CASE STUDY

The Challenge of Variable Costs in Decisions Based on Cost-Effectiveness Evidence: A Case Study for Brodalumab

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BACKGROUND: Payers often consider cost-effectiveness studies for new drugs when making decisions on coverage, formulary position, and budgets; however, cost-effectiveness studies are often calculated using estimated pricing before a drug's launch. If the drug's price changes on or after launch, or if rebate programs are initiated, cost-effectiveness studies need to be updated to prevent payers from making decisions using inaccurate value assumptions, which can lead to unexpected financial impacts and potentially delay patient access to drugs.

OBJECTIVE: To evaluate how lower at-launch drug pricing versus initial estimated pricing affects cost-effectiveness ratios and potentially influences treatment decisions, using the case study of brodalumab, a biologic drug indicated for the treatment of moderate-to-severe plaque psoriasis.

METHODS: We compared the estimated cost-effectiveness of brodalumab, which was published in a December 2016 Institute for Clinical and Economic Review (ICER) report based on estimated pricing, with the drug's cost-effectiveness based on its actual pricing after its approval.

DISCUSSION: The 2016 ICER report on the cost-effectiveness of targeted immunomodulators indicated for the treatment of moderate-to-severe plaque psoriasis, brodalumab's price was estimated to be $4267 by averaging the cost of its likely competitors. Brodalumab's effectiveness as a treatment for moderate-to-severe plaque psoriasis is high in clinical trials, but its estimated cost placed it as the fourth most cost-effective targeted immunomodulatory drug in the ICER report. On its approval in February 2017, brodalumab's newly estimated base price was $3900, based on its prelaunch price. Calculations using this base price placed brodalumab as the most cost-effective option among targeted immunomodulators in this setting. At the time this current article was written, brodalumab's cost was $3500, making it even more cost-effective.

CONCLUSION: Because payers, providers, and patients are all concerned with achieving better outcomes for the often painful and disfiguring disease of plaque psoriasis, while controlling costs, updating cost-effectiveness data when new pricing information becomes available may reveal significant cost differences to help stakeholders make better decisions about their population's healthcare outcomes and costs.

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KEY WORDS: brodalumab, cost-effectiveness, drug pricing, immunomodulators, plaque psoriasis, treatment decision-making

Cost-effectiveness studies of pharmaceutical agents that will soon be released to the market are an important tool that payers and health plans can use when making decisions on coverage, formulary positioning, and budgets. For payers, providers, and patients alike, price is a critical piece of the decision, with all parties seeking the best outcomes for the lowest costs; however, cost-effectiveness studies are often based on a drug's prelaunch estimated cost. When the drug's price changes at launch or postlaunch, some pharmacy benefit managers (PBMs) and health plans update their own budget impact and cost-effectiveness models.

Other PBMs and health plans that rely on outside sources may continue to use cost-effectiveness studies

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KEY POINTS

- Cost-effectiveness studies of new drugs are vital for payers and health plans when making coverage, formulary positioning, and budget decisions.
- This case study of brodalumab compares the at-launch pricing and the actual initial cost at approval to evaluate potential impact on clinical decisions.
- Based on the at-approval cost estimates, brodalumab was assessed as the fourth most cost-effective targeted immunomodulatory drug for moderate-to-severe plaque psoriasis.
- However, based on its actual cost at launch, brodalumab became the most cost-effective drug in this setting.
- Using the newest data to make decisions can result in accurate value assumptions and the avoidance of negative financial impact and delayed access to drugs for patients.
- As decision makers incorporate value into formulary and benefit designs, the impact of clinical and economic inputs on the outputs of cost-effectiveness models should be considered.

that have not been updated, which means that many payers are implementing decisions based on estimates that are no longer accurate. Therefore, it is important to reevaluate a drug's cost-effectiveness when updated pricing data become available. This article uses the example of brodalumab, a biologic drug indicated for the treatment of plaque psoriasis, to show how updated pricing can affect cost-effectiveness considerations.

Disease Description and Treatment Options

Plaque psoriasis is a chronic, inflammatory, autoimmune-related skin disease that results in red, scaly plaques caused by an abnormally high rate of skin-cell turnover.[1,2] Plaque psoriasis is estimated to affect approximately 2% of the population worldwide and approximately 4.5 million adults in the United States.[1,2]

Approximately 20% of patients with plaque psoriasis have moderate-to-severe disease.[3] Because the disease is chronic and often painful and disfiguring, it has a significant negative impact on patients' quality of life and has a disability burden that is similar to other major chronic diseases.[4] Plaque psoriasis is increasingly associated with comorbidities, such as cardiovascular disease and diabetes, as well as psychiatric disorders, such as depression and anxiety.[3,5-7]

Several options are available for the treatment of patients with moderate-to-severe psoriasis. Traditionally, patients with moderate-to-severe disease have received nonbiologic systemic therapies, such as methotrexate or cyclosporine A; immunosuppressant agents; or acitretin.[8] However, immunosuppressant agents may carry an elevated risk for adverse effects or potential drug interactions.[8] The introduction of biologic drugs, starting with tumor necrosis factor (TNF) inhibitors, has revolutionized the treatment of psoriasis.[7,9] As a whole, all the targeted immunomodulator agents available to date have shown higher efficacy than older nonbiologic drugs in managing moderate-to-severe psoriasis.[3,10]

The targeted immunomodulators used to treat psoriasis differ in the mechanisms that they target. TNF inhibitors, which target the elevated levels of TNF-α found in the skin and serum of patients with psoriasis, include adalimumab, etanercept, and infliximab. This early class of biologics showed improved efficacy in treating psoriasis versus nonbiologic drugs.[3,10]

The most recent biologic drugs, including those more focused on the interleukin (IL)-23 and IL-17 cytokine pathways and other cytokines in the body that are downstream of TNF-α, have even higher levels of efficacy.[11] Ustekinumab, the first mixed IL-23 inhibitor to come to market and bring high efficacy with a low risk for infection and a lower frequency of injection reactions, targets the shared p40 subunit of IL-12 and IL-23.[12] Subsequently, secukinumab and ixekizumab (IL-17A antagonists) and brodalumab (an IL-17 receptor A antagonist) were introduced, and all these drugs completely cleared the psoriasis in more than 25% of treated patients in phase 3 clinical trials.[3,9,11]

Finally, the oral agent apremilast (which is not a biologic drug) inhibits phosphodiesterase-4, which regulates cyclic adenosine monophosphate, which, in turn, modulates immune cell response.[13]

Despite the clinical improvements that biologic therapies (and apremilast) provide, the widespread use of biologics may be limited by their high cost relative to older, small-molecule drugs. Managed care plans control utilization of this category, in part, based on cost-effectiveness evidence—the incremental cost differences between drugs divided by their incremental clinical improvement. In the case of brodalumab, an estimated price was used in a nationally recognized cost-effectiveness analysis before launch.[9] Price transparency before a drug launch by the manufacturer would have avoided the need for estimating the Wholesale Acquisition Cost (WAC). In that analysis,[9] the estimated price was higher than the actual market price at launch, which necessitated a reanalysis.

Effectiveness Considerations

Because no current head-to-head comparisons have

Table 1 Ranges of PASI 75 Response Rates in Placebo-Controlled Clinical Trials

Medication	Treatment arm, PASI 75	Placebo arm, PASI 75
Adalimumab	71-80	7-19
Etanercept	40-59	3-7
Infliximab	76-80	2-3
Ustekinumab 45 mg	67	3-4
Ustekinumab 90 mg	66-76	3-4
Secukinumab	76-87	0-5
Ixekizumab	87-90	2-7
Brodalumab	83-86	3-8
Apremilast	29-33	5-6

PASI indicates Psoriasis Area and Severity Index.

Adapted from Institute for Clinical and Economic Review. Targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: effectiveness and value.[9]

Table 2 Ten-Year Summary Results for the Base Case

Drug	WAC, $	Cost, $	QALYs	ICER vs no treatment, $
Nontargeted		88,086	5.531	
Secukinumab	4064.57	221,704	7.018	89,843
Apremilast	43.10	161,741	6.353	89,610
Infliximab	1113.27	203,532	6.776	92,715
Brodalumab	4266.79	240,398	7.151	94,030
Ixekizumab	4469.00	254,287	7.187	100,389
Adalimumab	2048.54	208,881	6.649	108,040
Etanercept	1024.44	198,519	6.469	117,769
Ustekinumab	8840.22	269,843	6.930	129,904

ICER indicates Institute for Clinical and Economic Review; QALYs, quality-adjusted life-years; WAC, Wholesale Acquisition Cost.

Adapted from Institute for Clinical and Economic Review. Targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: effectiveness and value.[9]

been made between targeted immunomodulators, the Institute for Clinical and Economic Review (ICER) conducted a network meta-analysis to assess the relative effectiveness of immunomodulators for the treatment of psoriasis.[9] The Psoriasis Area and Severity Index (PASI), which is the most frequently used primary outcome measure in psoriasis studies, measures the reduction in skin surface involvement and lesion severity from a baseline score. PASI 75 represents a 75% reduction in the PASI score from baseline to follow-up and is a common threshold for improvement.[9] In clinical trials of patients with moderate-to-severe psoriasis, all the immunomodulators exhibited statistically significantly higher PASI 75 response rates compared with placebo (**Table 1**).[9] Using network meta-analyses, ICER concluded that ixekizumab and brodalumab had the highest relative effectiveness, whereas apremilast had the lowest relative effectiveness.[9]

In the effectiveness portion of the cost-effectiveness ratio, efficacy must be balanced with safety considerations between and within the classes. A common side effect of biologic and systemic treatments for plaque psoriasis is an increased risk for serious infection. Using data from 11,466 patients with psoriasis in the Psoriasis Longitudinal Assessment and Registry (PSOLAR), the risk for serious infection was higher in patients who received adalimumab or infliximab than in patients who received nonmethotrexate and nonbiologic treatments. However, no increased risk for serious infection was apparent with ustekinumab treatment, and there was only an insignificant increased risk noted with etanercept treatment.[14] Brodalumab has a boxed warning for the risks of depression and suicidal thoughts or behavior in patients, and the drug is only available through a Risk Evaluation and Mitigation Strategy program[15]; otherwise, the most common adverse reactions were similar to other IL-17 agents.[15-17]

Cost Considerations

Moderate-to-severe plaque psoriasis continues to be a costly disease for patients and for payers alike, as a result of increased cost-sharing based on the increased utilization of expensive biologics.[18] Almost 80% of patients with moderate-to-severe plaque psoriasis are prescribed 1 or more medications, with most of those drugs being either self-administered or systemic therapies.[19]

When comparing patients with psoriasis who are the most costly to health plans with the least costly patients, patients in the costliest tier have significantly more comorbidities, including diabetes, cardiovascular disease, psoriatic arthritis, depression, and anxiety, and they incur more unique prescriptions.[20] The costliest patients with psoriasis also have significantly higher inpatient and emergency utilization than patients in less costly drug tiers, but the use of biologic medications and biologic drug costs do not vary much across the 4 cost tiers.[20] Thus, there is not much differentiation between cost tiers and biologic drug use among these patients, which would support using the most cost-effective agent in a class.

Cost-Effectiveness

As health plans and other payers in the United States consider biologics for formulary inclusion and benefit design options, decision makers have increasingly turned to reports produced by ICER as a source for cost-effectiveness evidence.[21] ICER released its report, "Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value," at the end of 2016.[9] Because brodalumab was not approved until February 2017, after the ICER report was released,

ICER estimated the price for brodalumab by taking the average WAC for the marketed IL-17 drugs at that time (ie, secukinumab and ixekizumab) and then applying an estimated class-based discount of 40%.[22]

Table 2 presents the incremental cost-effectiveness ratios for each agent versus nontargeted therapy (a mix of no treatment, topical or systemic treatment, and phototherapy).[9] Based on that estimated price for brodalumab, secukinumab was the most cost-effective IL-17A drug—$89,843 per quality-adjusted life-year QALY)—compared with brodalumab ($94,030) and ixekizumab ($100,389), as well as the most cost-effective drug among all the targeted therapy alternatives. Brodalumab was estimated to be the second most cost-effective IL-17A drug and the fourth most cost-effective drug overall.[9]

Subsequently, at the May 2017 meeting of the International Society for Pharmacoeconomics and Outcomes Research, Hendrix and colleagues presented an update of the ICER cost-effectiveness calculations for targeted immunomodulators (**Table 3**).[22] The WACs of the drugs were updated, and the actual price of brodalumab was estimated to be $3900, based on its price before the launch date (ie, February 2017).[22]

The same 40% discount rate was applied to the IL-17 class. In that updated analysis, brodalumab was the most cost-effective of the IL-17 drugs, including secukinumab and ixekizumab. Brodalumab was also the most cost-effective option among all the drugs that were considered in the analysis.[22]

Table 3 Markov Model Summary of Results Over 10 Years

Drug	WAC, $	Cost, $	QALYs	ICER vs no treatment, $
No treatment		66,451	5.531	
Brodalumab	3900.00	160,834	7.173	57,478
Apremilast	43.10	139,042	6.403	83,283
Secukinumab	4064.57	209,810	7.045	94,716
Infliximab	1113.27	189,494	6.788	97,191
Ixekizumab	4469.00	244,824	7.208	106,379
Adalimumab	2048.54	195,397	6.681	112,141
Etanercept	1024.44	182,774	6.505	119,443
Ustekinumab	8840.22	256,611	6.959	133,137

ICER indicates Institute for Clinical and Economic Review; QALYs, quality-adjusted life-years; WAC, Wholesale Acquisition Cost.

Adapted from Hendrix N, et al. Cost-effectiveness of targeted therapy for moderate-to-severe plaque psoriasis.[22]

Updating Value Assessments

An important consideration when evaluating the results of cost-effectiveness models is to recognize the impact that variations in the clinical and economic inputs can have on the interpretation of the outputs. For example, the difference in dosing between ustekinumab 90 mg and 45 mg made a difference in whether the drug was cost-effective when compared with etanercept.[23] Perspective can also play a role, as was demonstrated when cost-effectiveness modeling was done from the perspective of the Spanish healthcare system, where adalimumab was the most cost-effective treatment choice.[24] Treatment sequencing also affects the calculated cost per QALY across medicines.[25]

Our case study specifically demonstrates the impact of price on the treatment hierarchy for moderate-to-severe plaque psoriasis. An adjustment in WAC from an estimated average of other agents at $4267 versus an actual price of $3900 moved brodalumab from being the fourth most cost-effective targeted therapy to the most cost-effective targeted therapy. In fact, at the time this article was written, the WAC price for brodalumab was $3500,[26] which would even further distinguish this agent from its comparators as being the most cost-effective agent for moderate-to-severe psoriasis.

However, the proprietary nature of the ICER model does not allow for a recalculation of outputs; it can be assumed that the cost-effectiveness ratio would be improved with a lower price. An important component of calculated net price was the inclusion of estimated rebates by drug class, and this could further distinguish drug pricing among medicines in clinical practice. Therefore, the reassessment of cost-effectiveness reports based on updated pricing is important to inform health plans; however, plans still need to consider how their net price compares with the model's inputs.

As decision makers incorporate value assessment into their formulary and benefit designs, the impact of clinical and economic inputs on the outputs of cost-effectiveness models are important to consider.[21] The choice of inputs for these medicines, including accurate and updated pricing information, is a dynamic process. As other new pharmaceutical entrants come to market, cost-effectiveness will need to be reevaluated.

Limitations

This study has limitations that are common to many modeling studies. Cost-effectiveness modeling studies are only as robust as their data inputs. With regard to cost, it is important to remember that WAC is only a convenient benchmark for establishing relative net price among various comparators. Pharmacy benefit design and actual plan rebates have a greater impact on net price, as well as on formulary placement and patient out-of-pocket costs. Although cost-effectiveness is an important consideration, Pharmacy and Therapeutics committees, as well as prescribers, must consider additional factors, including adverse events. For example, among

the IL-17A drugs (ie, secukinumab, ixekizumab, and brodalumab), brodalumab is the only one with a boxed warning for suicidal ideation and behavior.

Conclusions

Cost-effectiveness models and their outputs are often considered in formulary decisions, but changes in drug cost can have a significant impact on the conclusions drawn, as is seen in the model discussed by Hendrix and colleagues, or in the validation done within an individual health plan. The drug cost is a foundation to the value equation; variance in this cost, or any estimates or assumptions based on this cost, will likely influence the comparative benefit of the drug outcomes versus alternative therapy options. By providing a real-world example of the impact of changing drug costs on the hierarchy of cost-effective therapy in plaque psoriasis, this case study serves as an example for similar considerations in other drug class value assessments. ■

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