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Breakthrough Therapy Designation Awarded to Crizanlizumab, a New Treatment Option for Sickle Cell Disease

Cassandra Kuhn, PharmD Candidate 2021[1]
Olivia Reiber, PharmD Candidate, MBA Candidate 2021[1]
[1]University of Findlay College of Pharmacy

Abstract

Sickle cell disease is an inherited disease that affects hemoglobin of red blood cells. It can cause patients extreme pain due to the blockage of small blood vessels. These episodes of extreme pain are called vaso-occlusive crises, or pain crises, and they can lead to increased morbidity and mortality for patients with sickle cell disease. Crizanlizumab is a new therapy that recently received Breakthrough Therapy designation from the FDA. This medication helps reduce the amount of pain crises by blocking P-selectin on sickle cells from binding to one another, preventing the stasis of blood flow. This new therapy is unlike any treatment currently available and is very hopeful for patients with sickle cell disease.

Sickle cell disease, also known as SCD, is a group of disorders that affects red blood cells. The disease specifically affects hemoglobin, which is responsible for helping red blood cells with the delivery of oxygen throughout the body. This abnormal hemoglobin protein in SCD patients is referred to as hemoglobin S. While normal red blood cells are round in shape, hemoglobin S causes red blood cells to be shaped like a sickle or crescent.[1] Normal red blood cells are also flexible and move more easily through the bloodstream. However, sickle-shaped blood cells are harder and able to stick together more frequently and more easily. When the sickle cells adhere together, they can cause a block in blood flow that can lead to pain, infection, acute chest syndrome, a decline in the function of multiple organs, or stroke. Sickle cells also have a shorter lifespan than normal red blood cells resulting in a constant deficiency of red blood cells in patients with SCD.[2]

Sickle cell disease is caused by an inherited genetic mutation. It is inherited in an autosomal recessive pattern, which means that the HBB hemoglobin genes from both parents are mutated.[3] It is the most common blood disorder in the United States and most commonly affects people of African descent. Millions of people are affected worldwide, and up to 80,000 Americans are affected.[1]

There are several types of sickle cell disease. HbSS is a form of SCD called sickle cell anemia in which the patient inherits two "S" sickle cell genes, and it is usually the most severe form of SCD. HbSC is a form in which one of the abnormal genes inherited is for the S gene, and the other gene is for an abnormal hemoglobin called "C". Rarer types of SCD include HbSO, HbSE, and HbSD. All of these types have one abnormal hemoglobin gene along with one "S" sickle cell gene.[2]

Newborns are screened for SCD either before or after birth, but signs and symptoms may not appear until the child is about 6 months old.[3] Signs of SCD are usually due to complications of the disease and may include: yellowing of the skin due to widespread hemolysis of the red blood cells; fatigue, dizziness, and shortness of breath due to anemia; and painful swelling of the hands and feet called dactylitis. More serious complications of SCD include severe anemia, chronic pain, acute chest syndrome, chronic infections, stroke, and pulmonary hypertension.[3]

Currently, the only potential cure for SCD is a bone marrow or stem cell transplant.[3] However, these procedures pose great risks, and donors must be very closely matched with the recipient for the transplant to be effective.[2] Therefore, very few SCD patients are actually able to undergo this risky procedure. While a transplant may be the only cure for this disease, there are various treatment options utilized to prevent serious complications. Antibiotics, such as penicillin, are used in patients with SCD to prevent recurrent infections along with vaccinations. Blood transfusions are also a common treatment in patients with SCD to prevent stroke.[3]

A vaso-occlusive crisis (VOC), also called a pain crisis, is another major complication of sickle cell disease. Pain crises result from the blockage of blood flow due to the clustering of cells in the vasculature and inflammation. They cause patients excruciating pain and are the leading cause for SCD patients to be

admitted to the emergency department. Pain crises are directly correlated with increased morbidity and mortality in patients with SCD.[4] They can cause stroke, organ damage, and even death.[5] Most SCD patients have multiple pain crises each year, and the episodes can vary in both intensity and frequency.[5] Between pain crises, it's common for younger children to be pain free and have virtually no discomfort. On the other hand, older children and adults tend to experience a more continuous or chronic discomfort between crises.[3] Unfortunately, there are very few therapy options for preventing patients from experiencing pain crises.[4] Hydroxyurea is the most common medication used to reduce the number of pain crises in SCD patients. L-glutamine is another very common medication that was FDA approved in 2017 to reduce complications in patients with SCD.[5] Crizanlizumab is the latest drug in development for the treatment of SCD and the prevention of its complications.[5]

Crizanlizumab belongs in the drug class of humanized monoclonal antibodies. Monoclonal antibody therapy stimulates the patient's immune system to attack the cells that the medication targets. While there are many medications within this drug class used to treat various disease states, crizanlizumab is the only humanized monoclonal antibody used specifically to treat sickle cell disease and to reduce its corresponding pain.[6]

P-selectin is a cell adhesion molecule expressed on activated platelets and vascular endothelial cells. The role of P-selectin is to recruit leukocytes to the site of injury during inflammation. P-selectin normally works to control the flow and adherence of leukocytes to blood vessel walls. However, in patients with SCD, the abnormal sickle shape of hemoglobin causes red blood cells to adhere to blood vessel walls or other platelets when they shouldn't, which results in the stasis of blood flow in small vessels. This stasis is what causes pain crises.[6] Crizanlizumab works by preventing this stasis in SCD by blocking the specific P-selectin protein on the platelets to stop them from adhering to each other or blood vessel walls.[7]

In the SUSTAIN phase 2 clinical trial, crizanlizumab was evaluated for safety and efficacy. The study was double-blind, randomized, and placebo-controlled.[8] Participants in the study had at least two previous episodes of pain crises in the last year. There were a total of 198 patients included in the study, and they were given either a low dose of crizanlizumab (2.5 milligram per kilogram of body weight), a high dose (5 mg/kg) or a placebo. The injection was given about once every four weeks (14 out of 52 total weeks).[7] The results of the study showed that a high dose of crizanlizumab reduced the frequency of pain crises by 45.3% (P=0.01), and a low dose of crizanlizumab reduced pain crises by 32.6% (P=0.18). The results also showed that with high dose crizanlizumab, the median time to first pain crises was significantly longer than with placebo (4.07 vs. 1.38 months, P=0.001). The median time to second pain crises was significantly longer with treatment with crizanlizumab as well (10.32 vs. 5.09 months, P=0.02).[8] Some patients were also taking hydroxyurea to treat their SCD, and the reduction of pain crises occurred with crizanlizumab regardless of if they were also taking hydroxyurea.[7] The most common side

effects experienced during the trial were diarrhea, nausea and vomiting, itching, and pain in the back, chest, joints, and limbs.[6]

While the study demonstrated that crizanlizumab increased the time to a pain crisis overall, it also highlighted some limitations of the drug. The most common side effects observed from the trial were experienced in at least 10% of participants. There were also incidences of infections such as upper respiratory tract infections and urinary tract infections. More serious side effects included pyrexia and influenza, of which were recorded more frequently in the groups taking crizanlizumab.[5] Additionally, a life-threatening incidence of anemia and intracranial hemorrhage was also reported with one patient in the low-dose crizanlizumab group. This patient was also receiving concomitant ketorolac.[5]

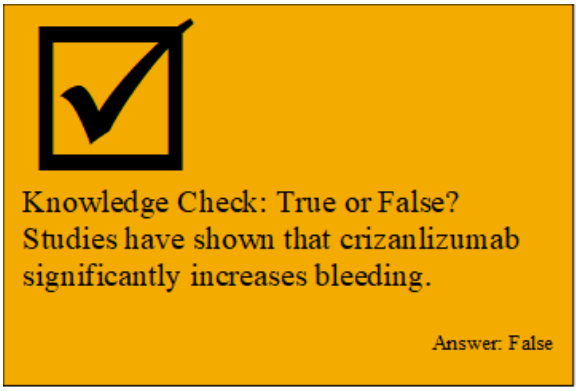
Death was also noted to have occurred during the trial. Included in the five total patients who died, there were two in the high-dose crizanlizumab group that died due to endocarditis and sepsis, and there was one death in the low-dose group due to multiple reasons such as ACS and respiratory failure.[5]

By inhibiting P-selectin and therefore platelet aggregation, crizanlizumab would be expected to increase bleeding risk upon reducing the formation of thrombi. This could potentially explain why one patient in the trial experienced life-threatening anemia and intracranial hemorrhage with low-dose crizanlizumab. However, there has been no conclusive evidence that crizanlizumab itself has increased bleeding-related adverse effects. This relationship between a P-selectin inhibitor and bleeding risk has only been studied in mice and baboons in regards to deep vein thrombosis.[9] The results have shown that a P-selectin inhibitor does not affect the rate of bleeding or increase bleeding risk.[9] This also could potentially explain why only one patient from the trial experienced increased bleeding. Furthermore, this patient was also taking ketorolac while receiving crizanlizumab which is known to significantly increase bleeding. Because crizanlizumab is the only medication in its class that selectively inhibits P-selectin, more trials and research must be completed in order to make a more definitive, human evidence-based conclusion on whether crizanlizumab increases bleeding risk.

The investigators of the trial have proposed that crizanlizumab could also be used to treat pain crises in patients with sickle cell anemia.[6] Currently, there are plans for another phase 2 trial to investigate the efficacy and the effects of the high dose of crizanlizumab in adult patients with sickle cell anemia.[6]

Patients with SCD experience healthcare costs of more than $30,000 annually due to pain crises and the corresponding hospitalizations.10 Hydroxyurea and L-glutamine are both taken orally and cost less than $2 and $1 per capsule, respectively.[11] Crizanlizumab is a monthly infusion, but since it is not yet FDA approved and therefore is not yet on the market, its cost is unknown. While the price of crizanlizumab is expected to be expensive after it gains approval, its benefits and status of an “FDA Breakthrough Therapy” are worth taking note of and considering for the treatment of SCD patients experiencing pain crises.

Crizanlizumab has been granted "Breakthrough Therapy designation" which means that the development and review of crizanlizumab has been accelerated due to it having already exhibited great potential benefit in the treatment of very serious instances of pain crises. The Phase 2 SUSTAIN clinical trial has shown a clear advantage over available therapy, which is why it was granted Breakthrough Therapy.[12] It shows such potential benefit that the FDA is trying to accelerate the approval process so that it can benefit patients sooner. Preventing pain crises is important because they disrupt patients' lives and cause pain, hospitalizations, and even death. Although crizanlizumab will be expensive once it is on the market and SCD patients already incur a heavy economic burden with the disease, it may be extremely beneficial for patients who experience a great number of pain crises annually. Decreasing the number of hospitalizations and emergency room visits due to VOCs could potentially save patients a lot of money.



In conclusion, crizanlizumab is a new Breakthrough Therapy for the treatment of patients with sickle cell disease suffering from vaso-occlusive crises. It is expected to provide great advancement in the prevention of these patients' pain crises and to improve their quality of life. However, it is not without limitations. The drug's potential major adverse events that include influenza, pyrexia, and various infections could restrict its use, especially in certain populations such as the elderly. There needs to be additional research and trials in order to firmly establish its effect on bleeding. Confirming whether it increases bleeding risk will allow more precise decision making regarding the prescribing of this drug for special populations.

Further clinical trials are needed for the approval of crizanlizumab to enter the drug market. A Phase 2 trial for this drug is currently undergoing development and may last a couple of years. Upon successful completion of Phase 2, the drug will move into the clinical trial of Phase 3 in which it may spend up to four years. Additionally, with crizanlizumab being deemed a Breakthrough Therapy drug and being granted accelerated review and approval, there is increased uncertainty of how long it will take it to gain FDA approval and reach the market.

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