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Economic Evaluation

Cost-Effectiveness Analysis of Etanercept 25 mg Maintenance Therapy After Treatment With Etanercept 50 mg for Moderate Rheumatoid Arthritis in the PRESERVE Trial in Japan

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ABSTRACT

Objectives: To use Markov modeling to estimate the cost-effectiveness of treatment with etanercept 25 mg once weekly plus methotrexate (MTX) in Japanese patients with rheumatoid arthritis who had achieved remission or low disease activity with etanercept 50 mg once weekly plus MTX.

Methods: Effectiveness data were estimated based on results from a clinical trial (PRESERVE) in patients with rheumatoid arthritis who had achieved remission or low disease activity and who were then randomized to receive etanercept 25 mg plus MTX or placebo plus MTX. A Markov model was established and included flare rates of 21% and 62% in the etanercept 25 mg and placebo groups, respectively. EQ-5D was calculated using an ordinary least-squares model that included the health assessment questionnaire disability index and pain visual analog scale. Worsening of the health assessment questionnaire score over 1 year was estimated to be 0.047 for patients with flare, and when associated with radiographic progression it was estimated to increase by 0.006 and 0.025 in the etanercept 25 mg and placebo groups, respectively. A cycle length of 1 year was applied to calculate the cumulative cost and effectiveness for a 10-year time span.

Results: Compared with the placebo group, the quality-adjusted life-years for the etanercept 25 mg group was increased by 0.841. The incremental cost-effectiveness ratio was ¥6 173 772.

Conclusion: These results suggest that maintenance treatment with etanercept 25 mg is cost-effective.

Keywords: cost-effectiveness analysis, etanercept, Japan, maintenance therapy, remission, rheumatoid arthritis.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by joint pain and stiffness that may progress to joint destruction and disability.[1] In addition to physical impairment and a shortened life expectancy, RA can result in substantial socioeconomic costs.[1,2] The prevalence of RA in Japan is estimated to be between 0.6% and 1.0%,[3] which is comparable with the prevalence in other parts of the world.[4] Thus, the socioeconomic impact of RA in Japan cannot be disregarded.

Targeted therapies such as biological disease-modifying antirheumatic drugs (bDMARDs) are effective in inhibiting the progression of structural damage and improving physical function in patients with RA and moderate to high disease activity.[5] Five tumor necrosis factor (TNF) inhibitors are available in Japan: etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab.[6,7] The interleukin-6 inhibitors, tocilizumab and sarilumab, as well as the cluster of differentiation (CD)-80/CD86 inhibitor, abatacept, are also available in Japan for the treatment of RA.[6,7] In the few head-to-head randomized clinical trials that have assessed the comparative effectiveness of biologics in the treatment of RA, comparable efficacy has generally been demonstrated.[8–14]

RA requires long-term treatment, and this can result in a high economic burden for patients, payers, and society.[15] In Japan, the annual drug cost of etanercept 50 mg/week is approximately ¥1.6 million.[16,17] The cost of treating RA varies widely across countries,[18] partly because of the varied use of bDMARDs, which are substantially more expensive than conventional synthetic DMARDs (csDMARDs).[15,19,20] The use of biologics for the treatment of RA has caused concern with regard to the impact of drug costs on direct medical expenses; data from 1 published study have shown, however, that the improvement in functional status and the reduction in healthcare resource use resulting from the use of biologic therapy largely offsets the increased drug costs.[21]

Once patients have achieved remission or low disease activity (LDA), physicians may decide to decrease the dose of the biologic for several reasons, including concerns about infection or adverse events, or to decrease costs.[22] According to systematic literature reviews, decreasing the dose of the biologic is an acceptable

option for certain patients.[23–26] Maintenance of remission or LDA following dose reduction of etanercept has been evaluated in several studies[27–29]; data on the cost-effectiveness of reducing the dose are, however, limited,[30] and we are not aware of such data for Japan. In Japan, etanercept is the only bDMARD approved for RA for which the higher dose (50 mg/week) is the standard dose rather than the lower dose (25 mg/week).[7] Therefore, it is of interest to analyze the cost-effectiveness of decreasing the dose of etanercept in Japan.

In this analysis, we used data from a randomized controlled clinical trial to conduct Markov modeling to estimate the cost-effectiveness of a maintenance dose of etanercept 25 mg/week plus methotrexate (MTX) in patients with RA in Japan who had achieved remission or LDA on etanercept 50 mg/week plus MTX.

Methods

Study design

A Markov model was developed to perform a cost-effectiveness analysis of etanercept 25 mg/week maintenance therapy after treatment with etanercept 50 mg/week and MTX in patients with moderate RA (see Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.06.012). Analysis cycles of 1 year and 10 years were used for the base-case analysis to evaluate long-term progression of RA. The discount rate for both cost and effectiveness was defined as 2%,[31] and the outcome measure was quality-adjusted life-years (QALYs). Analyses were performed assuming the use of public health insurance, and only direct health costs were included in the calculations.

Patients

This analysis included data from the randomized controlled clinical trial, PRESERVE.[28] PRESERVE was a global trial but it was not conducted in Japan. In PRESERVE, patients with RA and moderate disease activity who had achieved sustained LDA on etanercept 50 mg/week plus MTX in period 1 (mean disease activity score in 28 joints [DAS28] ≤3.2 from weeks 12 to 36 and DAS28 ≤3.2 at week 36) were randomized to 1 of 3 treatment arms in period 2: (1) etanercept 50 mg/week plus MTX, (2) etanercept 25 mg/week plus MTX, or (3) placebo plus MTX.[28] In this analysis, we compared the etanercept 25 mg/week plus MTX group to the placebo plus MTX group. A schematic illustration of the model is provided in Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.06.012. Patient-reported outcome (PRO) data were taken from an analysis conducted by Smolen et al[32,33] that evaluated PROs during period 2 of PRESERVE in patients with flare (DAS28 >5.1 or DAS28 >3.2 at 2 or more time points) and without flare (DAS28 ≤3.2).

Variables

Clinical parameters

The flare rates used in this analysis were taken from Smolen et al[32,33] and were 21% and 62% in the etanercept 25 mg and placebo groups, respectively ($P<.001$).

Utility parameters

Utility parameters were estimated based on the pain visual analog scale (VAS) and the health assessment questionnaire (HAQ) score from Smolen et al[32,33] and from a mapping study of the EQ-5D-3L.[34] That study investigated the mapping algorithm for the utility value of the EQ-5D-3L from the HAQ disability index (HAQ-DI), the DAS28 using C-reactive protein (DAS28-CRP), and the pain VAS value using a dataset of 2846 patients with RA in Korea.[34] Because the referenced study reported the DAS28 score based on the erythrocyte sedimentation rate rather than CRP,[32] the following ordinary least-squares model was used in the analysis:

$$\text{EQ-5D} = 0.93 - 0.22(\text{HAQ-DI}) - 0.26(\text{Pain VAS})$$

The change in HAQ scores in period 2 of the PRESERVE study was categorized based on the results of a study by Nikiphorou et al[35] that evaluated long-term progression of RA. In that study, HAQ progression was stratified according to disease activity category (eg, remission: DAS28 ≤2.6, LDA: DAS28 >2.6-3.2, low-moderate: DAS28 ≥3.2-4.19, high-moderate: DAS28 ≥4.2-5.1, and high: DAS28 >5.1).[35] The mean DAS28 at the beginning of period 2 in PRESERVE in the patients with flare was 2.3 and the change in DAS28 in these patients was 1.4[32]; thus, we calculated the mean DAS28 score at the end of period 2 to be 3.7 for patients with flare. In the study by Nikiphorou et al,[35] this value was categorized as low-moderate disease activity and the annual progression in HAQ scores for patients with this level of disease activity was 0.047. Therefore, we estimated the annual progression of the HAQ score to be 0.047 among patients with continuous flare. Table 1 shows the flare rate and quality-of-life parameters considered in this analysis.[32,33] As an example, a utility value for the patients with flare 2 years after baseline was estimated using the following calculation:

$$0.607 = 0.93 - 0.22(0.51 + 0.44 + 0.047 \times 2 \text{ years}) - 0.26(16.4 + 19.4)/100$$

Over 1 year, the worsening in the HAQ score associated with radiographic progression has been estimated to be 0.025 in patients with RA who are taking csDMARDs, including MTX, and 0.006 in patients who are taking a TNF inhibitor plus MTX.[36] We calculated the difference between these treatment regimens (0.019) and added an additional annual increase in HAQ score of 0.019 to the placebo group compared with the etanercept 25 mg group.

Cost parameters

The cost parameters considered in this analysis (Table 2) are from the National Health Insurance Medical Treatment Fees and Drug Prices, which are the latest sources of cost data for the analysis.[16,17] The frequency of outpatient visits was assumed to be once a month for the etanercept 25 mg and placebo groups. A management fee for self-injection at home was taken into account whenever etanercept was administered.

Table 1. Flare rate and quality-of-life parameters.

Parameter	Value
Flare rate[32,33]	
Placebo group*	62%
Etanercept 25 mg/week group*	21%
QoL (baseline value + amount of change)[33]	
Patients with flare, overall study population	
HAQ-DI	0.51 + 0.44
Pain VAS	16.4 + 19.4
Patients without flare, overall study population	
HAQ-DI	0.44 + 0.01
Pain VAS	11.8 + 2.8

HAQ-DI indicates health assessment questionnaire disability index; QoL, quality of life; VAS, visual analog scale.
*Both study groups also included methotrexate.

Table 2. Cost parameters

Items	Cost (¥/month)		
	Placebo group (Maintenance treatment)	Etanercept 25 mg/wk group (Maintenance treatment)	Etanercept 50 mg/wk group (Induction treatment)
A001 Outpatient visit	720	720	720
A001 Outpatient management premium	520	520	520
F400 Prescription fee (Others)	680	680	680
C101 At home self-injection guidance and management fee	0	6500	6500
D005 Blood count test	210	210	210
D026 Physician's fee for blood count test	1250	1250	1250
D007 Biochemical test (more than 10 items)	1150	1150	1150
D026 Physician's fee for biochemical test	1440	1440	1440
D015 CRP	160	160	160
D026 Physician's fee for CRP	1440	1440	1440
Drug cost	0	15 944 × 4	31 069 × 4
Total	7570	77 846	138 346

From the National Health Insurance Medical Treatment Fees and Drug Prices.[16,17]
CRP indicates C-reactive protein.

Table 3. Results of base-case cost-effectiveness analysis.

Parameter	Placebo group	Etanercept 25 mg/week group	Difference
Cost (¥)	5 278 091	10 471 283	5 193 191
QALY	5.929	6.770	0.841
ICER (¥/QALY)			6 173 772

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

For the cost of flare episodes, patients in the flare group were assumed to experience 2 flares per year (the length of period 2 in the PRESERVE study), for which they were treated with etanercept 50 mg/week for 3 months and then achieved remission or LDA again.

Data Sources and Data Management

All parameters (clinical, utility, and cost) used in the analysis were based on published data and information from government agencies. The TreeAge Pro 2019 software package (TreeAge Software Inc., Williamstown, MA) was used to develop the analysis model.

Data analysis

A cycle length of 1 year was applied to calculate the cumulative cost and effectiveness throughout a 10-year time span. Following the Japanese guidelines for cost-effectiveness analysis, the analysis was conducted from the perspective of the health-care payer.[31] QALYs were used as an effectiveness measure, and only direct medical costs incurred for treatment were considered in the analysis.[31] An annual discount rate of 2% was adopted for future costs and effectiveness to evaluate the results as current values.[31]

A 1-way sensitivity analysis was performed to evaluate the impact of each parameter on the result. The range for each parameter in the sensitivity analysis was the 95% confidence interval (95% CI); nonetheless, we used ±20% of the base-case values of the cost parameters. These were calculated using the fixed official medical fee and drug cost in Japan. In addition, a probabilistic sensitivity analysis was performed with 10 000 Monte Carlo simulations to evaluate the uncertainty of the results. Stochastic parameters and utility parameters were assumed to have a beta distribution, normal distribution of coefficient data in the mapping algorithm was assumed, and cost parameters were assumed to have a gamma distribution.

Results

Base-case Cost-effectiveness Analysis

The expected QALYs were 6.770 for etanercept 25 mg and 5.929 for placebo; an increase of 0.841 QALYs was expected for etanercept 25 mg (Table 3). Total medical costs were ¥10 471 283 for etanercept 25 mg and ¥5 278 091 for placebo. Thus, the incremental cost-effectiveness ratio (ICER) for etanercept 25 mg was ¥6 173 772.

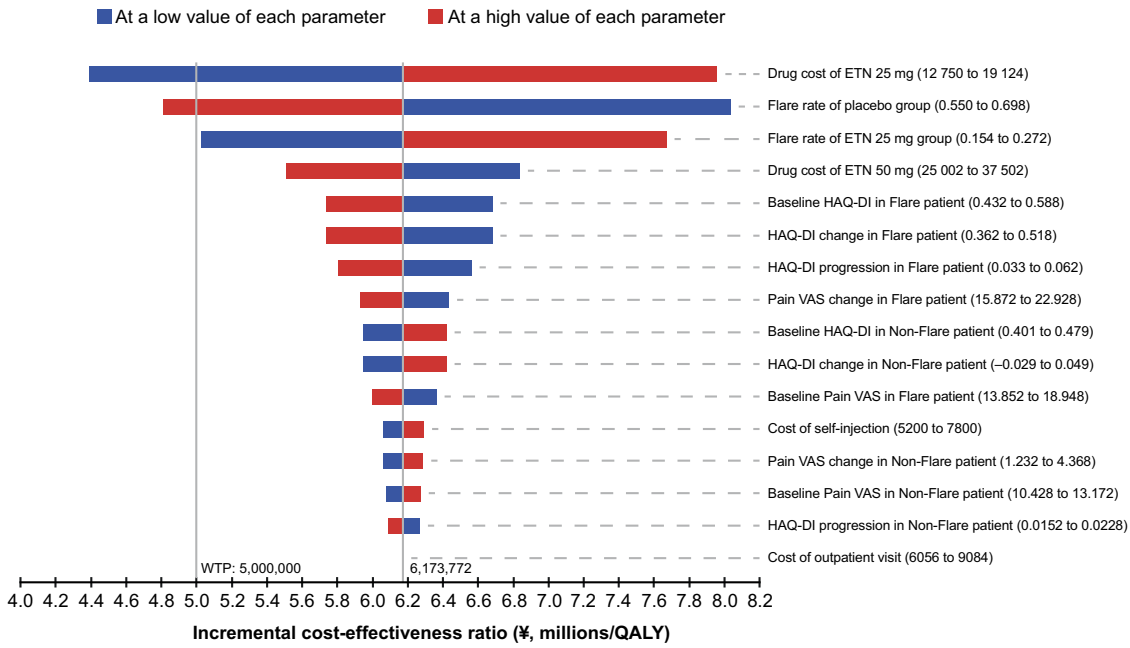
Sensitivity Analysis

Figure 1 shows the results of the 1-way sensitivity analysis, and Figures 2 and 3 show the results of the probabilistic sensitivity analysis. The variables that primarily influenced the analysis are the flare rates in the 1-way sensitivity analysis. Assuming an ICER threshold of ¥10 million, the probability that the ICER was below the threshold was 97.8% for etanercept 25 mg (the probabilities of cost-effectiveness were 19.8%, 80.0%, and 99.9% with thresholds of ¥5 million, ¥7.5 million, and ¥15 million, respectively).

Discussion

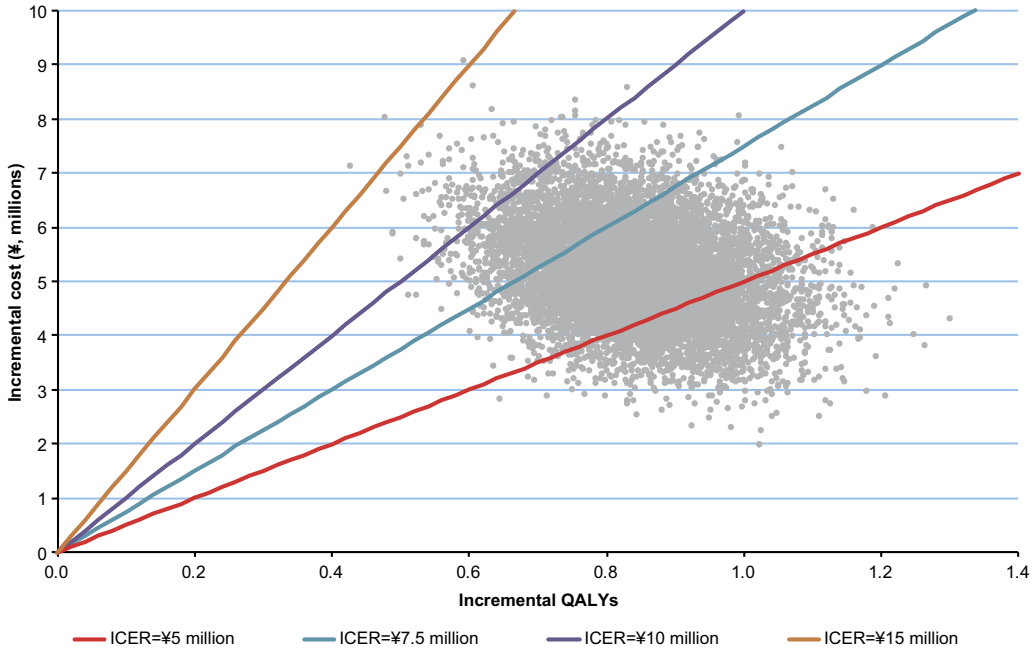
In general, a treatment is considered to be cost-effective if the ICER is lower than the prespecified threshold for the analysis[37]; however, no clear threshold for ICER has been defined in Japan. In other countries, there are fixed criteria for cost-effectiveness, eg,

Figure 1. Results of 1-way sensitivity analysis. The base-case value is shown as the central vertical line. The red bar represents the result when the parameter was changed to a high value (ie, the parameter changed to +20%), and the blue bar represents the result when it was changed to a low value (−20%).



ETN indicates etanercept; HAQ-DI, health assessment questionnaire disability index; QALY, quality-adjusted life-year; VAS, visual analog scale; WTP, willingness-to-pay.

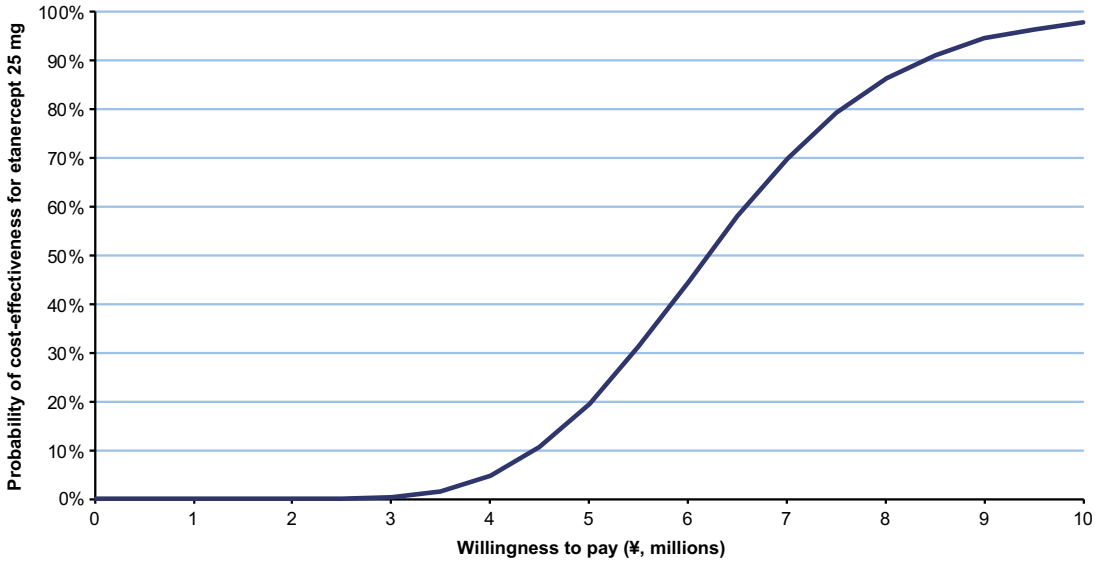
Figure 2. Scatter plot of probabilistic sensitivity analysis. The lines indicate the reference value of ICER. The probability of being cost-effective (eg, ICER <¥5 million) can be evaluated by counting the number of plots that are located below the reference line.



ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

the National Institute for Health and Care Excellence lists the threshold for ICER in the range of £20 000/QALY to £30 000/QALY (from ¥3 000 000/QALY to ¥4 500 000/QALY at the exchange rate of ¥150 to £1[38]) in its guideline for cost-effectiveness analyses.[39] Laupacis et al[40] list the threshold as $20 000/QALY to $100 000/QALY (from ¥2 200 000 to ¥11 000 000 at the exchange rate of ¥110 to $1).[38] If the upper limit of these reference values is used, then the ICER of ¥6 173 772 is considered cost-effective.

Figure 3. Cost-effectiveness acceptability curve. The curved line shows the relationship between the probability of being cost-effective and the willingness to pay per 1 QALY gained.



QALY indicates quality-adjusted life-year.

Additionally, the World Health Organization has stated that one method of determining a cost-effectiveness threshold is to base it on a country's per capita gross domestic product (GDP).[41] Specifically, a treatment that costs less than 3 times the GDP is considered cost-effective.[41] The per capita GDP in Japan is ¥4 321 000[42]; if the per capita GDP is tripled to ¥12 963 000, then the ICER of ¥6 173 772 is considered cost-effective.

Surveys conducted in Japan found the willingness to pay (WTP) for 1 QALY to be approximately ¥6 700 000 and ¥5 000 000, as reported by Ohkusa et al[43] and Shiroiwa et al[44], respectively. Tanno et al[45] conducted Markov modeling to calculate the ICER of etanercept 25 mg compared with csDMARDs in Japanese patients with RA in which treatment with bucillamine failed. They calculated the ICER to be ¥2 500 000/QALY.[45] Importantly, our analysis evaluated the cost-effectiveness of etanercept 25 mg in patients who had already achieved treat-to-target. We are not aware of any other studies that have conducted such an analysis in Japan. Interestingly, the ICER that we calculated falls between the WTP survey results from Ohkusa et al and Shiroiwa et al.[43,44]

Although the PRESERVE study was not conducted in Japan, we have applied the results to Japanese health economics. Our approach took into consideration that there are only minor discrepancies in the prevalence and severity of RA (particularly among patients receiving bDMARDs) between the European/US and Japanese populations.[3,46]

Markov modeling was also conducted by Kobelt to evaluate the cost-effectiveness of etanercept 25 mg/week in Sweden, using data from the PRESERVE trial and from a registry in Sweden to extrapolate the results to 10 years.[30] Unlike the current analysis, that study compared the cost-effectiveness of continuing etanercept 50 mg/week, decreasing the dose to 25 mg/week, or discontinuing etanercept. The analysis found that the 25 mg/week dose of etanercept was advantageous over the 50 mg/week dose, based on the cost/QALY gained. The model predicted a higher cost/QALY over time due to increases in the cost of etanercept; nonetheless, the 25 mg/week dose was still the preferred option. Another Markov modeling study was performed by Verhoef et al[42] in The Netherlands to evaluate the cost-effectiveness of tapering TNF inhibitors. The authors used data from the Dose Reduction Strategy of Subcutaneous TNF inhibitors clinical trial[47] and the Spacing of TNF-blocker injections in Rheumatoid Arthritis Study,[48] as well as the Nijmegen RA cohort[49] to model several dose-tapering regimens for etanercept and adalimumab over 18 months. The authors found that a 4- or 5-step tapering strategy was more cost-effective than continuing treatment at the full dose; nonetheless, patients did experience more short-lived flares.[42]

This analysis has several limitations. First, we made the assumption that the patients who flared were treated with etanercept 50 mg/week plus MTX. Because this information was not provided,[32] long-term prognoses were estimated using information from the literature.[35,36] It has been reported that although intermittent treatment of flares has clinical efficacy,[50] fluctuation of disease activity is associated with radiographic progression.[50,51] In clinical practice, the frequency of medical visits in patients with flare may be higher than in patients without flare, and we did not account for this difference. In addition, it is possible that the results for the MTX plus placebo group may be an overestimation of the effectiveness of MTX alone, due to the placebo effect.

Another limitation is that the costs of medical visits should be included and should be based on real-world data. Radner et al[52] reported that in patients with RA, indirect costs increase with an increase in the HAQ score. The authors assigned indirect costs to 3 categories of HAQ scores, and the lowest score catergory was HAQ $\leq$1.2.[52] Because the mean HAQ scores in our study only ranged from 0.4 to 0.5 for all patients,[33] the data from Radner et al[52] were not meaningful in our analysis. Lastly, a new, more up to date WTP analysis may be required to determine the threshold that is currently appropriate.

Conclusion

Maintenance therapy with etanercept 25 mg/week plus MTX appears to be cost-effective if the upper limit of the reference value is $100 000 or if the World Health Organization's standard cost-effective value of triple the per capita GDP is applied as the threshold.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2021.06.012

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Data Availability: Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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