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Evaluating Gene Therapy for Sickle Cell Disease: Advantages and Barriers

Ryan Quigley:
This is *Project Oncology* on ReachMD. I'm Ryan Quigley with ReachMD, and joining me to discuss advances in gene therapy for sickle cell disease is Dr. David Jacobsohn. He's the Division Chief of the Blood and Marrow Transplantation Program at Children's National Hospital and Full Professor of Pediatrics at the George Washington University in Washington, DC.

Dr. Jacobsohn, thanks for being here today.

Dr. Jacobsohn:
Oh, it's great for me to be joining you all today.

Ryan Quigley:
So, Dr. Jacobsohn, to set the stage, how do you see developments in gene therapy changing the treatment landscape for sickle cell disease?

Dr. Jacobsohn:
There's been a lot of newer therapies in the gene therapy landscape for sickle cell disease. We have two approved products in the last few years, and we're all learning how to use them. What are some of the positives? What are some of the limitations? And, in general, this is an evolving field. I do think that over time it will change many lives of patients with sickle cell disease.

Ryan Quigley:
And with that in mind, could you walk us through the three main strategies being used in gene therapy—gene addition, gene editing and fetal hemoglobin induction—and how they differ?

Dr. Jacobsohn:
Sure. Let's start with fetal hemoglobin induction. This is a CRISPR CAS 9-based gene therapy. It's really interesting. They get the CRISPR CAS 9 into the stem cell using electroporation, and then the CRISPR CAS 9 basically targets and reduces the expression of the BCL11 A gene in patients with sickle cell disease. And what happens is that this reduction in BCL11A eventually leads to a much higher production of fetal hemoglobin. So if you remember your drugs like hydroxyurea—that cause an increase in hemoglobin F and therefore reduce symptoms of sickle cell disease—this causes a much higher increase of fetal hemoglobin and more reduction of symptoms. So patients after the treatment will end up with a fetal hemoglobin of about 40 or 50 percent and a much higher total hemoglobin.

Let me contrast this with a gene addition therapy for sickle cell disease. They get the product into the stem cell using lentivirus, and this involves adding a modified beta globin gene into the cells. So after the treatment, you end up with a higher total hemoglobin, and part of the total hemoglobin is coming from this modified beta globin gene, and all of this results in a reduction or elimination of the symptoms of sickle cell disease.

Ryan Quigley:
Now, how did these approaches compare to hematopoietic stem cell transplantation in terms of safety and efficacy?

Dr. Jacobsohn:
All of the gene therapy approaches require high-dose chemotherapy, so that is similar to a lot of bone marrow transplantation approaches. In fact, some of the gene therapies require a higher amount of chemotherapy, leading to potentially more nausea and

vomiting, mucositis, potentially more veno-occlusive disease, and possibly a higher incidence of infertility. Where it differs significantly from bone marrow transplant is that because you are using your own stem cells, there is no risk of rejection, and there is no risk of graft-versus-host disease, which we often see with bone marrow transplant. So there's no need to be on prolonged immunosuppression, and because of this, the risk of infection is much lower. So we discuss all of these pros and cons with families and patients as they are making the decision between gene therapy and allogeneic bone marrow transplant for cure of sickle cell disease.

Ryan Quigley:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Ryan Quigley with ReachMD, and I'm speaking with Dr. David Jacobsohn about the evolving role of gene therapy in sickle cell disease care.

So, Dr. Jacobsohn, let's shift gears and talk about barriers. How do access and logistical challenges affect the real-world delivery of gene therapy?

Dr. Jacobsohn:
There's currently a number of barriers and logistical issues. In terms of barriers, gene therapy is a costly product, meaning that it can take a few weeks and sometimes more to get the product approved by the insurance company. We have not had any patients denied as of yet by the insurance company, which is really, really good, but it is a potential problem if it takes too long to get the product authorized for the patient. Other logistical issues are the fact that sickle cell patients are quite difficult to collect stem cells from. This is for a variety of reasons. Number one, given their sickle cell, disease their bone marrow niche is probably inflamed and may be more difficult to collect from, and number two, patients with sickle cell disease cannot receive the drug called filgrastim, which is typically used for mobilizing stem cells and collecting stem cells. So we can only use the drug plerixafor, and collections in general because of these reasons are much less efficient, so we get less stem cells per collection than we do, for example, in a beta thalassemia patient that is undergoing the same type of therapy.

Ryan Quigley:
And looking forward, developments like in vivo delivery and CD117-based conditioning seem to be on the horizon. How do you think these approaches could help expand access or improve patient safety?

Dr. Jacobsohn:
Some of the newer developments on the horizon could really revolutionize the care of the sickle cell patients and lead to a logarithmic increase inpatients being treated, so in vivo delivery and not needing ex vivo genetic manipulation obviously would allow us to treat many more patients, as we would not be sending the product for manipulation at the pharmaceutical company, so this could lead to a huge ramp-up. And CD117-based conditioning would also be transformative because if successful, it would allow a patient to receive the genetically modified stem cells but not endure the significant side effects of the high-dose chemotherapy.

Ryan Quigley:
Now, before we wrap up, Dr. Jacobsohn, do you have any final takeaways you'd like to share with our audience about the future of gene therapy for sickle cell disease?

Dr. Jacobsohn:
The future is bright for gene therapy for sickle cell disease. However, there's a lot of logistical challenges involving the need for frequent stem cell collections, and there's issues with the treatment, specifically the high-dose chemotherapy, needed for the gene therapy and some of the long-term side effects. So I think we're just at the beginning, but I do think the ground has been set, and as we see improvements and tweaks in the process, we will see an ability to collect more great patients and to treat more patients safely.

Ryan Quigley:
And that's a great way to round out our discussion. I want to thank my guest, Dr. David Jacobsohn, for joining me to discuss managing sickle cell disease with gene therapy.

Dr. Jacobsohn, it was great having you on the program.

Dr. Jacobsohn:
It was great being here today. I really enjoyed talking about gene therapy for sickle cell disease. This is an area that I'm very passionate about, and we have so many patients at our institution that we are treating with these cutting-edge therapies.

Ryan Quigley:
For ReachMD, I'm Ryan Quigley. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.