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ORIGINAL ARTICLE

Expert consensus on the management of infusion-related reactions (IRRs) in patients with sickle cell disease (SCD) receiving crizanlizumab: a RAND/UCLA modified Delphi panel

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Abstract

Crizanlizumab, a monoclonal antibody against P-selectin, has been shown to reduce vaso-occlusive crises (VOCs) compared to placebo in patients ≥ 16 years with sickle cell disease (SCD). However, there have been rare reports of patients experiencing severe pain and subsequent complications within 24 hours of crizanlizumab infusions. These events are defined as infusion-related reactions (IRRs). Informed by current literature and clinical experience, a group of content experts developed clinical guidelines for the management of IRRs in patients with SCD. We used the RAND/University of California, Los Angeles (UCLA) modified Delphi panel method, a valid, reproducible technique for achieving consensus. We present our recommendations for managing IRRs, which depend on patient characteristics including: prior history of IRRs to other monoclonal antibodies or medications, changes to crizanlizumab infusion rate and patient monitoring, pain severity relative to patient's typical SCD crises, and severe allergic symptoms. These recommendations outline how to evaluate and manage IRRs in patients receiving crizanlizumab. Future research should validate this guidance using clinical data and identify patients at risk for these IRRs.

Keywords Vaso-occlusive crises · Allergy · Crizanlizumab · Monoclonal antibody · Hematology

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Introduction

In the US, sickle cell disease (SCD) affects approximately 100,000 individuals and is most prevalent in the African American population (1 in 360) [1, 2]. The clinical manifestations of SCD appear to be driven by vaso-occlusion with ischemia-reperfusion injury and hemolytic anemia. Vaso-occlusive crisis (VOCs) (also called acute painful events or sickle cell crises) are thought to result from microvascular occlusions with subsequent tissue ischemia and may require emergency department or hospital care. In addition, SCD also causes end-organ dysfunction due to vascular damage in several areas that can lead to life-long disabilities, poor quality of life, and even death.

The survival of individuals with SCD who have access to comprehensive care has improved dramatically, with survival to the age of 18 now greater than 93% in the US [3, 4]. Despite these improvements in childhood survival, people with SCD have a lifespan that is shortened by at least 20 years and significant morbidity, infections, anemia, organ dysfunction (including stroke), and acute and chronic pain are still common [5].

Crizanlizumab is a monoclonal antibody (mAb) that blocks interactions with P-selectin, a type 1 transmembrane protein contributing to the pathogenesis of vaso-occlusions and sickle-cell-related pain crises. SUSTAIN, a phase 2 trial, showed a 45% reduction in VOCs in the crizanlizumab-treated group and increased the times to first and second VOCs [6]. A post hoc analysis of SUSTAIN showed that regardless of the number of VOCs in the previous year, concomitant hydroxyurea use, or SCD genotype, treatment with crizanlizumab decreased the crisis rate [7].

Once crizanlizumab became commercially available, there were reports of patients with SCD experiencing severe pain and subsequent complications during their infusion. These were defined as infusion-related reactions (IRRs). Importantly, these IRRs were not noted during the SUSTAIN study, although joint pain was noted as an adverse event (AE). IRRs have subsequently been recognized as a potential AE of crizanlizumab [8–11]. The IRRs seen with crizanlizumab differ from IRRs seen in other conditions treated with mAbs in that they often present with severe pain instead of hypersensitivity or anaphylaxis [8]. Using a standardized consensus method (RAND/UCLA modified Delphi panel), this study aimed to develop guidelines for the management of IRRs following crizanlizumab infusion in patients with SCD.

Methods

The RAND/UCLA modified Delphi panel methodology systematically and quantitatively combines expert opinion and published literature (Fig. 1). This method is consistent with the reference case for expert elicitation in health care decision making [12]. Our panel included 10 physicians (nine hematologists, one transfusion medicine physician) with an average of 16 years of clinical experience in pediatric and/or adult hematology, internal medicine, or pathology. Nine experts worked in academic practice settings, and one worked in a combined academic/community practice. All were from the United States (five from the Northeast, four from the South, and one from the West). Although the panel was not blinded while work was ongoing, the sponsor (Novartis Pharmaceuticals) did not provide input on study design, methods, results, or interpretation of findings. Experts received honoraria for their participation. Modified Delphi panels do not involve human subjects as defined by 45 CFR part 46, and therefore this study did not require institutional review board approval.

Experts reviewed a comprehensive, relevant literature review on the etiology, mechanism, and management of IRRs in SCD. After reviewing the literature summary, experts rated 568 unique clinical scenarios as to the appropriateness of prescribing treatments, monitoring, ordering labs, and escalating to a higher level of care.

Patient scenarios were grouped based by clinical situation and stratified by patient characteristics: (1) first infusion, stratified by history of allergies to other drugs, transfusion reactions, or IRRs to other mABs (i.e., not crizanlizumab); (2) management of IRRs that present with new or worsening pain during a crizanlizumab infusion, stratified by severity and location of pain; (3) management of IRRs that present with allergic symptoms during a crizanlizumab infusion, stratified by severity and type of symptom (i.e., hypotension, angioedema, respiratory distress or shortness of breath, rash or pruritis, and fever); (4) continued monitoring in patients whose symptoms did not significantly improve with initial treatment; and (5) exploratory laboratory tests to conduct after an IRR.

For each scenario, the panelists rated the listed action (e.g., treatment, laboratory test, care escalation) on a scale of 1 (highly inappropriate, risks outweigh the benefits) to 9 (highly appropriate, benefits outweigh the risks). Ratings of 1–3 were used when an action would be considered inappropriate, and ratings of 7–9 were used for actions they considered appropriate. As is typical in a RAND/UCLA modified Delphi panel, consensus was defined as being present when no more than two panelists gave a response that differed significantly from the other eight panelists.

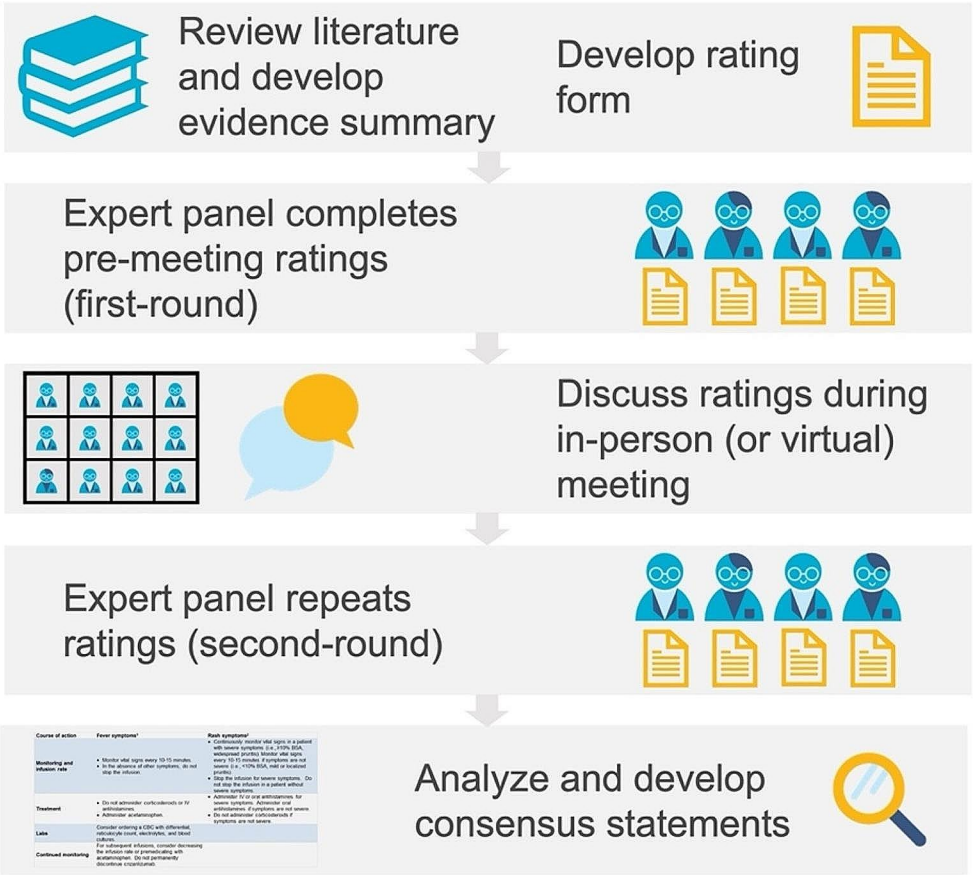

Fig. 1 Overview of modified Delphi panel process

Table 1 First infusion

Type of patient	Recommendation
All patients	• Check vital signs before and after first crizanlizumab infusion; monitor for 30 min after each of the first two infusions. • Do not premedicate any patient with normal saline, NSAIDs, or corticosteroids.
Patients with no history of allergies or IRR to another monoclonal antibody	• Administer crizanlizumab per prescribing information without premedication.

All experts completed a first round of ratings independently before a virtual panel meeting, which was held over two days in June 2022. During the meeting, experts were provided with their individual ratings as well as the panel's median ratings for all scenarios. During the professionally moderated group discussion, panelists shared the logic behind their ratings, focusing on areas of disagreement. After the meeting, panelists re-rated all scenarios. These second-round ratings were used to develop consensus statements. These consensus statements were then circulated to all experts who reviewed and provided feedback. The final consensus statements were approved by all panelists.

Results

The 10 panelists agreed on how to manage crizanlizumab-related IRRs in patients with SCD for 85% ($n=485$) of scenarios (see Supplementary Materials). The final recommendations are intended for general guidance and are not meant to supersede shared patient-physician decision-making. Refer to Tables 1, 2 and 3 for full panel recommendations.

First infusion

When considering a patient's first infusion of crizanlizumab, patients were stratified into three groups: patients without a history of allergies or IRRs to any medications, patients with one or more medication allergies or a history of transfusion reactions, and those with a history of IRR to another monoclonal antibody. Experts rated the appropriateness of vital sign monitoring, infusion time, and premedication. These recommendations are listed in Table 1.

Table 2 Pain and severe allergy events

Action	Pain symptoms[1]	Severe allergy symptoms[2,3]
Monitoring and infusion rate	• If severe pain or pain similar to patient's typical SCD crisis, and chest pain, monitor vital signs either every 10–15 min or continuously. • If pain is not severe and it is a patient's typical site of SCD pain, it is not necessary to continuously monitor vital signs. • If pain is similar to a typical SCD crisis, but in an atypical location (including chest pain), stop the infusion and consider restarting it at a slower rate with symptomatic improvement. • In a patient with severe pain with: (1) chest pain, stop the infusion; (2) without chest pain stop the infusion and consider restarting it at a slower rate with symptomatic improvement.•	• In a patient experiencing any severe allergic symptoms, continuously monitor vital signs. • In a patient with hypotension or in a normotensive patient with shortness of breath or difficulty breathing with desaturation, stop the infusion and do not restart.
Treatment	• Treat pain per patient's individualized SCD pain plan (if available) or per ASH and/or institutional SCD pain management guidelines. • Do not administer corticosteroids or IV antihistamines. • Do not administer oxygen in a patient who maintains oxygen saturation ≥ 95%.	In a patient with: - respiratory difficulties or angioedema, consider administering IV antihistamines. - isolated hypotension, consider administering oral antihistamines with IV fluids. - shortness of breath and oxygen desaturation, consider administering albuterol, oxygen therapy, epinephrine, and/or corticosteroids. - wheezing but no oxygen desaturation, consider administering albuterol. - isolated angioedema or isolated wheezing without oxygen desaturation, consider administering oral antihistamines; however, in a patient with isolated angioedema, do not administer corticosteroids or epinephrine. • In a normotensive patient with angioedema and wheezing without oxygen desaturation, do not administer epinephrine.
Labs [footnote 4]	Consider ordering: - CBC with differential and reticulocyte count for a patient with severe pain or with chest pain. - Electrolytes, LDH, ALT, AST, and bilirubin for a patient with severe pain in an atypical location without chest pain.	• In a normotensive patient with shortness of breath, consider ordering a CBC with differential and a reticulocyte count. • If the patient becomes hypotensive, additionally order electrolytes, LDH, ALT, and AST.
Continued monitoring and subsequent infusions	• Escalate care (e.g., refer to emergency room) if a patient's pain is severe and not significantly improved after 1 h of observation and appropriate treatment, or if the patient experiences hypoxia, progressive urticaria, or hypotension that has not improved with appropriate treatment. • Keep patient in the current care setting (e.g., clinic or hospital outpatient center), assuming the care setting can appropriately meet the patient's needs, if pain is not severe and has not improved with appropriate treatment and 1 h of observation. • If the prior IRR resulted in an emergency department visit or hospitalization, consider either decreasing the rate of subsequent infusions and premedicating with acetaminophen and an antihistamine or discontinuing crizanlizumab.	

[1]Panelists considered pain that was severe, of the same severity as a patient's typical SCD crisis, or not severe; including typical vs. atypical pain location

[2]If a patient experienced both a severe allergic symptom and a rash, pruritis, or fever, the treatment of the severe allergic symptom would supersede that of the rash, pruritis, or fever.

[3]Experts considered one or more of the following severe allergic symptoms: hypotension (i.e., systolic blood pressure < 90mmHg or diastolic blood pressure < 60 mmHg); respiratory difficulties such as wheezing without respiratory distress or desaturation (< 5% O2 saturation decrease from baseline) or hoarse voice OR shortness of breath or difficulty breathing with desaturation (> 5% O2 saturation decrease from baseline), chest tightness, stridor, or hoarse voice (i.e., whispered speech); angioedema

[footnote 4] If these laboratory tests were not already ordered prior to the infusion

IRR symptoms during any crizanlizumab infusion

New or worsening pain

It is difficult to adequately characterize or quantify pain levels, especially in people with SCD who may experience chronic pain or acute VOC due to the disease itself. Thus, in the rating form, pain was characterized by location and severity relative to that patient's typical VOC. Experts defined severe pain as pain that is worse than a patient's typical VOC. Pain described as not severe represented pain that is less severe than a patient's typical VOC. Pain was also characterized by whether it was in a typical or atypical site of pain for this patient. Lastly, experts differentiated between atypical pain that does versus does not include chest pain because atypical chest pain could portend a more severe complication such as acute chest syndrome. When

Table 3 Fever and urticaria, maculopapular rash, or pruritis

Course of action	Fever[1]	Urticaria, maculopapular rash, or pruritis[2]
Monitoring and infusion rate	• Monitor vital signs every 10–15 min. • In the absence of other symptoms, do not stop the infusion.	• Continuously monitor vital signs in a patient with severe symptoms (i.e., ≥ 10% BSA, widespread pruritis). Monitor vital signs every 10–15 min if symptoms are not severe (i.e., < 10% BSA, mild or localized pruritis). • Stop the infusion for severe symptoms. Do not stop the infusion in a patient without severe symptoms. • During subsequent infusions, decrease the infusion rate and premedicate with antihistamines in a patient with either severe or non-severe symptoms. • In a patient with non-severe symptoms, do not permanently discontinue crizanlizumab.
Treatment	• Do not administer corticosteroids or IV antihistamines. • Administer acetaminophen.	• Administer IV or oral antihistamines for severe symptoms. Administer oral antihistamines if symptoms are not severe. • Do not administer corticosteroids if symptoms are not severe.
Labs	• Consider ordering a CBC with differential, reticulocyte count, electrolytes, and blood cultures.	
Continued monitoring	• For subsequent infusions, consider decreasing the infusion rate or premedicating with acetaminophen. Do not permanently discontinue crizanlizumab.	

[1]Panelists were asked to consider fevers of either Grade 1–100.4-102.2 °F; Grade 2–102.3-104 °F; or Grade 3 - >104 °F per CTCAE V5.0

[2]Panelists were asked to consider rash symptoms including: Grade 1, 2, and 3 urticarial lesions or macules/papules covering < 10%, 10–30%, or > 30% body surface area respectively

considering each scenario, experts were also asked to assume the patient was being treated with crizanlizumab per the indications listed in the prescribing information, including not experiencing a pain crisis (i.e., VOCs) before the infusion. Further, experts recognized individuals may be taking opioids to treat chronic pain. Expert recommendations for the treatment of new or worsening pain are outlined in Table 2.

Severe allergic symptoms

Experts considered one or more of the following to be severe allergic symptoms: hypotension (i.e., adults with systolic blood pressure < 90mmHg or diastolic blood pressure < 60mmHg), respiratory difficulties (e.g., wheezing without respiratory distress/desaturation or hoarse voice; shortness of breath [SOB] or difficulty breathing with desaturation [≥ 5% O_2 saturation decrease from baseline], chest tightness, stridor, or hoarse voice), or angioedema. Expert recommendations for the treatment of patients experiencing severe allergic symptoms are outlined in Table 2.

Urticaria, maculopapular rash, or pruritis and fever

Urticaria, maculopapular rash or pruritis are stratified by severity. Severe symptoms affect ≥ 10% body surface area (BSA) or include widespread pruritis. Mild symptoms affect < 10% BSA or include mild or localized pruritis. These symptoms, in addition to fever, were rated separately from the allergy symptoms in Table 2 because they were considered less severe (if occurring in isolation). If a patient experienced both a severe allergic symptom and a rash, the treatment of the severe allergic symptom would supersede that of the rash or fever. Expert recommendations for the treatment of urticaria, maculopapular rash, or pruritis and fever are outlined in Table 3.

Subsequent infusions after an IRR

Experts acknowledge that the decision of whether to give future infusions is heavily dependent on patient-physician shared decision-making and the severity and outcome of prior IRRs. If the prior IRR resolved with treatment during the infusion or post-infusion monitoring time, consider proceeding with subsequent infusions at a slower rate and premedicate with acetaminophen and/or an antihistamine. However, if the prior IRR resulted in an emergency department visit or hospitalization, experts recommend considering either decreasing the rate of subsequent infusions and premedicating with acetaminophen and an antihistamine or discontinuing crizanlizumab.

Exploratory labs

Experts were also asked to consider a list of laboratory tests that might provide information on the etiology of a patient's IRR, though unlikely to aid in acute treatment. Based in part on the possible role of immune dysregulation and complement in various SCD complications in general [13–15], these laboratory tests were considered: CRP,

CH50, complement Ba fragment level assay, complement Bb fragment level assay, total C3, total C4, C3a, C5b-9, serum tryptase, and ferritin. There was insufficient evidence available for experts to recommend or discourage these assessments.

Discussion

After reviewing published evidence and independently rating 568 patient scenarios, experts developed guidance on appropriate courses of action for the management of varying crizanlizumab-related IRR symptoms. This study was not a clinical study of patient care, but rather an expert consensus process focused on common IRR patient symptoms specific to the use of crizanlizumab.

Due to data limitations and confounding manifestations of SCD, pain events occurring within 24 hours of crizanlizumab infusion in SUSTAIN were not identified as potential IRRs [7]. Post-approval, these reactions are uncommon and many clinicians have limited experience treating them. There has been one case series that reviewed reports of IRRs presenting with pain [10]. Multiple case reports [9, 16] have also described IRRs presenting with pain, however, these publications do not provide treatment recommendations. By convening a panel of experts with experience treating these IRRs, we developed guidance to treat these reactions. Further, providing more streamlined treatment guidance may enhance our ability to study outcomes using these treatments in subsequent assessments.

Panel experts agreed that corticosteroids should be avoided whenever possible and should be used only for the most severe allergic reactions, such as shortness of breath with oxygen desaturation. The experts also agreed they should not be used as premedication or to treat pain, as studies have noted an increased risk of hospital readmission due to VOCs associated with corticosteroid therapy [17–22]. The connection between corticosteroids and VOCs is not well understood but likely involves an interaction between established corticosteroid-induced neutrophil migration triggering VOC [23–25].

Patients who are prescribed crizanlizumab tend to have SCD associated with more VOCs. Panelists were hesitant to recommend permanently discontinuing crizanlizumab unless a patient experiences severe complications, such as an acute chest syndrome or extended hospitalization due to the IRR, given the limited number of medication options to prevent VOC in SCD [26, 27]. The panel preferred to attempt subsequent infusions through a combination of slowing the infusion and administering acetaminophen and antihistamines as premedication.

The mechanism of IRRs during crizanlizumab administration remains unclear. Crizanlizumab is a humanized IgG2 mAb, and while minimizing non-human protein sequences in biologics reduces reactivity, hypersensitivity reactions (HSRs) have been reported with humanized mAbs [28]. The incidence of mAb-induced IRRs ranges from < 1% for some humanized mAbs (e.g., bevacizumab) to > 10% with some chimeric antibodies (e.g., rituximab) [28]. However, allergic reactions mediated by anti-drug IgE are immediate (type I HSR) and typically require prior exposure to the mAb and usually do not occur on the first infusion except in cases where patients have pre-existing antibodies that cross-react with the drug. In contrast, most reported IRRs occur during the first or second infusion of crizanlizumab [8]. The existence of IRRs during the first infusion argues against type I HSR. Non-IgE-mediated mast cell activation from certain biologics may be attributable to the presence of surfactants, such as polysorbate (PS) 20 and PS80 [21]. Notably, crizanlizumab contains PS80 [8]. Immunoglobin G (IgG)-mediated reactions (type II or III HSR) leading to immune complex deposition tend to be subacute or chronic [29]. It is estimated that most acute immune-mediated IRRs are not mediated by pre-existing antibodies, but are "pseudoallergic", mediated directly by complement or immune cells [28]. In a retrospective review of 104 patients, Isabwe et al. proposed a classification system for HSRs to mAbs; most reactions (63%) were Type I (mast cell mediated, IgE dependent) and manifested with pruritis, urticaria, shortness of breath, hypotension, and anaphylaxis [30]. In patients with type I HSR, if treatment with the responsible drug is needed, rapid drug desensitization can be effective [29]. There is no standard lab panel that can provide a clear understanding of an IRR's etiology. Experts discussed a series of exploratory laboratory tests that might be helpful in determining the cause of IRRs (or prevention of future IRR). These tests included measurements of various components of the complement cascade (e.g., C3, C4, CH50) to assess for a "pseudoallergic" reaction, however, the panel acknowledged the limited evidence available, recognized these laboratory tests are unlikely to aid in acute treatment, and therefore, were unable to recommend these tests be ordered after an IRR.

This study has several limitations. First, no patient data were collected to develop our recommendations nor were patient data used to test the validity of our consensus statements, and these results reflect the clinical opinion of ten experts. However, the RAND/UCLA modified Delphi panel method has been used extensively to develop quality measures and clinical guidance in various areas [31]. Guidelines developed using this method have content, construct, and predictive validity [32]. The method has been shown to produce guidance that improves health outcomes [33–36].

Ratings of appropriateness from this method have been found to be reliable with test-retest reliability > 0.9 using the same panelists 6–8 months later [37] and kappa statistics across several panels with different members similar to those of some common diagnostic tests [38]. Experts had less experience with patients experiencing allergic reactions than with painful reactions, which is mirrored by higher levels of uncertainty in the allergy ratings. We did not provide separate guidance for adult and pediatric patients. Crizanlizumab is presently approved for patients ≥ 16 years. Although there may be some differences between children and adults living with SCD, experts agreed treatment of IRRs would be similar. There are other clinical and non-clinical factors beyond those included in the patient scenarios that might affect decision-making (e.g., individual patient characteristics, clinic settings). Further, the scenarios presented ideal situations and did not assume real-life constraints (e.g., waiting periods, potential health insurance constraints) and the recommendations provided should not supersede clinical decision-making. Experts provided recommendations assuming that they were the primary physician caring for the patient as they experienced the IRR and agreed they would manage patients more conservatively if they were being consulted over the phone (i.e., patient in transfusion center and physician off-site). Lastly, our panel consisted of experts from the US only, so our guidelines may not be generalizable to other countries.

Conclusion

Little guidance exists on the management of crizanlizumab-related IRRs in patients with SCD. We developed recommendations for the management of IRRs in these patients. These recommendations reflect the areas of agreement among a panel of hematology and transfusion medicine experts based on current available evidence. The clinician-supported consensus statements developed through this validated method allow for faster dissemination of management recommendations than would waiting to base recommendations on a clinical study. We hope that these recommendations can aid in further developing IRR management care plans for patients with SCD taking crizanlizumab. Studies to demonstrate whether these recommendations improve health outcomes will further advance the management of these IRRs.

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Declarations

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