sensitivity analysis did the incremental cost-utility of etanercept exceed these U.S. or U.K. thresholds.

In this modeling of cost-effectiveness analysis, we estimate the direct medical cost and cost of lost productivity. These kinds of cost are accumulated through the simulation. Annual drug acquisition of etanercept and MTX is the one of parameter of this model. Because the final costs of both treatment groups consist of these kind of cost, cost difference between groups are smaller than the difference of drug acquisition costs.

Using similar methodology, Brennan et al.[20] calculated that the incremental cost-effectiveness of etanercept for adult RA patients in the U.K. was £16330 (¥3.1 million) per QALY compared with DMARDs. This value is in close agreement with the base-case analysis for Japanese RA patients. Few other comparable studies have been performed. Kobelt et al.[35] calculated that cost-utility ratios for anti-TNF agents (etanercept or infliximab) among Swedish RA patients were €36900 to €53600 (approximately ¥4.8 million to ¥7.0 million at €1 = ¥130). However, these ratios were based on comparison of the first year of therapy versus baseline, not parallel-group comparison of anti-TNF therapy versus standard therapy. We study the cost-effectiveness analysis of etanercept using many parameters and modeling. In the actual clinical situation, total costs of patients with etanercept therapy increase in the high rate of inpatient, mortality and inability to work.

This study has limitations. The most serious of these is that many important model parameters, including the values for ACR20 response to DMARD therapy, the background rate of HAQ score change, and improvements in HAQ scores with therapy, were derived from clinical trials and epidemiologic studies conducted in Europe and the U.S. It is possible that racial differences may exist between Japanese and Western RA patients in disease progression and response to therapy. For example, Japanese RA patients report lower disability, higher utility scores and better general health than Western patients with similar disease duration.[36] It was not possible to adjust for potential differences in patient populations, given the paucity of data on the evaluation and response to therapy of RA patients in Japan. Not only is there little outcomes information for Japanese patients with long-term DMARD administration, but also the methods used to evaluate disability differ between Japan and the West. Whereas ACR20 is widely used to evaluate response to RA therapies in Europe and North America, ACR20 is rarely employed in Japan; instead, physicians primarily use the Lansbury index or their own judgment. Consequently, there was no option other than to use unadjusted data for non-Japanese patients. This was partially addressed by varying key model variables in sensitivity analyses. Nevertheless, improved collection of clinical and epidemiologic data for Japanese RA patients would allow more sophisticated economic analyses of etanercept in Japan.

The doses of MTX and SSZ used in the clinical trials from which HAQ score decreases were derived were higher

than the doses used in this model, which were based on clinical practice in Japan. MTX recipients in the study by Strand et al.[21] received 7.5–15.0 mg/week compared with 6 mg/week in our model, and SSZ recipients in the study by Smolen et al.[22] received a median dose of 2000 mg/day compared with 1000 mg/day in the model. These differences were not adjusted for since no equation describing a dose-response relationship was available.

This analysis did not include an option for combination therapy with etanercept plus a traditional DMARD. Clinical trials have shown that addition of etanercept to MTX yields greater improvements in function and disease activity than monotherapy.[11,37,38] To be conservative regarding possible future restrictions on prescribing etanercept in Japan, however, combination therapy with etanercept was not included in the therapeutic pathway in this study. It is possible that results may be more favorable than shown here when combination therapy is considered.

In conclusion, this study suggests that the cost utility of etanercept for Japanese patients who have failed a prior course of bucillamine is below thresholds considered to be acceptably cost-effective in the U.S. and U.K. Despite its high acquisition cost, etanercept should be considered a reasonable therapeutic option for treating RA in Japan.

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