COMMENTARY

blood advances

TO THE EDITOR:

Transfusion therapy for sickle cell disease: what's new?

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The American Society of Hematology (ASH) 2020 guidelines for transfusion support for individuals with sickle cell disease (SCD)[1] included recommendations on specific indications and administration of transfusion, as well as screening, prevention, and management of alloimmunization, delayed hemolytic transfusion reactions (DHTRs), and iron overload. The ASH Guideline Monitoring Expert Working Group conducted an updated literature search that did not identify new studies that would change the current recommendations.

No randomized control trials or systematic reviews that would impact the current recommendations were identified. However, since publication, additional therapeutics for SCD that could impact clinical transfusion practice have been approved by the US Food and Drug Administration or reported.

1. Voxelotor (Oxbryta): Hemoglobin S (HbS) polymerization inhibitor that was shown in a phase 3 randomized, placebo-controlled trial involving participants with SCD to significantly increase hemoglobin levels and reduce markers of hemolysis. For recommendation 3, which addresses immunosuppressive therapy for patients with SCD with a history of multiple or life-threatening DHTRs, one should consider voxelotor as a preventive maintenance therapy to improve the baseline hemoglobin of patients at high risk of DHTR if red cell transfusion is required.[2]
2. Tocilizumab (Actemra): Monoclonal antibody directed against interleukin 6 (IL-6) receptor. Case reports have described individuals with DHTRs who have shown marked improvement after targeted anti–IL-6 receptor therapy, suggesting that blockade of macrophage activation may be an effective treatment strategy for ongoing DHTR. Tocilizumab could be added as a potential therapeutic strategy to recommendation 4 that suggests immunosuppressive therapy (IV immunoglobulin, steroids, rituximab, and/or eculizumab) over no immunosuppressive therapy in patients with SCD with a DHTR and ongoing hyperhemolysis.

Red blood cell (RBC) transfusion remains a critical component of care for patients with SCD. Despite improvements to optimize RBC antigen matching, minimize iron overload, and to transfuse judiciously, individuals with SCD may still experience adverse effects. As this issue of *Blood Advances* describes, the ASH 2020 Guidelines for Management of Sickle Cell Disease: Transfusion Support[1] continue to be relevant, without sufficient new data to recommend revision or retirement. Several recently approved therapeutics provide alternatives or adjunctive therapy related to the ASH recommendations for transfusion support, and there are multiple ongoing efforts and studies relevant to SCD and transfusion therapy which we summarize here.

Prevention of HTRs in high-risk patients (recommendation 3)

Hemolytic transfusion reactions (HTRs) occur in 3% to 5% of transfusions in individuals with SCD and up to 11% of such reactions are fatal. Mitigation is achieved through judicious use of transfusions and provision of RBCs lacking the cognate antigens against which a recipient has alloantibodies.

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New SCD-modifying agents (SCDMAs), which increase baseline hemoglobin levels and reduce markers of hemolysis, offer the potential to minimize the need for RBC transfusions in individuals with SCD at high risk of HTRs. Voxelotor (Oxbryta), a HbS polymerization inhibitor, is a Food and Drug Administration–approved SCDMA for ages ≥4 years, which significantly increases hemoglobin levels and reduces markers of hemolysis in individuals with SCD.[2,3] Although unable to directly prevent HTRs, voxelotor, in addition to hydroxyurea, should be considered to improve the baseline hemoglobin in patients at high risk for hemolytic reactions to minimize future RBC transfusions. Pyruvate kinase activators are another class of agents being investigated to reduce hemolysis and increase baseline hemoglobin in individuals with SCD. Phase 2/3 trials of pyruvate kinase activators mitapivat (AG-348) and etavopivat (FT-4202) are ongoing (www.clinicaltrials.gov, #NCT05031780 and #NCT04624659) and may be added to the repertoire of SCDMAs to minimize RBC transfusion in high-risk individuals.

Given that most RBC antibodies in individuals with SCD evanesce over time,[4,5] identification of RBC antibodies when they are present is critical. Equally important is RBC antibody data sharing between hospitals. Since the guidelines were published, the Department of Health & Human Services' Advisory Committee on Blood and Tissue Safety and Availability has published support for the need of a national RBC antibody registry. Furthermore, there is ongoing research to increase data interoperability and, in the longer term, to require the uniform recording of RBC antibodies using ISBT-128 codes in the electronic medical record.

Management of severe DHTRs with hyperhemolysis (recommendation 4)

A DHTR with hyperhemolysis can be a life-threatening transfusion reaction in individuals with SCD.[6] The 2020 ASH SCD transfusion support guidelines suggested immunosuppressive therapy over no immunosuppressive therapy for DHTRs, including the use of IV immunoglobulin, steroids, rituximab, and/or eculizumab. Since that time, case reports have described individuals with SCD and HTRs successfully treated with an IL-6 receptor antagonist (tocilizumab [Actemra]).[7-10] The binding of tocilizumab to the IL-6 receptor inhibits, among other things, IL-6–mediated macrophage activation. As such, tocilizumab could be considered as a potential therapeutic strategy to recommendation 4; however, further investigation of tocilizumab is warranted. Driven in part by the success of eculizumab in disorders resulting from complement-mediated intravascular hemolysis (eg, cold agglutinin disease and paroxysmal nocturnal hematuria), a range of new inhibitors targeting distinct components of the complement cascade are currently under investigation.[11] Although these agents have not been used in treatment of SCD, they may provide additional future treatment options for individuals with SCD suffering from severe DHTRs with hyperhemolysis.

RCE with or without IHD for chronically transfused patients with SCD (recommendation 7)

The 2020 ASH SCD transfusion support guidelines suggested red cell exchange (RCE) over simple transfusion for patients requiring chronic transfusion therapy as it minimizes iron accumulation and can improve maintenance of the target HbS percentage. Isovolemic hemodilution (IHD) RCE is a procedure available in which, before the RCE, the patient undergoes an RBC depletion with concurrent volume replacement with normal saline or 5% albumin. The intent of IHD-RCE, also known as depletion exchange, is to decrease the number of RBC units needed to attain the target HbS percentage. The ASH guideline panel was unable to provide a recommendation for IHD-RCE vs conventional RCE because of a lack of evidence suggesting the impact of IHD-RCE on RBC unit utilization was superior.[12,13] Since the 2020 ASH guidelines were finalized, a French study of 50 patients reported a 16% reduction of RBC units when comparing IHD-RCE to standard RCE (average requirement decreased from 13 to 11 units).[14] All patients underwent IHD-RCE every 2 months to maintain the HbS <50% and unit savings were calculated from the RBC unit number required by the instrument software to perform standard RCE. RBC unit savings may occur with IHD-RCE when patients require large volume procedures, but studies are needed to determine blood unit utilization for patients who require RCE to maintain the HbS <30%. In addition, the 2020 ASH guidelines panel highlighted a need for further studies evaluating the safety of IHD-RCE in patients with chronically transfused SCD. Since its report, a single institution study reported on the incidence of RCE adverse events and found no association between the use of IHD-RCE and procedural adverse events.[15] Despite this report, more investigation is needed to determine long-term impact of IHD-RCE compared with conventional RCE on neurologic outcomes.

Transfusion management during pregnancy (recommendation 8)

The 2020 ASH SCD transfusion support guidelines included recommendations on transfusion management during pregnancy. The panel concluded that there was insufficient evidence to recommend prophylactic transfusion rather than standard of care for pregnant women with SCD. However, consideration of prophylactic transfusions at regular intervals was recommended for women with a history of severe SCD-related complications before current pregnancy (including during previous pregnancies), additional features of high-risk pregnancy (eg, additional comorbidities), or women who develop SCD-related complications during the current pregnancy (conditional recommendation based on very low certainty of evidence). Consequently, the panel identified this as a research priority. Currently, there is an ongoing multicenter feasibility trial comparing standard of care with serial prophylactic RBC exchange (to maintain HbS <30%) starting in the first trimester in women with SCD, which intends to assess willingness of pregnant women with SCD to participate in a chronic RCE regimen and to evaluate maternal and fetal outcomes (Transfusion Antenatally in Pregnant Women With SCD [TAPS2]; www.clinicaltrials.gov, #NCT03975894).

Conclusion

The purpose of the 2020 guidelines was to provide evidence-based recommendations for RBC transfusion support in patients with SCD. Because high-quality evidence was not uniformly available for each transfusion topic, the panel's goal was to provide clinical decision support for shared decision-making by patients and clinicians based on the available evidence. Ongoing clinical

trials studying chronic transfusion therapy for pregnant women with SCD, or adults with SCD and pulmonary arterial hypertension (SCD and CardiovAscular Risk–RBC Exchange trial [SCD-CARRE]; www.clinicaltrials.gov, #NCT04084080), will guide future recommendations. As new therapeutics are approved and ongoing clinical trials provide new evidence, guideline monitoring will continue to incorporate new management approaches and highlight top research priorities.

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