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Cost-effectiveness analysis of ixekizumab versus etanercept and their manufacturer recommended dosing regimens in moderate to severe plaque psoriasis

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Abstract

Introduction—Biologic therapies have revolutionized the treatment of psoriasis; however, their use is limited by costs. Ixekizumab was more effective than etanercept in the UNCOVER trials, and the Food and Drug Administration (FDA) approved ixekizumab for treating psoriasis. Evaluating the cost-effectiveness of these therapies is crucial for medical decision making and our objective was to determine the cost-effectiveness of various ixekizumab dosing frequencies compared with etanercept.

Methods—We utilized published data from the UNCOVER comparative efficacy trials, including transitional probabilities and treatment response rates, to create a Markov model simulating the clinical course and cost-effectiveness of three treatment algorithms for patients with moderate to severe plaque psoriasis over 60-weeks: (1) ixekizumab every 2 weeks for 12 weeks then every 4 weeks, (2) ixekizumab every 4 weeks throughout the treatment period, (3) biweekly etanercept for 12 weeks then once weekly. We utilized a standard willingness-to-pay (WTP) threshold of $150,000 per quality adjusted life year (QALY) and Medicaid drug acquisition costs for our calculations.

Results—Ixekizumab every 4 weeks was $28,681 (USD) less expensive than biweekly etanercept, and $21,375 less expensive, and 0.006 QALY less effective, than ixekizumab every 2 weeks-- a savings of $28.7 and $21.4 million respectively per 1,000 patients. A 95.6% cost reduction to $197.83 per dose is required for ixekizumab every 2 weeks to be more cost-effective than every 4 weeks. Biweekly etanercept requires a 29.5% cost reduction ($743.82 per dose) to be competitive with ixekizumab every 4 weeks.

Discussion—This cost-effectiveness model utilizes strong input data but is a limited approximation of real-life scenarios. Treatment with ixekizumab every 2 weeks is unlikely to be cost-effective compared with ixekizumab every 4 weeks at current U.S. market prices. Yet, the U.S. FDA approval and manufacturer's recommendation are for ixekizumab every 2 weeks. Accordingly, we suggested selecting biologic therapies using cost-effectiveness analyses.

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Keywords

biologics; cost-effectiveness; etanercept; ixekizumab; psoriasis

Introduction

The landscape of psoriasis therapies underwent a dramatic transformation with the introduction of efficacious biologic therapies. Many of these, such as etanercept (Enbrel®), a tumor necrosis factor-alpha blocker, are widely used for other diseases and adapted for use in psoriasis, while others, such as ixekizumab (Taltz®), an interleukin-17 antagonist, were recently introduced for plaque psoriasis. Although these treatments are extremely effective, they carry a large price tag. One dose of etanercept costs $1055.80 and ixekizumab is $4513.69 per dose.[1] These are truly remarkable treatments and have the ability to change the lives of their users. In addition to the efficaciousness of these therapies, they are usually safe, well-tolerated, and not accompanied by the organ specific side effects of other systemic treatments.[2]

Psoriasis is one of the most common inflammatory skin diseases and affects approximately 2% of the U.S. population.[3] The physical symptoms and discomfort, mental-health impact, comorbidities, and effect on social relationships of psoriasis have significant negative effects on patients leading to an overall diminished quality of life.[4–7] In addition, psoriasis exerts a large economic burden on both society and the patient, and the utilization of cost-effective therapies that decrease disease severity are of the utmost importance.[8–11]

The recent UNCOVER-1, 2, and 3 trials compared ixekizumab to etanercept and placebo in the treatment of moderate to severe plaque psoriasis.[12,13] Ixekizumab was found to be superior to etanercept and 48.1% more patients being treated with ixekizumab achieved a Psoriasis Area Severity Index (PASI) reduction of more than 75% (indicative of *treatment responders*) over 12-weeks of treatment in the UNCOVER-2 trial.[13]

An additional benefit of biologic therapies over conventional treatments is their infrequent administration. The United States Food and Drug Administration (FDA) approved a 12-week induction period with biweekly etanercept or ixekizumab every two weeks, followed by weekly etanercept or ixekizumab every four weeks respectively.[14,15] Ixekizumab requires only one quarter the number of etanercept injections. Both of these treatments may be administered from home through the use of an auto-injecting syringe. Given the similarities in delivery method, the clinical question of which therapy to use partially relies on their cost-effectiveness.

To address this, we created a Markov cost-effectiveness model that demonstrates the differences in costs and effectiveness between etanercept and ixekizumab using the UNCOVER trials' data. It is our hope that these results will aid in the creation of much needed health-policy and clinical practice guidelines for biologic agents as a whole, and ixekizumab therapy in particular. The decision of which therapy to use is imminent and we propose that both cost and effectiveness be considered.

Methods

We conducted the cost effectiveness analysis according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement produced by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[16]

Model construction

We constructed a Markov model to calculate the cost-effectiveness of etanercept and ixekizumab treatments from a limited societal perspective [Fig. 1]. The objective was to elucidate the appropriate medication and dosing regimen to be prescribed for patients. Accordingly, we included costs for medications, annual healthcare utilization, laboratory tests, and physical exams.[17] Medicaid drug acquisition costs were utilized. Etanercept was $1055.80 per dose and ixekizumab was $4513.69 per dose.[1] Costs in 2016 U.S. dollars were compared using the effectiveness of treatments as measured by the quality adjusted life years (QALY) gained. Five health states and their associated health utilities were considered: PASI change of <75%, 75 to <90%, 90 to <100%, and 100% [Tables 1 and 2]. Health utility scores from the UNCOVER trials were available for these health states adding superiority to this analysis.[18]

A Markov model considers different transitional probabilities based upon the current state. This type of model was chosen to allow us to include an induction and maintenance phase with different transitional probabilities. In addition, healthcare providers have the ability to adjust treatment regimens at relatively frequent intervals and the Markov model approximates this behavior.

The UNCOVER-2 and 3 trials included 2,570 patients and compared ixekizumab with various dosing patterns to etanercept as well as a placebo group (n = 361). This design allowed us to directly compare the cost-effective of ixekizumab to etanercept without involving other studies. The trials evaluated an ixekizumab loading dose of 160mg followed by 80mg dosed at two (n = 736) and four week (n = 733) intervals versus biweekly 50mg etanercept (n = 740). These patterns are in concordance with the FDA licensed doses and we chose these comparisons for our model.[14,15] In our model, we instituted that patients not responding to the initial ixekizumab or etanercept treatment should not graduate to the less frequent dosing pattern [Fig. 1].

The end-point was the calculation of the incremental cost effectiveness ratios (ICER) of 12-week courses of bi-weekly etanercept, ixekizumab every 2 weeks and ixekizumab every 4 weeks over a 60-week time horizon (5 Markov cycles). This 60-week time period was chosen to emulate the use of ixekizumab in the UNCOVER trials.[12,13] Subjects entering the ixekizumab every 2-weeks subtree that displayed a PASI 75 or greater response, graduated to ixekizumab every 4-weeks subtree. Similarly, subjects with a PASI 75 or greater response to biweekly etanercept began weekly dosing. Subjects in the ixekizumab every 4-weeks subtree continued this regimen throughout the time horizon—although the transitional probabilities varied from the induction to maintenance phases [Table 2].

To ensure that the model used the same criteria as the data set being examined, the theoretical patient cohort entering the model included adults with moderate to severe plaque psoriasis with 10% or greater body surface area involvement as characterized by the UNCOVER trials.[12,13] These patients had not undergone previous treatment with ixekizumab or etanercept.

Software and troubleshooting

TreeAge Pro 2016 was used to create the model, graphs, and to perform the Monte Carlo simulations, model calibration, sensitivity analysis and ICER calculations. In addition, we performed various sensitivity analysis and applied modular verification techniques to assist in validating and building our model. RStudio version 0.99.903 with the *BCEA* package was used for manual verification of the model.

Model assumptions and limitations

The discontinuation rates within the UNCOVER trials varied: UNCOVER-2 had 7% discontinue etanercept and 3% discontinue ixekizumab, while UNCOVER-3 had 7% discontinue ixekizumab and 3% discontinue etanercept. Accordingly, we chose to forgo including these discontinuation rates in the model as they are very similar overall and the second-line therapy would likely be another biologic therapy. We assumed the second line therapies to be etanercept for those that failed ixekizumab, and ixekizumab for those that failed etanercept; however, this may not be the case in all clinical practice settings.

Increased utilization of over-the-counter therapies to treat the adverse effects of the biologic treatments, as seen in a previous analysis,[17] were not found to significantly affect our model (given the magnitude of our results) and were excluded. Although various studies have reported an increased incidence in Candida infections with ixekizumab, the overall frequency of Candida infection did not differ significantly between the ixekizumab and placebo groups in the UNCOVER trials and we did not include this in the model.[19,20]

There appears to be a slight increase in inflammatory bowel disease flares in patients being treated with ixekizumab.[21] However, this adverse event was not considered in our analysis due to its scarcity (0.3%) in the ixekizumab treatment arms.[12] Additionally, IBD was considered a serious adverse event, yet the overall incidence of serious adverse events were equal across the ixekizumab every 2 and 4 weeks, placebo, and etanercept treatment arms (1.9%).[13]

We used a single study to obtain the model's transitional probabilities. From a statistical perspective, using the results of a single randomized control trial instead of combining multiple trials vastly decreases the effects of confounding variables as the randomized subjects are similar in baseline characteristics and study methodology.[22] It is easily conceivable that modifying the ratio of patients responding to the various treatments will significantly alter the results of this analysis. According, we chose to forgo uncertainty distributions in the transitional probabilities.

The transitional probabilities for etanercept were extrapolated from the 12-week induction period in the UNCOVER-2 and 3 trials.[13] This method was employed in a previous cost-

effectiveness analysis of etanercept[17] and the extrapolated transitional probabilities from 12-weeks to 60-weeks are similar to and consistent with other long-term etanercept trials.[23,24]

After the initial 12 week induction period, the subjects included in the UNCOVER-1 and 2 trials were randomly assigned to withdrawal therapies that included ixekizumab dosed every 4 to 12 weeks as well as a placebo group. This resulted in varied treatment groups and smaller sample sizes than the UNCOVER-3 trial. Accordingly, maintenance PASI response data for ixekizumab every 2 weeks (n = 385) and every 4 weeks (n = 386) groups were taken from the UNCOVER-3 trial. The 12-week interval responses during the maintenance period were equal to the response values at 60 weeks. We used a standard annual discount of 3.0% for both costs and QALYs per previous analysis.[17,25] Mortality was omitted from the model due to insufficient data associated with these treatments.

The addition of patient-centered indirect costs to our model would have strengthened the difference between ixekizumab and etanercept therapy. One such example is the annual reduction in work productivity loss while on ixekizumab ($8,265) compared with etanercept ($2,739) that dramatically increased the cost-effectiveness of ixekizumab.[10] These data were not included in our analysis as they were not specific towards ixekizumab dosed every 4 weeks or every 2 weeks and may have artificially increased the difference between etanercept and ixekizumab every 4 weeks while decreasing the difference between the two ixekizumab groups. Thus, our model was created using a limited societal perspective.

Variables

We selected variables for use in the model from previous analyses and the UNCOVER trials [Table 2]. PASI response variables were taken from the pooled UNCOVER-2 and UNCOVER-3 data for the first 12-weeks of therapy, and from the UNCOVER-3 trial for the maintenance phase.[13]

All costs were converted into adjusted 2016 U.S. dollars using the United States bureau of labor statistics consumer price index calculator.[26]

We converted the PASI percent improvement into health utility scores using EuroQol 5-Dimension Health Questionnaire (EQ-5D) health utility scores produced from the UNCOVER trial's data.[18]

Most of the data sources included uncertainty distributions for the variables; however, a conservative triangular distribution, with 10% variation, was applied to variables without this information.

The *healthcare costs* variable includes the annual mean healthcare costs that a patient with moderate to severe psoriasis is expected to incur in the emergency, in-patient, and outpatient settings.[8] However, it excludes the costs associated with ixekizumab or etanercept therapy.

A standard willingness-to-pay (WTP) threshold of $150,000 per QALY was chosen for these analyses.[27,28]

Results

The results of a 10,000 sample Monte Carlo probabilistic sensitivity analysis showed ixekizumab every 4 weeks to be more cost-effective than either ixekizumab every 2 weeks or biweekly etanercept. Despite the uncertainty distributions applied to the variables, the model demonstrated ixekizumab every 4 weeks to be the most cost effective intervention over 100% of iterations across all WTP thresholds up to and beyond $500,000 per QALY.

This simulation demonstrated ixekizumab every 4 weeks to have a mean cost of $79,734.18 and effectiveness of 0.857 QALY over the 60-week time horizon [Table 3]. Ixekizumab every 2 weeks had a mean cost of $101,108.87 with an incremental effectiveness of 0.006 and an ICER of $3,422,386.62 when compared to ixekizumab every 4 weeks. The mean cost difference between ixekizumab every 4 weeks and every 2 weeks was of $21,374.69. The savings would be $21,374,690 if this cost difference is applied to 1000 patients over a 60-week time horizon.

The bi-weekly etanercept cost was $108,415.63 with a mean effectiveness of 0.825 QALY and an ICER of -$913,870.47 when compared to ixekizumab every 4 weeks. The negative ICER in this instance is indicative of etanercept therapy being vastly more expensive and less effective than ixekizumab every 4 weeks (*dominated*).

The observed results were robust through a wide variety of sensitivity analyses. A tornado univariate analysis and plot of ixekizumab every 4 weeks versus biweekly etanercept demonstrates that the two most sensitive variables are the costs per dose of ixekizumab and etanercept [Fig. 2]. Yet, despite a 25% change in these variables, etanercept remained more costly and less effective. The upper and lower limits for the other variables included twice their standard deviation.

Using a threshold analysis, we determined that given the published cost of $1055.80 per dose of etanercept, ixekizumab every 4 weeks would remain the cost-effective therapy despite a 41.9% increase in cost ($6,406.69 per dose) at the WTP threshold of $150,000 per QALY.[27] Ixekizumab every 2 weeks was more cost-effective than every 4 weeks at a cost-per-dose of $197.83 (95.6% reduction). In contrast, etanercept would need to cost 29.5% less ($743.82 per dose) to be competitive with ixekizumab every 4 weeks at the $150,000 WTP threshold.

Discussion

The UNCOVER trials were the most comprehensive evaluation of ixekizumab to date and displayed high efficacy rates. However, despite the recent popularity of this medication, to our knowledge, this is the first evaluation of the data from the UNCOVER comparative effectiveness trials using cost-effectiveness modeling.

The FDA does not require new therapies to be evaluated against a standard of care therapy to be approved for medical use—they must only be superior to vehicle. Nonetheless, the UNCOVER trials compared various ixekizumab dose intervals with etanercept, which is a well-established psoriasis therapy. This design is uncommon and should be commended. It

allowed us to directly compare these interventions against each other without the need to include weaker comparisons. Health utility scores from the UNCOVER trials were also directly available, further strengthening the model.

Our model's primary purpose is to aid in future health policy decisions and we utilized a limited societal perspective. Although cost-effectiveness models cannot exactly approximate real life scenarios, the drastic results that we produced should be thoughtfully considered. Induction with ixekizumab every 2 weeks was more costly with little effectiveness gained compared to ixekizumab every 4 weeks, and both ixekizumab regimens were superior to etanercept in both costs and effectiveness.

The manufacturer's FDA approved dosing regimen usually dictates the standard-of-care and providers are wary of deviating from this when using a new treatment. This recommendation may be in the manufacturer's best interests as it is usually the most effective therapy, but is not necessarily the most cost-effective utilization, nor the most convenient for our patients—as this analysis shows. While it seems logical for the FDA to approve the most effective medication regimen, should they have a responsibility of choosing the most cost-effective and practical approach, or does this responsibility lie in the creation of therapeutic guidelines?

Acknowledgments

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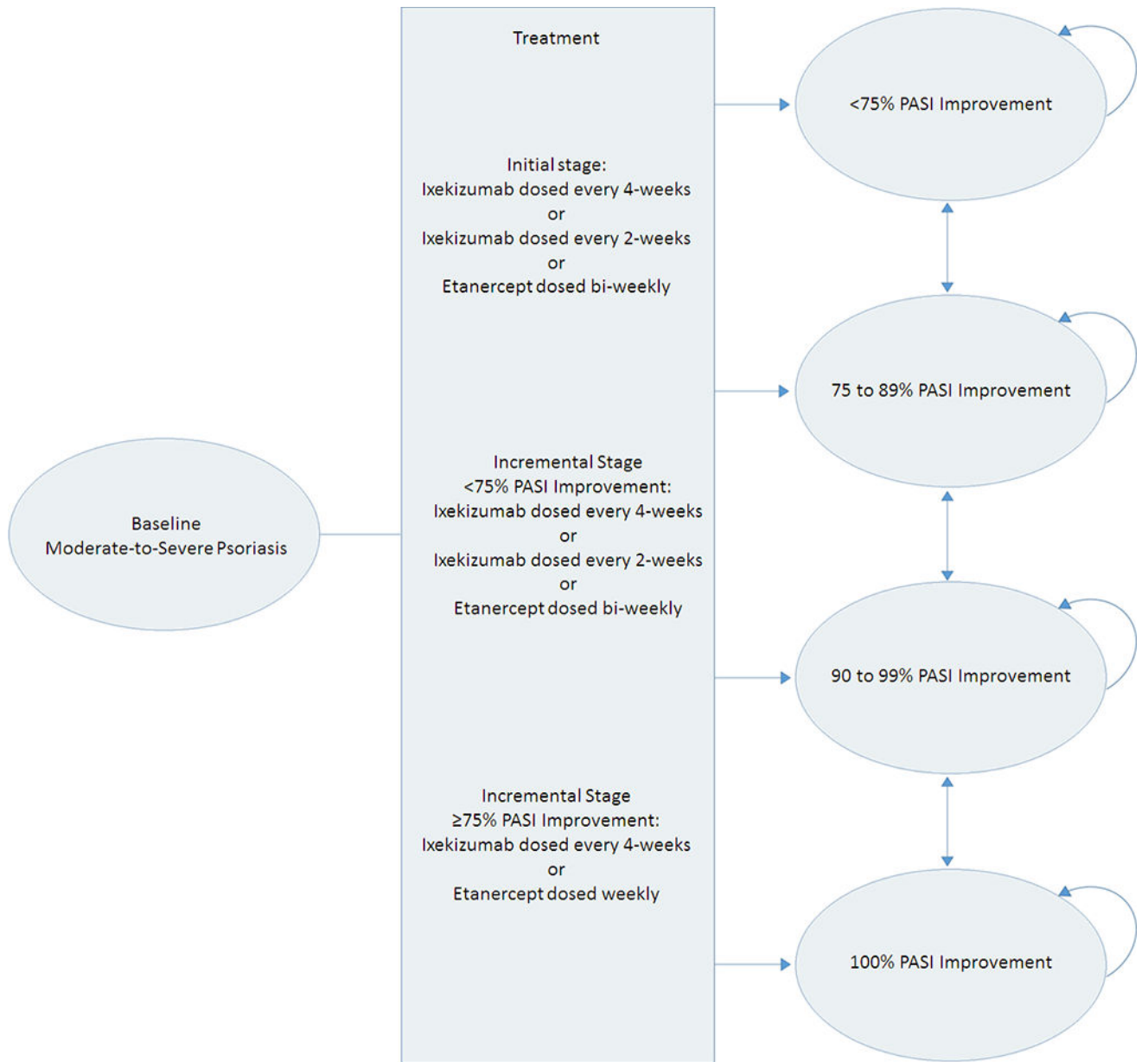
Figure 1.

Markov model design. Patients occupy health states (ovals) and transition between states via the various treatments (arrows) and their transitional probabilities.
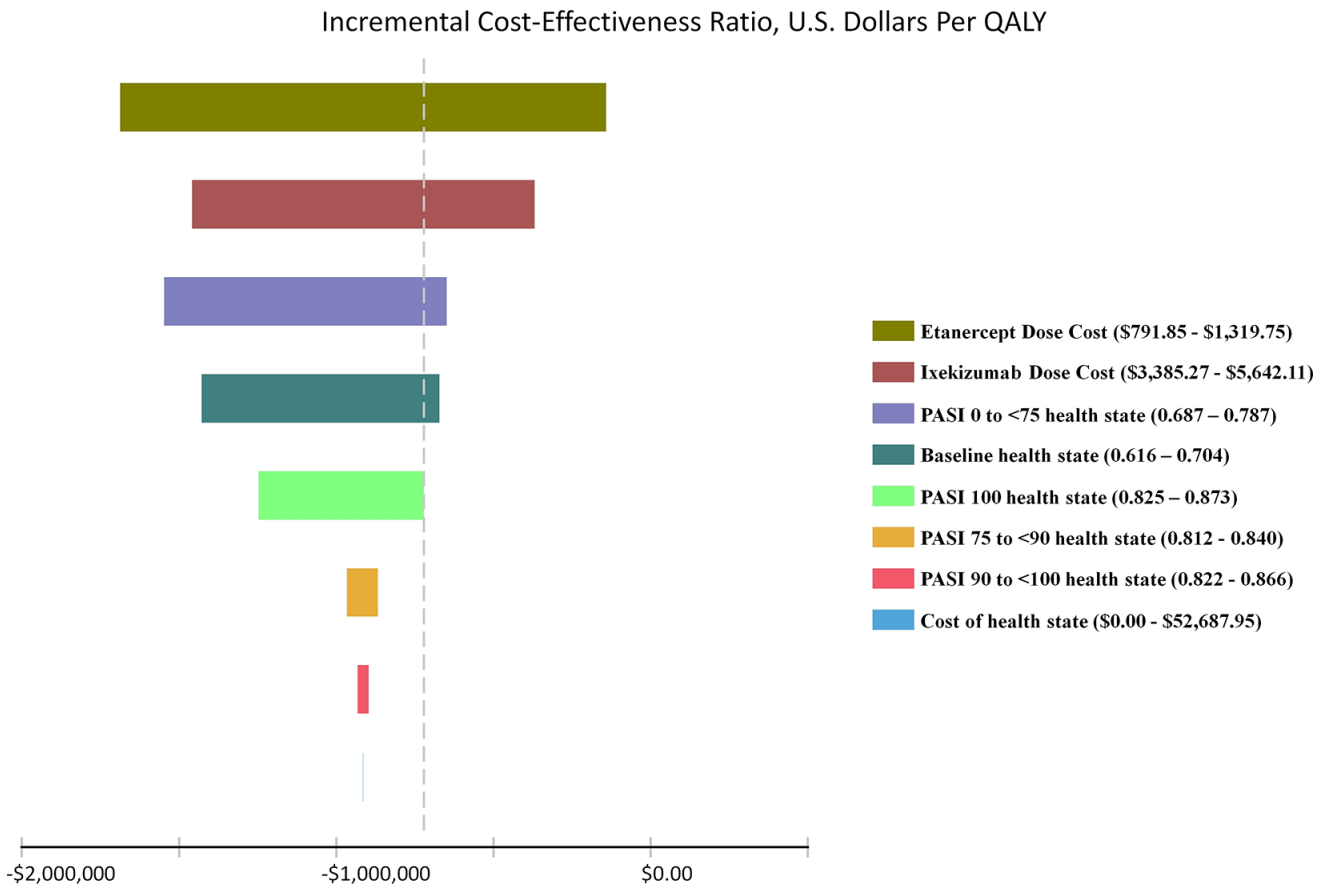
Incremental Cost-Effectiveness Ratio, U.S. Dollars Per QALY

Figure 2.
Tornado diagram displaying the results of multiple univariate sensitivity analyses comparing the effect of each variable's uncertainty on the incremental cost-effectiveness ratio. The width of the bars corresponds to the model's sensitivity to changes in the variable of interest. The central dashed line represents the base-case analysis. The etanercept treatment regimen remained inferior to ixekizumab every 4 weeks at a willingness-to-pay threshold of $150,000 per quality adjusted life year across this range of sensitivity analyses.

The figure legend includes the color-coded variable names and their respective uncertainty distribution upper and lower limits.

The *annual physical exam, quarterly liver function tests, quarterly complete blood count*, and *annual purified protein derivative test* variables had no significant effect on this analysis and were excluded to simplify the graphic.

Table 1

Variables utilized within the model and their uncertainty distributions tested in the probabilistic sensitivity analysis.

Variable	Base Case	Standard Error or Range	Distribution	Reference
Cost inputs				
Healthcare costs for moderate to severe psoriasis	$10,320.67	21,183.64	Gamma	[8]
Ixekizumab 80mg	$4,513.69	4062.32, 4965.06	Triangular[a]	[1]
Etanercept 50mg	$1,055.80	950.22, 1161.38	Triangular	[1]
Annual physical exam	$109.16	98.24, 120.08	Triangular	[29]
Quarterly liver function tests	$15.94	14.35, 17.53	Triangular	[29]
Quarterly complete blood count	$15.16	13.64, 16.68	Triangular	[29]
Annual purified protein derivative test	$10.35	9.32, 11.39	Triangular	[29]
Health utilities				
Health utility for PASI response of 100%	0.849	0.012	Beta	[18]
Health utility for PASI response of 90–<100%	0.844	0.011	Beta	[18]
Health utility for PASI response of 75–<90%	0.826	0.0071	Beta	[18]
Health utility for PASI response of <75%	0.737	0.025	Beta	[18]
Baseline health utility	0.660	0.22	Beta	[18]

[a]A conservative triangular distribution was applied to variables without distribution data.

Table 2

Probabilities, by treatment group, for transitions between health states.

Treatment Group	PASI percent response				Reference
	<75%	75 to <90%	90 to <100%	100%	
Etanercept 50mg - Initial 12 weeks and incremental 12 weeks	0.523	0.254	0.159	0.064	UNCOVER-2 and 3 pooled[12]
Ixekizumab 80mg every 2 weeks - Initial 12 weeks	0.115	0.192	0.303	0.390	UNCOVER-2 and 3 pooled[12]
Ixekizumab 80mg every 2 weeks - Incremental 12 weeks	0.170	0.100	0.180	0.550	UNCOVER-3[13]
Ixekizumab 80mg every 4 weeks - Initial 12 weeks	0.190	0.184	0.296	0.330	UNCOVER-2 and 3 pooled[12]
Ixekizumab 80mg every 4 weeks - Incremental 12 weeks	0.200	0.090	0.190	0.520	UNCOVER-3[13]

Table 3

Mean cost, mean cost difference, effectiveness in quality adjusted life years (QALY), and incremental cost effectiveness ratios (ICER) of the three treatment groups over a 60-week time horizon.

Treatment Group	Mean cost and 95% CI[a]	Mean cost difference (incremental cost)	Effectiveness and 95% CI	ICER
Ixekizumab every 4 weeks with maintenance every 4 weeks[b]	$79,734.18 (68682.90, 145290.75)	Reference group	0.857 (0.747, 0.929)	Reference group
Ixekizumab every 2 weeks with maintenance every 4 weeks	$101,108.87 (90057.60, 166665.45)	$21,374.69	0.863 (0.754, 0.936)	$3,422,386.62
Etanercept biweekly with maintenance once weekly	$108,415.63 (97364.31, 173972.01)	$28,681.45	0.825 (0.716, 0.898)	−$913,870.47[c]

[a]Confidence interval

[b]Most cost-effective therapy and reference group

[c]Negative ICER is indicative of etanercept being vastly less effective and more costly than ixekizumab every 4 weeks.