ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

New and Experimental Agents for Sickle Cell Disease

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H&O What treatments are available for patients with sickle cell disease?

KA Sickle cell disease (SCD) can be cured with allogeneic hematopoietic stem cell transplant. However, this treatment modality is limited by its toxicity, the inadequate availability of stem cell donors, and its cost. More recently, hope is increasing that gene therapy and genetic engineering approaches will become more widely available as treatment modalities.

Red blood cell transfusion is a modality that is used in the prevention and treatment of several complications of SCD.

Despite the testing of multiple agents, only 2 drugs have been approved by regulatory agencies for SCD—hydroxyurea, in 1998, and L-glutamine (Endari, Emmaus Medical), in July 2017.

H&O When is red blood cell transfusion used?

KA Transfusion can be used to reduce the risk for a first or recurrent stroke and to treat acute chest syndrome and several other acute complications of SCD. These complications include, but are not limited to, symptomatic anemia, aplastic crisis caused by infection with parvovirus B19, and episodes of sequestration in which blood becomes trapped in the spleen or liver. Of course, transfusion therapy entails its own complications, so the benefits need to be balanced against the drawbacks. The complications of red blood cell transfusion include allergic reactions, febrile reactions, iron overload, and infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). Another potentially serious consequence of transfusion is the development of alloimmunization, which increases the risk for delayed hemolytic transfusion reactions.

H&O When is hydroxyurea used?

KA Hydroxyurea is used to treat several complications in SCD. In the multicenter, placebo-controlled MSH trial (Multicenter Study of Hydroxyurea in Patients With Sickle Cell Anemia) of 299 patients with sickle cell anemia, which was published in 1995, hydroxyurea was shown to decrease the frequency of acute pain episodes, also known as pain crises. Hydroxyurea also reduced the likelihood of acute chest syndrome, hospitalizations, and the need for transfusion of red blood cells. More recently, hydroxyurea has been shown to prolong survival, decrease the risk for stroke, and possibly decrease albuminuria.

Common side effects of hydroxyurea include myelosuppression, skin and nail changes, decreased sperm counts, and in some cases nausea, vomiting, and hair loss.

H&O When is L-glutamine used?

KA L-Glutamine has been shown to decrease the frequency of acute pain episodes, the incidence of acute chest syndrome, and the cumulative number of days that patients with sickle cell anemia spend in the hospital. Although the experience with this medication is still

somewhat limited, I use it in my practice for patients with sickle cell anemia who have frequent episodes of pain or acute chest syndrome. I often use L-glutamine in combination with hydroxyurea following the maximization of hydroxyurea therapy, but L-glutamine alone is also an appropriate treatment for patients who are unable to take hydroxyurea or refuse this medication.

H&O Can you discuss the study that served as the basis for the approval of L-glutamine?

KA A double-blind, placebo-controlled phase 3 study evaluated 230 patients with sickle cell anemia or sickle $ß_0$-thalassemia who were at least 5 years of age and had experienced at least 2 acute pain episodes in the previous 12 months (NCT01179217). The patients were randomly assigned in a 2:1 ratio to receive either L-glutamine or placebo, and patients on a stable dose of hydroxyurea were continued on this therapy. Treatment for 48 weeks was followed by a 3-week taper. The study showed that L-glutamine decreased the frequency of acute pain episodes, incidence of acute chest syndrome, and number of days spent in the hospital. Although this study was presented by Dr Yutaka Niihara at the American Society of Hematology (ASH) Annual Meeting in 2014 and was used as the basis for the approval of L-glutamine, it has not yet been published in a peer-reviewed journal. As a result, knowledge of the details of the study is still somewhat limited.

Common side effects of L-glutamine in the trial included constipation, nausea, headache, abdominal pain, cough, and pain in the extremities, back, and chest, although these did not appear to occur more frequently in the L-glutamine group than in the placebo group.

H&O What is crizanlizumab, which is being investigated for use in sickle cell anemia?

KA Crizanlizumab, also known as SEG101 (formerly SelG1), is a humanized monoclonal antibody that binds to P-selectin and blocks its interaction with its ligand, P-selectin glycoprotein ligand 1. Evidence is increasing that vaso-occlusive complications occur in SCD because of interactions between white blood cells, red blood cells, and the vascular endothelium. By blocking the binding of P-selectin to its ligand and decreasing the adhesion of cells to the vascular endothelium, crizanlizumab likely improves microvascular blood flow.

H&O Could you describe your work on this agent?

KA In a multicenter, randomized, placebo-controlled phase 2 study, we tested the safety and efficacy of crizanlizumab in patients with SCD; the results were published in the *New England Journal of Medicine* in 2017. The primary goal was to determine the effect of this monoclonal antibody on the rate of acute pain episodes after 52 weeks of treatment. Secondary endpoints included the annual rate of days hospitalized, the times to the first and second painful episodes, and the annual rate of uncomplicated pain crises—that is, pain episodes other than acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism. We also looked at the annual rate of episodes of acute chest syndrome and patient-reported outcomes.

> Researchers are evaluating several other antiadhesion agents in addition to crizanlizumab for the treatment of sickle cell disease.

We enrolled 198 patients in this study. Patients were randomly assigned to receive low-dose crizanlizumab (2.5 mg/kg), high-dose crizanlizumab (5 mg/kg), or placebo. Patients received 2 loading doses of the agent 2 weeks apart as intravenous infusions and subsequently received monthly infusions, so they received a total of 14 treatments over a 52-week period.

We found that the annual crisis rate was lower in the patients who received high-dose crizanlizumab than in those who received placebo; the median number of crises per year was 1.63 in the high-dose group and 2.98 in the placebo group, representing a 45.3% decrease in the crisis rate with high-dose crizanlizumab. The difference was not only statistically significant but also clinically meaningful. We also found that the median time to a first crisis was significantly longer in the patients who received high-dose crizanlizumab than in those who received placebo: 4.07 vs 1.38 months. The median time to a second pain crisis was 10.3 vs 5.09 months, and the median rate of uncomplicated crises per year was 1.08 with high-dose crizanlizumab vs 2.91 with placebo. The results for treatment with low-dose crizanlizumab were not significantly different from those with placebo.

Crizanlizumab was overall well tolerated. However, the adverse events that occurred in at least 10% of the patients who received active treatment and that were at least twice as likely to occur in the crizanlizumab groups

Table. Agents in Planned or Ongoing Phase 3 Trials for Sickle Cell Disease

Agent	Drug Class (Mechanism of Action)	Identifier	Sponsor
Omega-3 fatty acid (DHA)	Anti-inflammatory	NCT02604368	Sancilio Pharmaceuticals
Rivipansel	Antiadhesive (pan-selective inhibitor)	NCT02187003	Pfizer
Tinzaparin	Anticoagulant (antiadhesive agent)	NCT02580773	Assistance Publique – Hôpitaux de Paris
Voxelotor	Antisickling (increases hemoglobin affinity for oxygen)	NCT03036813	Global Blood Therapeutics

DHA, docosahexaenoic acid.

as in the placebo group were arthralgia, diarrhea, pruritus, vomiting, and chest pain.

H&O What other studies are looking at crizanlizumab?

KA An ongoing study is characterizing the pharmacokinetics and pharmacodynamics of crizanlizumab in patients with SCD (NCT03264989); this study is required by the US Food and Drug Administration for drug approval. In addition, a phase 2 study to confirm and establish appropriate dosing and to evaluate the safety of crizanlizumab in pediatric patients is planned. The results of the completed phase 2 trial are very important because they point to a new treatment for painful crises. If the pharmacokinetics and pharmacodynamics study goes well, I expect that the sponsor will file for approval of this monoclonal antibody as a treatment for SCD.

H&O What other agents are being developed for use in SCD?

KA Researchers are testing a variety of compounds on the basis of our increased understanding of SCD pathophysiology. For example, researchers are evaluating several other antiadhesion agents in addition to crizanlizumab for the treatment of SCD. A phase 3 study of rivipansel, which is a pan-selectin inhibitor (NCT02187003; Table), and a phase 2 study of sevuparin, which is a derivative of low-molecular-weight heparin (NCT02515838), are ongoing.

Researchers are also testing a variety of antisickling agents. The multicenter phase 3 GBT_HOPE study (Study to Evaluate the Effect of GBT440 Administered Orally to Patients With Sickle Cell Disease; NCT03036813) is evaluating voxelotor (Vosevi, Gilead), which increases the affinity of hemoglobin for oxygen. A phase 2 study is testing pegylated bovine carboxyhemoglobin, a carbon monoxide–releasing/oxygen transfer agent known as Sanguinate, for use in SCD (NCT02672540). In addition to antiadhesive and antisickling agents, researchers are testing a variety of anti-inflammatory and antioxidant agents, including N-acetyl cysteine (NCT01800526), omega-3 fatty acids (NCT02947100 and NCT02604368), canakinumab (NCT02961218), and montelukast (NCT01960413). Anticoagulants such as rivaroxaban (Xarelto, Janssen; NCT02072668), apixaban (Eliquis, Bristol-Myers Squibb; NCT02179177), and the low-molecular-weight heparin tinzaparin (Innohep, Leo Pharma; NCT02580773) are being tested as well. Vasodilators that are being investigated include ambrisentan (Letairis, Gilead; NCT02712346), macitentan (Opsumit, Actelion; NCT02651272), riociguat (Adempas, Bayer; NCT02633397), and sodium nitrite (NCT02863068).

H&O What is the status of gene therapy for SCD?

KA Gene therapy has significant potential as a curative approach to SCD. A case report by Ribeil and colleagues of a patient with SCD who appears to have been cured following gene therapy has generated considerable excitement. In this study, a lentiviral vector was used to insert antisickling ß-globin gene into autologous hematopoietic stem cells, which were subsequently transplanted into a patient with SCD. After approximately 15 months, the patient's hemoglobin level was close to normal, without sequelae of SCD. We are awaiting the results of this therapeutic approach in more patients.

Studies are also evaluating a variety of genetic engineering approaches, based on zinc-finger nucleases and transcription activator–like effector nucleases, in the treatment of SCD. Techniques such as clustered regularly interspaced short palindromic repeats (CRISPRs), which enable precise replacement of a specific region of DNA, are another promising gene therapy approach to SCD. Long-term follow-up studies will be needed to confirm the safety and efficacy of these techniques.

H&O Why have so few drugs been approved for the treatment of SCD?

KA The first reason is that the pathophysiology of SCD is somewhat complex. A second and perhaps more important reason is the limited financial investment in the development of drugs for this condition. The good news is that the situation appears to be changing, and many stakeholders, including pharmaceutical companies and foundations, are investing more funds in the development of new drug therapies for SCD.

H&O What changes do you see in the next few years?

KA This is an exciting time for those of us who care for patients with SCD. In addition to L-glutamine, which was approved last year, many more drugs are being tested in phase 2 and phase 3 trials. I am optimistic that within the next 5 years, we will have more agents available for treating patients with SCD, the vast majority of whom will not have access to curative treatment with bone marrow transplant or gene therapy. We need drugs that are effective, safe, and affordable.

Disclosures

Dr Ataga has served on the clinical advisory boards and/or as a consultant for Global Blood Therapeutics, Modus Therapeutics, Novartis, and Bioverativ.

Suggested Readings

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