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Expert consensus on the management of infusion-related reactions (IRRs) presenting with pain in patients receiving crizanlizumab

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Background

- Vaso-occlusive crises (VOCs) are a common, painful complication of sickle cell disease (SCD) that can significantly decrease quality of life.[1]
- Crizanlizumab, a monoclonal antibody, has been shown to reduce the rate of VOCs compared to placebo in patients ≥16 years with SCD.[2]
- However, there have been reports of patients experiencing severe pain and subsequent complications within 24 hours of crizanlizumab infusions, and these events are defined as infusion-related reactions (IRRs).[3]
- IRRs are rare and most clinicians will have limited experience managing them.

1. Kavanagh et al. *Pediatrics*. 2015;136(4):e1016–25.
2. Ataga et al. *N Engl J Med*. 2017;376(5):429–39.
3. Safety of crizanlizumab [Internet]. [cited 2020 Oct 26]. Available from: https://www.crizanlizumab.info/

Aims

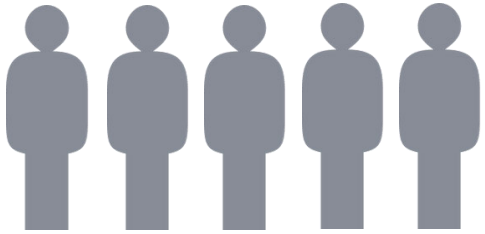
- **Our goal was to develop clinical guidelines on the management of IRRs** presenting with pain in SCD patients receiving crizanlizumab.
- The RAND/UCLA modified Delphi panel method is a valid, reliable, and reproducible method that can be used to generate consensus.

Methods

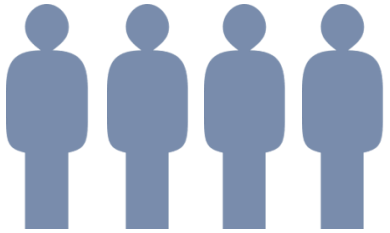
RAND/UCLA modified Delphi panel method

- Convened 10 expert clinicians from various backgrounds.
- Average professional experience: 17 years.
- Provided experts with a review of evidence on the management of IRRs in patients with SCD receiving monoclonal antibodies.

5 pediatric hematologists



4 hematologists



1 transfusion medicine pathologist

Variable Types of IRR Scenarios

- Pain response (i.e., pain severity similar to or different from previous pain crises)
- Allergic response (i.e., difficulty breathing, swallowing, etc.)
  - Allergy symptoms were also discussed in this Delphi panel. These results will be presented in an upcoming publication.

Variables included in patient scenarios

Clinical characteristics: Usual site of SCD pain, atypical site of SCD pain

Vital sign monitoring: Monitor every 10-15 minutes, continuously monitor

Administration: Slow infusion, temporarily stop, stop

Medications/treatment: Treat pain per individualized pain plan/institution guidelines, IV fluids, O_2 therapy, oral antihistamines, IV antihistamines, IV corticosteroids

Ordering laboratory tests: CBC, reticulocyte count, chem-7, LDH, ALT+AST, bilirubin, troponin

Course of action: Continue to monitor in clinic/hospital/outpatient infusion center, escalate care

204 patient scenarios

Rated each scenario on multiple axes

How appropriate would these treatments or tests be in this scenario?	Highly inappropriate, risks outweigh the benefits	Not sure (e.g., due to inadequate data) or the risks and benefits seem balanced	Highly appropriate, benefits outweigh the risks
How appropriate would it be to either continue monitoring the patient or escalate care in this scenario?	Highly inappropriate, risks outweigh the benefits	Not sure (e.g., due to inadequate data) or the risks and benefits seem balanced	Highly appropriate, benefits outweigh the risks

Convened virtually to discuss ratings

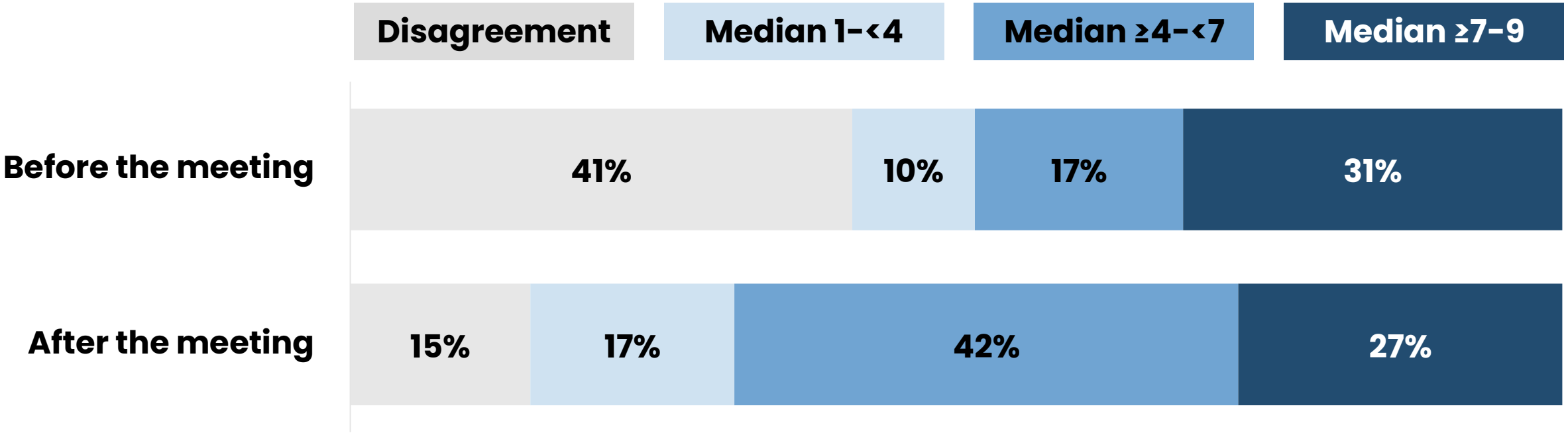
- Ratings were completed independently before a virtual meeting.
- Areas of disagreement were discussed at the meeting.
- Ratings were completed a second time at the conclusion of the meeting.

Disagreement: ≥2 ratings outside the median category
Median 1-<4 without disagreement, highly inappropriate
Median ≥4-<7 without disagreement, risks & benefits are balanced
Median ≥7-9 without disagreement, highly appropriate

Results

Guidance on the management of IRRs presenting with pain

Overall rating from results



Percent of scenarios in each rating category

Vital sign monitoring

- If patient is experiencing severe[1] pain:
  - monitor vital signs either every 10-15 minutes or continuously.
- If the patient's pain is of similar severity to a typical SCD crisis and includes chest pain:
  - monitor vital signs either every 10-15 minutes or continuously.
- If pain is not severe and in the typical site of SCD pain:
  - do not continuously monitor vital signs.

[1]When we describe pain as severe, we mean that pain is *more* severe than a patient's typical SCD crisis. When we describe pain as not severe, we mean that pain is *less* severe than a patient's typical SCD crisis.

*Statements that make a recommendation for or against an action were rated as highly appropriate or highly inappropriate, respectively; statements that ask clinicians to consider an action were rated as having balanced risks and benefits.

Crizanlizumab administration

- If patient is experiencing severe pain:
  - with chest pain, stop the infusion.
  - without chest pain, stop the infusion and consider restarting it at a slower rate with symptomatic improvement.
- 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.
- If pain is not severe:
  - do not stop the infusion.

*Statements that make a recommendation for or against an action were rated as highly appropriate or highly inappropriate, respectively; statements that ask clinicians to consider an action were rated as having balanced risks and benefits.

Treatment for pain

- 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%.

*Statements that make a recommendation for or against an action were rated as highly appropriate or highly inappropriate, respectively; statements that ask clinicians to consider an action were rated as having balanced risks and benefits.

Laboratory tests

- If these laboratory tests were not conducted prior to the infusion, consider ordering the following:
- If patient is experiencing severe pain:
  - with chest pain, CBC with differential and reticulocyte count.
  - without chest pain and in an atypical location, electrolytes, LDH, ALT, AST, and bilirubin.
- If pain is is similar to a typical SCD crisis:
  - with chest pain, CBC with differential and reticulocyte count.

*Statements that make a recommendation for or against an action were rated as highly appropriate or highly inappropriate, respectively; statements that ask clinicians to consider an action were rated as having balanced risks and benefits.

Continued monitoring

- If pain is not significantly improved with appropriate treatment after 1-hour observation and:
- Pain is severe:
  - Escalate care (e.g., refer to emergency room, inpatient admission).
- Pain is not severe:
  - Keep the patient in the current care setting (e.g., clinic or hospital outpatient center), assuming the care setting can appropriately meet the patient's pain needs.

*Statements that make a recommendation for or against an action were rated as highly appropriate or highly inappropriate, respectively; statements that ask clinicians to consider an action were rated as having balanced risks and benefits.

Summary/Conclusions

- These recommendations outline how to evaluate and manage IRRs presenting with pain in patients receiving crizanlizumab.
- A valid, reproducible method was used to develop these guidelines based on expert consensus informed by current literature and clinical experience.
- Future research should validate this guidance using clinical data and identify patients at risk for these IRRs.