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Hematologists Consider Where New Therapies Fit In Sickle Cell Treatment Paradigm

Potential Cures May Not Be Available To All

by Mandy Jackson

The first gene editing medicine and gene therapy for sickle cell disease were approved as the ASH meeting got under way, but novel oral drugs may be key to making treatment more accessible.

The US Food and Drug Administration approvals of *Vertex Pharmaceuticals Incorporated*/C*CRISPR Therapeutics AG*'s gene editing medicine Casgevy (exagamglogene-autotemcel, exa-cel) and *bluebird bio inc.*'s gene therapy Lyfgenia (lovotibeglogene autotemcel, lovo-cel) gave doctors two new options to consider for patients with sickle cell disease (SCD) and a lot to discuss about how these novel treatments will be used going forward during the recent American Society of Hematology (ASH) annual meeting.

The 8 December approvals for both products to treat SCD patients aged 12 and older with recurrent vaso-occlusive crises (VOCs) or a history of vaso-occlusive events (VOEs) were hailed as breakthroughs for the field. However, the complex administration of the one-time therapies and their high list prices – $2.2m for Casgevy and $3.1m for Lyfgenia – also aroused skepticism throughout the ASH conference 9-12 December in San

Key Takeaways

- Vertex/CRISPR's Casgevy and bluebird's Lyfgenia are the first two genetic medicines to treat sickle cell disease, giving doctors and patients a new potentially curative option, but at high costs and with complex administration

Diego about how broadly the genetic medicines will be used.

Even Vertex conceded when it announced Casgevy's approval that the gene editing treatment would address only a fraction of the 100,000-patient SCD population in the US, noting that about 16,000 patients would be eligible for treatment. But those numbers may be difficult to attain based on the number of SCD patients who typically pursue hematopoietic stem cell (HSC) transplants, since less than 100 of the procedures have been performed in the US annually in sickle cell disease since they began in 1984.

Both Casgevy and Lyfgenia are autologous HSC therapies. With Casgevy, a patient's CD34-positive HSCs are edited *ex vivo* with CRISPR/Cas9 technology to reduce BCL11A gene expression and increase fetal hemoglobin (HbF) production. Lyfgenia is an *ex vivo* gene therapy that uses a lentiviral vector to add a functional beta-globin gene to the patient's HSCs for long-lasting production of adult hemoglobin (HbAT87Q) with anti-sickling properties. Both treatments require myeloablative conditioning with busulfan and take about six months to deliver to patients.

that may limit the treatments' use, both within and outside the US.

- Doctors are trying to determine where the gene editing medicine Casgevy and gene therapy Lyfgenia will fit in the treatment landscape where oral drugs and transplants also are options.

- Hematologists and drug makers used the recent ASH meeting as a forum for talking through the challenges and opportunities in the shifting sickle cell disease landscape.

Vertex/CRISPR Nab First-Ever Gene Editing FDA Nod, Overshadow Bluebird's Same-Day Win

By Mandy Jackson

09 Dec 2023

The two first-ever therapies to offer sickle cell disease patients the possibility of lifetime relief from painful vaso-occlusive events or crises are hitting the market, but face tough commercial challenges.

Read the full article here

Cynthia Dunbar, chief of the Translational Stem Cell Biology Branch and head of the Molecular Hematopoiesis Section of the National Heart, Lung and Blood Institute (NHLBI), said during a media call to preview the ASH conference that the long-term clinical trial results for both Casgevy and Lyfgenia are "really encouraging."

Encouraging Progress With Costly, Complex Medicines

"Both lovo-cel and the CRISPR-based exa-cel appear to result in comparable, very impressive

efficacy in terms of lower pain crises and organ dysfunction," Dunbar said. "I think, over time, they are likely to be quite similar in terms of their efficacy, and I think it's going to be market forces that kind of decides which way this goes. But the hurdle is going to be figuring out how to deliver what will be very expensive and complicated therapies, but likely curative therapies, to patients."

In the US, she noted, many patients who would be eligible for treatment with Casgevy and Lyfgenia are disabled and unable to work, so their health care expenses are reimbursed by Medicaid or commercial health plans that may be reluctant to cover high-cost therapies. However, most SCD patients live outside of the US in regions like Sub-Saharan Africa, where health care resources are hard to come by.

"Figuring out how to deliver some of these curative therapies in a cheaper way, in a more feasible way, that doesn't involve stem cell collections and transplant, is probably going to be very important," Dunbar said.

She pointed to *Novartis AG*'s data at ASH for an oral therapy in preclinical development that targets BCL11A, the same gene that Casgevy edits, to treat SCD by increasing fetal hemoglobin.

Vertex also is conducting research into novel drugs that aim to boost fetal hemoglobin, the company's vice president of hematology clinical development Bill Hobbs told *Scrip*. He noted the global nature of SCD and said Vertex plans to file for approval of Casgevy in all countries where clinical trial participants were located. The product is approved in the US and UK, has been recommended for approval in the EU and is on file in Saudi Arabia. (Also see "*First Gene Editing Therapy Among Seven Drugs On Track For EU-Wide Approval*" - Pink Sheet, 15 Dec, 2023.)

"I think for other places of the world, our approach has been that it's really important to develop additional treatment options that can be available there," Hobbs said. "One way to do that is to optimize exa-cel by changing the requirement for busulfan conditioning to a conditioning agent that is less toxic and can be administered in a place that doesn't require all of the infrastructure of a stem cell transplant that exa-cel currently does."

While working on new conditioning agents that could broaden access to Casgevy into additional geographies, he said Vertex is also developing new SCD treatments.

"Now that we've demonstrated that the reactivation of fetal hemoglobin can lead to the elimination of vaso-occlusive crises, it also opens up the possibility that you could develop other modalities to do that, including potentially with a small molecule that could be a once-a-day pill," Hobbs said. "And so, we have additional programs as well to try to do that. … [Casgevy] is step one, it's a major step, a historic step, but we have more to do."

Infrastructure, Adherence Are Challenges In US As Well

There still is a lot of infrastructure that has to be established, even in the US, to facilitate treatment with Casgevy and Lyfgenia. Vertex announced nine activated treatment centers for Casgevy upon approval with plans to open more at stem cell transplant centers throughout the US. The initial sites are in Boston; Washington, D.C.; Los Angeles; Dallas and San Antonio, TX; Columbus, OH; Nashville, TN; and Chicago.

Lyfgenia will be administered at qualified treatment centers that bluebird is establishing for the SCD treatment and its beta-thalassemia gene therapy Zynteglo (betibeglogene autotemcel). The 40 sites in place so far primarily are located in the Northeast and Midwest with three centers in Texas, four in California and Arizona, and one each in Durham N.C., Nashville, Washington, D.C. and Baltimore, MD.

Without treatment centers in key Southern states, such as Mississippi, James Taylor, director of the Center for Sickle Cell Disease at Howard University in Washington, D.C., said in an interview with *Scrip* that patients who may be eligible for treatment may not be able to access Casgevy and Lyfgenia.

Hobbs noted that Vertex is working on expanding its network of Casgevy treatment centers. “We've identified a lot of treatment centers that have experience both with sickle cell disease and doing transplant for sickle cell disease, including across the South, where there is a higher proportion of patients with sickle cell disease,” he said. “And so, we've been able to identify treatment centers in almost all of the states with the highest populations of patients, because the point is really to make sure that patients have access to those treatment centers in a region or a state that's close to them.”

But even if patients can get access to the treatments, Taylor said many patients still are wary of the treatments, despite the potential for long-term relief from painful VOCs for individuals with multiple pain crises per year, because the genetic medicines have only been tested in a few dozen patients each in their clinical trials or because they’ve been through HSC transplants previously that did not deliver the cures they were promised.

“I know the right therapy for the right patient and can find something that fits their lifestyle, risk tolerance, their insurance, all of that, but you've got to have a good relationship with a patient and that's where sickle cell has fallen short,” he said. Taylor cited a publication in the journal *Blood* earlier this year that found that less than 2% of SCD patients are using the three drugs approved for sickle cell disease in the US since 2017, as evidence of patients’ skepticism about new treatments.

There are eight treatments for SCD in the US, including blood transfusions, HSC transplants and now six FDA-approved drugs – Casgevy, Lyfgenia, hydroxyurea, Endari (L-glutamine), *Pfizer*

Inc.'s Oxbryta (voxelotor) and Novartis's Adakveo (crizanlizumab). Endari was approved in 2017, followed by Oxbryta and Adakveo in 2019.

Choosing Treatments To Match Patients' Needs

Kenneth Ataga from the Center for Sickle Cell Disease at the University of Tennessee Health Sciences Center in Memphis began an 11 December ASH session about improving outcomes for SCD patients by describing the medicines that the FDA has approved for SCD and how he thinks about prescribing them in his practice.

If adult patients that come to see Ataga are not already taking hydroxyurea, he prescribes the drug as a foundational therapy and then decides which therapy to add on top of the well-known drug, he said.

"For patients who are having frequent painful episodes or frequent vaso-occlusive complications, whether it's pain episodes or acute chest syndrome, I would add medications that have been shown to be beneficial in the setting of decreasing vaso-occlusive complications," Ataga said. That means hydroxyurea to start plus Endari or Adakveo.

"For patients who have increased hemolytic anemia, I will typically start medication that has been shown to increase hemoglobin and decrease hemolysis," he said. That means hydroxyurea plus Oxbryta.

Taylor said the problem with oral medications is that patients have a hard time remembering to take a daily pill, with only 16% of pediatric SCD patients and 10% of adults getting a year's worth of hydroxyurea in the US, according to Department of Health and Human Services data. That is why he said he likes Adakveo, because patients have to come into the doctor's office to get their infusions, so he can track their compliance with the once-monthly dosing schedule.

But for as much as each new SCD treatment has hurdles to overcome, Taylor said pharmaceutical companies have done something in recent years that public health efforts have been challenged to do over the last several decades – bring attention to the need for new therapies. "At the end of the day, they have advanced the field and that's a good thing for patients," he said.

Bone Marrow Transplant Versus Genetic Medicines

Vanderbilt University professor Adetola Kassim presented Phase II data in an ASH late-breaker session on 12 December for a non-pharmaceutical approach that he said is an effective and less costly alternative to Casgevy and Lyfgenia, particularly for sicker patients with organ dysfunction due to damage from frequent VOCs. The dataset included 42 patients who underwent reduced intensity human leukocyte antigen (HLA)-haploidentical bone marrow transplant (BMT) because they did not have HLA-matched siblings for an allogeneic HSC transplant.

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Only about 8%-14% of SCD patients have an HLA-matched sibling, so a haploidentical BMT may be a potentially curative alternative to allogeneic HSC with a relatively low price tag of $200,000 to $400,000, but it comes with a slight risk of graft versus host disease (GvHD), which was not observed in clinical trials of Casgevy and Lyfgenia.

Sickle Cell Drug Development Gains Momentum Across Disease Spectrum

By Mandy Jackson

15 Dec 2023
The recent ASH meeting began with US FDA approvals of the first genetic medicines for sickle cell disease, but doctors and biopharma companies still see a need for new oral therapies and other options.

Read the full article here

"In terms of scaling this up to the epicenter of sickle cell disease, I think with haplo transplant, it actually offers the best option, because if you really look at Sub-Saharan Africa, most families have two, three, four children and they have very extensive extended family, so getting a [haploidentical] match should be easier," Kassim said during the 11 December session about the impact of new SCD therapies. "The question then becomes how can we custom design this approach to make it safe and scalable in low- to middle-income countries?"

He noted that haploidentical BMTs are being done in countries such as Armenia, Turkey and India, so it may be possible to provide the procedures in Sub-Saharan Africa.

In the same ASH session, John Tisdale from the Cellular and Molecular Therapies Branch at NHLBI pointed out that blood supplies needed for haploidentical BMTs and administration of genetic medicines for SCD may be a challenge in Sub-Saharan Africa, given the lack of blood banks relative to the US.

But in terms of expanding potentially curative treatments for SCD to patients with more advanced disease, Tisdale noted that haploidentical BMT may be a good option for patients with organ dysfunction, since busulfan used as a conditioning agent in Casgevy and Lyfgenia treatment regimens is contraindicated in patients with organ damage. Also, he noted that clinical trials for both medicines excluded patients with a history of stroke, but stroke is a major indicator for HSC transplants.

"It's going to be, I think, an interesting experience for physicians to figure out how they're going to place [Casgevy] in the treatment landscape and we're really excited to at least have that discussion with another treatment option," Vertex's Hobbs said. "Particularly, the thing about allo transplant is that patients have to have a donor and we know that a lot of these patients don't have a donor. And so, the other place that this really makes a difference is for those patients who don't have a donor to even consider transplant, in addition to another option for

even those who do, because there are pros and cons of the different types of approaches."

Chronic Therapy Still Most Likely Treatment Option

However, even with the curative potential of transplants and the two approved genetic medicines, given the cost and complexity of those one-time treatments, it is likely that they will be reserved for SCD patients with the highest disease burden. Most patients will continue to receive hydroxyurea and other oral or injectable medicines administered chronically.

Agios Pharmaceuticals, Inc. CEO Brian Goff noted in an interview with *Scrip* that SCD patients have to navigate a lot of complicated factors in determining whether to move forward with a transplant, gene therapy or gene editing treatment. "Our goal is, with Pyrukynd, to keep that burden of decision making very, very low," Goff said. "So, have a great product profile, have oral therapy that is simple to use, keep the bar low and let the patients navigate through that first."

Pyrukynd (mitapivat) is a pyruvate kinase (PK) activator approved in the US for PK deficiency that is in Phase III for alpha- and beta-thalassemia as well as SCD, with pivotal data due in 2024 for thalassemia and 2025 for SCD. Phase II results presented at ASH from the ongoing Phase II/III trial in SCD showed that the drug increased hemoglobin levels and decreased VOCs. (Also see "*With Sickle Cell Results For Pyrukynd, Agios Enters Increasingly Competitive Market*" - Scrip, 26 Jun, 2023.)

"For our profile, the best aspect is that this is a small molecule, it's oral therapy, which means we can strive for ubiquity around the world," Goff said. However, he added that Agios is looking for a partner with a larger global footprint to commercialize the drug outside of the US.