Original Article

Cost-Effectiveness Analysis of Crizanlizumab in Sickle Cell Disease in Iran

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What's Known

- Crizanlizumab is a medication approved by the Food and Drug Administration, effective in reducing the severity and rate of vaso-occlusive crisis in sickle cell disease, with the highest cost-saving on hospitalization expenses, compared with voxelotor and L-glutamine. Therefore, a dilemma arises regarding its clinical use as monotherapy or in combination with hydroxyurea, depending on its cost-effectiveness.

What's New

- To the best of our knowledge, this is the first cost-effectiveness analysis of crizanlizumab as monotherapy and in a concomitant setting from a healthcare system perspective in Iran. A novel decision tree combined with a cost-utility analysis assessed clinical effectiveness, costs, and health-related quality of life, ultimately concluding that crizanlizumab is not cost-effective.

Abstract

Background: Sickle cell disease (SCD) prevalence is predicted to rise dramatically in the upcoming years. Although several medications have received Food and Drug Administration (FDA) approval in recent years, low- and middle-income countries (LMICs) still struggle to access these medications due to their remarkably high prices. Crizanlizumab, owing to its clinical and economic privileges, appears to be the most suitable option for addition to pharmacotherapy guidelines. However, no study has yet investigated its cost-effectiveness in Iran's healthcare system.

Methods: This cost-effectiveness evaluation was conducted in 2022 at the Pharmacoeconomic and Pharmaceutical Administration Department of the Faculty of Pharmacy at Tehran University of Medical Sciences, Tehran, Iran. A decision-tree model was designed, followed by a cost-utility analysis for crizanlizumab in two separate scenarios, targeting not only monotherapy with crizanlizumab in SCD compared with placebo, but also crizanlizumab's concomitant use with hydroxyurea compared with hydroxyurea. The study reports the outcomes from Iran's healthcare system perspective. Direct medical costs, quality-adjusted life years related to vaso-occlusive crisis, hospitalizations, and adverse effects were calculated. Incremental cost-effectiveness ratios were compared. SUSTAIN trial was the main clinical source for modeling crizanlizumab's effectiveness in SCD. A sensitivity analysis was performed to measure the sensitivity of outcomes to changes in medication costs. Microsoft Excel 2020 was utilized for calculations and modeling.

Results: Concomitant therapy with low-dose crizanlizumab added to hydroxyurea led to the lowest Incremental Cost Effectiveness Ratio (ICER) of 398,881 United States dollars (USD), exceeding Iran's accepted cost-effectiveness threshold. Sensitivity analysis results demonstrate that even a 20% reduction in the price of crizanlizumab does not lead to its cost-effectiveness in Iran.

Conclusion: Crizanlizumab administration in sickle cell disease is not found cost-effective in Iran, neither as a monotherapy nor added to hydroxyurea.

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Keywords ● Cost-effectiveness analysis ● Crizanlizumab ● Sickle cell disease ● Sickle cell anemia ● Adakveo

Introduction

The number of people with sickle cell disease (SCD), as the most prevalent genetic disorder, is increasing, with 14 million newly

predicted cases by 2050.[1, 2] Low- and middle-income countries (LMICs) are most affected by this rise, with 95% of the SCD population residing in these countries.[3] Therefore, to prepare for the upcoming financial burden, it is essential to conduct economic evaluations of SCD management. This will help healthcare decision-makers identify and implement cost-effective interventions for SCD.[4]

Patients with sickle cell anemia are subject to mortality rates 11 times higher than other cause-specific death rates.[2] Furthermore, SCD patients experience significantly lower health-related quality of life (HRQOL) than those with other chronic conditions, such as cancer,[5] primarily due to severe pain episodes, known as vaso-occlusive crisis (VOC), that occur throughout their lifetime.[6] This phenomenon occurs when sickled blood cells obstruct blood flow, leading to ischemic injury of body organs and causing a painful emergency. VOCs are rated as the most frequent acute complication of SCD and the main reason for hospital visits. The frequency and intensity of these episodes are directly linked to the causes of SCD death, including infection, stroke, splenic sequestration, and acute chest syndrome.[7, 8] These characteristics have been considered as the main clinical endpoint in SCD clinical trials.[9]

Regarding the pharmacotherapy of SCD, hydroxyurea has been established as the main pharmaceutical standard of care in SCD patients for many years. However, several new pharmacological treatments were approved by the FDA during the past decade, including crizanlizumab, L-glutamine, and voxelotor. These treatments focus on either lowering VOCs frequency (crizanlizumab, L-glutamine)[10] or reducing the severity of VOCs through binding reversibly to hemoglobin and preventing HbS polymerization (voxelotor).[11]

Amongst these medications, crizanlizumab is the most efficacious in terms of lowering the number of VOCs a patient experiences in a lifetime; 27 VOC episodes, compared with 34 and 42, respectively, seen with L-glutamine and voxelotor.[12] Furthermore, crizanlizumab reduces the median annual rate of VOCs from three to two episodes, prolongs the occurrence of 1st and 2nd VOCs, reduces the hospitalization rate, and increases the number of opioid-use-free and pain-crisis-free days that patients experience.[13, 14] Economically speaking, the highest out-of-pocket expenses avoided and lowest caregiver burden have been attributed to crizanlizumab, amongst others.[12] Despite these clinical/economic advantages, crizanlizumab has not yet found its way to SCD clinical guidelines, mainly due to its remarkably high price, especially in LMICs.[3] This study investigates the cost-effectiveness of crizanlizumab both as monotherapy and concomitantly with hydroxyurea from Iran's healthcare system perspective.

Materials and Methods

This study was conducted at the Pharmacoeconomic and Pharmaceutical Administration Department of Tehran University of Medical Sciences, Tehran, Iran, in 2022, with the ethics committee approval code of IR.TUMS.MEDICINE.REC.1401.361. However, cost-related outcomes are updated based on 2024 costs and Iran's Ministry of Health tariffs' renewed report. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022, as the preferred method for reporting economic evaluations, was adopted.[15] A decision tree was designed to represent scenarios of monotherapy and concomitant therapy with crizanlizumab, followed by a cost-utility method to investigate cost-effectiveness for both scenarios in an annual horizon.

Model Selection

A decision tree was selected as the model of choice in our study for several reasons. Firstly, decision trees are the most appropriate model for measuring outcomes of similar independent events.[16] In our setting, VOCs and hospitalization are firm examples of such events. These events impact the outcomes both in terms of health costs and utilities, with VOC-related hospitalization being the primary source of imposed expenses and reduction in health utilities. Secondly, decision trees are favored over Markov models in terms of event occurrence probability calculations in the short term. Given the annual horizon of the SUSTAIN trial, coupled with the unavailability of long-term clinical data regarding crizanlizumab, we decided to choose a decision tree. Finally, decision trees are the most comprehensive for healthcare policymakers.

Next, we conducted a cost-utility analysis based on differences in the clinical effectiveness of hydroxyurea and crizanlizumab in lowering the VOC frequency. The rate of adverse effects experienced was incorporated to capture medication-related quality-adjusted life years (QALY) differences. Patients were divided into two scenarios based on receiving crizanlizumab or crizanlizumab in combination with hydroxyurea. For cost calculations, the hydroxyurea standard dose of 20 mg/Kg/day for the average adult with 70 kg weight, monthly injections of low-dose (2.5

mg/Kg), and high-dose (5 mg/Kg) crizanlizumab were calculated for one year of treatment. Based on crizanlizumab's dose and VOC occurrence in each treatment arm, six separate lines were designed for decision trees of each scenario. Only pain episodes leading to hospital/emergency facility referrals were incorporated. Based on expert opinion, the pain management protocol included intravenous hydration and opioid therapy with no requirement for blood transfusion. Therefore, transfusion-related outcomes were excluded. Due to the annual horizon of the study, no discount rates were applied for costs and QALYs. Details of the decision tree model can be seen in figures 1 and 2 in the results section.

Clinical Effectiveness

According to the SUSTAIN trial,[17] The primary health outcome reported was the annual rate of VOC occurrence, which was 45.3% lower with high-dose crizanlizumab than placebo (P=0.01). The secondary outcome introduced was a delay between the occurrence of the 1st and 2nd VOCs (P≤0.02), resulting in a lower number of annual VOCs (reduced from three to two events). A 41.8% lower rate of annual hospitalizations was also calculated (P=0.45), which was incorporated into the model due to its clinical importance and impact on hospitalization costs avoided.[13] Other outcomes were not applied in the model due to the rarity of occurrence in the annual context.

Cost Calculations

Direct medical costs were calculated from a healthcare system perspective. Mutual costs for each scenario included medication price, specialist appointment expenses, and VOC-related hospitalization costs. The costs for hydroxyurea, including periodic monitoring costs (every 2-3 months) and the expenses for IV administration services, were incorporated into the treatment costs with crizanlizumab. Cost extraction for hydroxyurea was performed using Iran's FDA drug list. However, due to crizanlizumab's unavailability in Iran's pharmaceutical market, the average wholesale price (AWP) reported from Wolters Kluwer MediSpan@ was considered as the base price for calculations, and import tariffs were added to the final cost calculations. Hospitalization costs charges for VOC management, such as a 2-day observation and 1-night hotel stay, specialist consultations, routine laboratory tests, and opioid and IV liquid therapy services. All costs were extracted from Iran's Ministry of Health tariffs for medical, diagnostic, and treatment services, published in 2024. The USD exchange rate of 1 USD equaling 480,000 Iranian Rials (IRRs) was applied for all cost calculations.

Utility Calculations

Utility for SCD in the asymptomatic state, disutility resulting from VOC, hospitalization, and adverse effects occurrence were extracted from the literature. Pyrexia had the highest disutility value of -0.11, while other pain-related adverse effects shown in table 1 led to disutilities as low as -0.069. Utility gain/loss after receiving each therapeutic regimen was extracted from the literature review. QALYs were calculated using utilities at the end of one year of treatment with each pharmaceutical regimen. QALYs were assigned to the final node of each branch in the decision tree. Probabilities of VOC occurrence, adverse effects, and hospitalization were calculated and incorporated into our decision-tree.

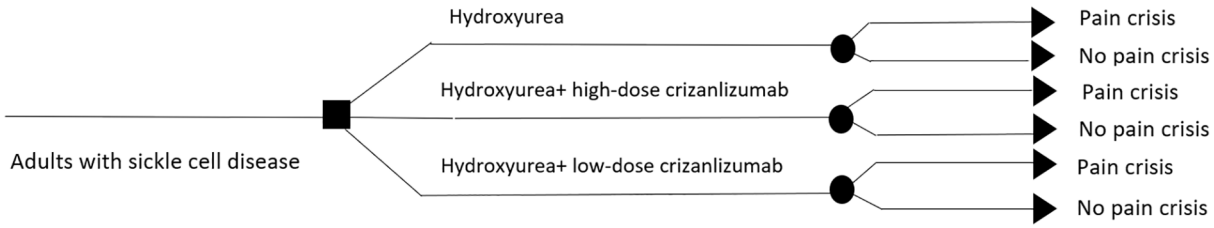

Figure 1: Decision tree model compares administration of high-dose and low-dose crizanlizumab concomitantly with hydroxyurea with hydroxyurea monotherapy scenario in adults with SCD.

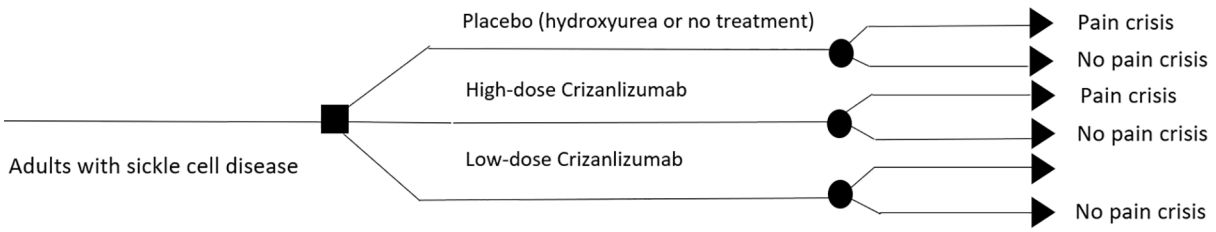

Figure 2: Decision tree model compares administration of high-dose and low-dose crizanlizumab with placebo, which is defined as either receiving hydroxyurea or no treatment, in adults with SCD.

Table 1: Probability calculations of vaso-occlusive crisis (VOC) episodes, health utilities before and after VOC occurrences, and disutilities associated with VOCs and adverse effects

Probability of VOC occurrence in therapeutic settings	VOC^+	VOC^-
Low-dose crizanlizumab	0.33	0.67
Low-dose crizanlizumab+hydroxyurea	+0.18	0.82
High- dose crizanlizumab	0.17	0.83
High-dose crizanlizumab+hydroxyurea	0.25	0.75
Hydroxyurea	0.4	0.6
No treatment (placebo)	0.33	0.67
Base utility in SCD patients		0.75[18]
VOC-associated disutility in SCD patients	-0.1 [19]	
Disutility of adverse effects[20]		
Headache	-0.069	
Back pain	-0.069	
Nausea	-0.048	
Arthralgia	-0.069	
Pain in the extremities	-0.069	
Pyrexia	-0.110	
Musculoskeletal pain	-0.069	
Vomiting	-0.048	

VOC^+: Vaso-occlusive crisis occurrence; VOC^-: Lack of vaso-occlusive crisis; SCD: Sickle cell disease

Table 2: Direct medical costs for annual treatment of SCD

Items	Setting	Costs (USD)
Medication and monitoring tests	Low-dose Crizanlizumab	13,393
	High-dose Crizanlizumab	6,696
	Hydroxyurea	118.38
Hospitalization per pain crisis episode	_	44.36
IV administration services	Crizanlizumab	39.92

Cost Effectiveness Analysis

The incremental cost-effectiveness ratio (ICER) was calculated for each scenario based on decision trees targeting a Δ of costs imposed on Iran's healthcare system for one complete unit of QALY. This is calculated through dividing the Δ of costs by Δ of QALYs for each scenario using the following formula.

$$\text{ICER} = \frac{\text{Total Cost (New Therapy)} - \text{Total Cost (Alternative Therapy)}}{\text{QALY (New Therapy)} - \text{QALY (Alterantive Therapy)}}$$

Statistical Analysis

One-way sensitivity analysis (OWSA) was performed to evaluate how changes in the prices of hydroxyurea and crizanlizumab lead to changes in the outcomes of the study. The sensitivity of ICER to a 20% reduction in crizanlizumab's price and to various prices of hydroxyurea brands available in Iran's pharmaceutical market was calculated.

Results

Details of decision tree models for different treatment scenarios in patients with SCD can be found in figures 1 and 2, respectively. Costs associated with each scenario in an annual setting were incorporated into the model based on cost calculation results in table 2. The probability of vaso-occlusive crisis occurrence and respective utilities were calculated and added to the model, details of which are provided in table 1. In the final step, the incremental cost-effectiveness ratio (ICER) for each scenario is outlined in table 3, followed by an investigation of the sensitivity of the results through a sensitivity analysis test seen in table 4.

Monotherapy with Crizanlizumab

In annual settings, the costs of placebo, low-dose, and high-dose crizanlizumab were calculated as 6, 6,742, and 13,482 USD, respectively. Similarly, QALYs of 0.723, 0,723, and 0.735 were attributed to placebo, low-dose, and high-dose crizanlizumab arms.

Concomitant Therapy with Crizanlizumab

Costs of one-year treatment with hydroxyurea, followed by concomitant use of hydroxyurea with low-dose and high-dose crizanlizumab were calculated as 27, 6,759, and 13,456 USD, respectively. The QALY of patients under treatment with hydroxyurea was 0.716. Concomitant therapy with low-dose and high-dose crizanlizumab resulted in QALYs of 0.733 and 0.727, respectively.

Table 3: Incremental cost-effectiveness ratio and differences in quality-adjusted life years and costs

Treatment setting	Δ of costs (in USD)	Δ of QALYs	ICER
Low-dose crizanlizumab vs. placebo	6,736	-0.00046	-
Low-dose crizanlizumab+hydroxyurea vs. hydroxyurea	6,733	0.0169	398,881
High-dose crizanlizumab vs. placebo	13,476	0.0124	1,088,612
High-dose crizanlizumab+Hydroxyurea vs. hydroxyurea	13,430	0.0112	1,194,054

USD: United States Dollar; QALY: Quality adjusted life years; ICER: Incremental cost-effectiveness ratio

Table 4: Sensitivity analysis results in terms of incremental cost-effectiveness ratio percentage of change, differences in quality-adjusted life years, and costs in each scenario

Parameter	Δ of costs (in USD)	Δ of QALY	ICER	Percentage of change in ICER (%)
The hydroxyurea price of 0.0167 USD per capsule	13,430	0.01	1,194,054	0%
The hydroxyurea price of 0.028 USD per capsule	13,430	0.01	1,194,054	0%
Crizanlizumab with a 20% lower than the base price in the concomitant scenario	10,755	0.01	956,189	-19.92%
Crizanlizumab with a 20% lower than the base price in the concomitant scenario	10,801	0.01	872,494	-19.85%

USD: United States Dollar; QALY: Quality adjusted life years; ICER: Incremental cost effectiveness ratio

Incremental Cost-Effectiveness Ratio (ICER)

ICER was calculated for each scenario by dividing the Δ of costs by the Δ of QALYs. ICER observation demonstrated that crizanlizumab was not cost-effective considering the cost-effectiveness threshold of 2,500 USD in Iran, regardless of the treatment dose applied or the frequency of VOCs experienced. Details are provided in table 3.

Sensitivity Analysis

Our results were not sensitive to either variations in hydroxyurea price or to a 20% reduction in crizanlizumab's price. This indicated that cost-effectiveness analysis results remain unchanged even if a 20% decline in crizanlizumab's price occurs. Sensitivity analysis results are outlined in table 4

Discussion

The result of our study demonstrated that using crizanlizumab is neither cost-effective as a monotherapy nor as an adjuvant to hydroxyurea. However, there are important points that should be further discussed.

Crizanlizumab was found not to be cost-effective in our model for two main reasons. First, it is a notably high-priced medication compared to its affordable alternative. Second, crizanlizumab's cost-effectiveness is closely linked to the healthcare system of the target country.[21] In fact, crizanlizumab owes its cost-effectiveness to its hospitalization cost avoidance. Hospitalization costs are the main source of SCD costs in developed countries with high healthcare service expenditures. For instance, in the United States, hospitalization costs are eight times higher than pharmaceutical expenses, for SCD patients experiencing three VOCs annually.[22, 23] In Iran, the same calculated ratio is as low as 0.008; therefore cost savings associated with hospitalization are almost negligible. The same logic applies to transfusion costs avoided in studies that model transfusion events. As expected, crizanlizumab tends to be found cost-effective in countries with considerable hospitalization costs such as the United States, where there is evidence that crizanlizumab in the concomitant setting is capable of saving up to 60% of the crizanlizumab's price.[24] However, the ICER report of SCD still does not consider crizanlizumab cost-effective under the 50,000 cost-effectiveness per QALY threshold with the current price.[12]

To improve the modeling of SCD, it is advisable to account for the impact of medications in reducing the number of VOCs, especially over extended timelines. This approach highlights the accumulation of pain-free and opioid-free days, as well as a lower-than-expected occurrence of VOCs. Markov models are known to best capture these chronic effects and are advised to be implemented once long-term data for crizanlizumab is available.[25] Furthermore, the risk of opioid misuse and dependency in SCD is critical.[26] While opioid underdosing in SCD patients increases opioid tolerance and leads to higher doses required for the next episodes,[27] a 10-fold morphine clearance increase in VOC events worsens opioid dependency as more and more potent doses are required.[28] Opioid dependency, being associated with lower HRQOLs and its related outcomes, is advised to be included. Another concern is that a substantial number of VOCs (up to 50%) remain unreported in patients' medical records.[29] However, these

unreported pain episodes are directly linked to future VOCs that may lead to hospitalization.[7] It is advised that future studies use real-world data, such as pharmacy refills, to predict the frequency of such episodes based on patterns of analgesic use in SCD patients.

Based on the previous literature review, 12 out of 13 cost-effectiveness studies in sickle cell anemia reported the results from a healthcare system perspective,[30] whereas the social perspective is equally prominent due to 70% productivity disruption caused by SCD in the working-age population.[31] A cost-effectiveness study in Qatar compared crizanlizumab with L-glutamine and concluded that low-dose crizanlizumab (2.5 mg/Kg) was cost-effective.[32] Other studies investigating crizanlizumab's cost-effectiveness, however, report that crizanlizumab is not cost-effective, including a retrospective analysis in Germany in favor of crizanlizumab's revocation from the market[33] and a lifetime cost-utility model, both targeting the payer's and societal perspectives.[34]

We faced several limitations in conducting this CEA. First of all, due to crizanlizumab's recent FDA approval, long-term clinical data regarding its efficacy and frequency of VOCs experienced in extended time horizons were not available. For this reason, long-term Markov modeling was not possible at the time of this study; it is advised to be undertaken once adequate data is published. Secondly, SCD is a genetic disorder, and therefore, genetic phenotype differences play an important role in terms of response to treatment. It is recommended to conduct population-specific randomized clinical trials to accurately evaluate the cost-effectiveness of crizanlizumab for this reason. There are no existing clinical trials or health utility evaluations of crizanlizumab specific to the Iranian population in the literature.

To the best of our knowledge, this is the first study aiming at designing a model to evaluate crizanlizumab's cost-effectiveness from the perspective of the healthcare system in Iran. Our novel decision-tree model facilitates evidence-based healthcare decision-making regarding crizanlizumab's clinical use in SCD in Iran and can be adopted as a reference for future crizanlizumab's economic evaluations in different settings.

Conclusion

Management of SCD patients with high-dose/low-dose crizanlizumab is not cost-effective in Iran, either as a monotherapy intervention or added to hydroxyurea as the pharmaceutical standard of care. All calculated ICERs exceed Iran's ICER threshold of 1312 USD. Compared with high-dose, low-dose crizanlizumab imposes higher costs and less effectiveness, which puts ICER in the dominated area of cost-effectiveness.

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Authors' Contribution

M.N: Study design, data gathering, data interpretation and analysis, and drafting, Sh.I: Study design, data gathering, data interpretation and analysis, drafting and revising manuscript, Sh.N: Study concept and design, data gathering, data interpretation and analysis, and revising manuscript; FS.H: Study concept and design, data gathering, data interpretation and analysis, and revising manuscript; All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Conflict of Interest: None declared.

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