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Gene Therapy for Hemoglobinopathies: Focus on Sickle Cell Disease

Dr. Krieger:
Hello, thank you all for joining us today. My name's Beth Krieger. I'm a cellular therapy physician at the Children's Hospital of Richmond at VCU.

Dr. Shah:
And I'm Nirmish Shah. I'm the director of the sickle cell transition program at Duke University, taking care of both kids and adults with sickle cell disease and other hemoglobinopathies.

Dr. Krieger:
The subject of today's program is LYFGENIA. We'll be discussing efficacy, safety, and identifying eligible patients.

Dr. Krieger:
This program is presented on behalf of bluebird bio for U.S. Healthcare Professionals, and the information being presented is consistent with LYFGENIA's full prescribing information.

Dr. Shah and I have been compensated by bluebird bio for our participation.

This is a non-CME program provided and developed by bluebird bio.

This program is intended to provide general information about LYFGENIA and is not medical advice for any particular patient.

I'm a principal investigator in the clinical program.

Dr. Krieger:
Here are the objectives for today's program. We'll be providing an overview of sickle cell disease.

We'll want to understand the clinical data, treatment pathways, and referral processes for LYFGENIA and we'll be discussing considerations for identifying potential patients for LYFGENIA, and most importantly, how to start that conversation.

Dr. Krieger:
Dr. Shah, would you like to get us started? Could you give us a refresher on what practitioners need to know about sickle cell disease?

Dr. Shah:
Thanks, Beth. I think it's always great to start with the basics. Sickle cell disease is a lifelong genetic condition, and it's caused by a single mutation, one small change in the beta globin gene that leads to this production of hemoglobin S and ultimately, the potential for vaso-occlusive episodes.

Now, what we see here is that the body naturally switches from hemoglobin F to hemoglobin A, and it does so, because hemoglobin A is much more efficient at delivering oxygen where it needs to, as an adult. But in this graph here, you see that the alpha gamma, which is hemoglobin F, changes to alpha beta, which is hemoglobin A, and that production occurs shortly after birth, that transition.

…Now, hemoglobin S is a hemoglobin A that now has this mutation, and the hemoglobin S causes the hemoglobin to change its conformation, cause this polymerization of the organization of those hemoglobins, and then cause the cells to be rigid, to be inflexible, and ultimately, lead to a cascade of issues that causes obstruction.

Dr. Shah:

Now, with those obstructions of vaso-occlusive episodes, we have complications that we see with patients that are living sickle cell, and an interesting issue that we need to always recognize is that it's unpredictable, and it has a significant impact.

Now, there are numerous studies to show the impact of the hallmark, being vaso-occlusive episodes, and a number of studies have shown, and one that we have listed here is that shows that 67% of patients have had at least 3 VOEs per year, and those can be triggered by a number of issues and this can include inflammation, stress, hemolysis, and the list is actually quite large, and that then leads to an issue with quality of life.

Now, what you see on the right here is the other additional data points to really emphasize this point, and one is a population of patients that is really, of course, near and dear my heart, the transition patients, which are those that are just moving to adult world, who are 18-30, and you can see 88% of had at least one acute care encounter for vaso-occlusive episode in the past year. The other data point that I think I really have to emphasize is that, on a yearly basis, greater than a third of individuals with sickle cell are re-hospitalized from a VOE.

And so that means that they're coming into the hospital for a VOE, in and of itself being a big issue, but a 1/3 of those patients are coming right back to the hospital and being re-hospitalized. And that really, I think, puts a big emphasis on why we understand that this is a big impact on their life and why we need focus on what we can do to help them get better.

Dr. Krieger:
Wow, Nirmish, those are really impactful statistics. Can you tell us about how you interact with your patients and discuss this?

Dr. Shah:
I think it's a really good point. I think how we interact with our patients and have conversations is really quite important. When I come in to see my patients in clinic, the emphasis is actually not just about vaso-occlusive episodes, but just what is that impact on their lives. So, the fact that they've been in the hospital, the fact that they're recovering from the hospital, or even the time period where they're trying to stay out of the hospital - all that leads to not only the unpredictability but time periods where they're unable to get to school, unable to get to work, and so, I'm really just trying to understand how the disease itself is impacting my patient, and then what are the next steps to understand what else can I do.

…Now, in that sense, I think the other aspect that we need to understand is how is the patient doing now, and how is the patient doing before you saw them a year ago, or two years ago. So, it's the progression of the disease that is also important. So, not only am I asking patients how they're doing today, and what issues and the impact of having pain crises has on their lives, but I'm asking, well, you know, a year ago, compared to a year ago or two, where are we going. What's your trajectory? How can we talk about where we stand today and where we hope to get you in the future?

Dr. Krieger:
Thanks, Nirmish. Now, let's get down to gene therapy. LYFGENIA is a gene therapy indicated for the treatment of patients greater than 12 years of age with sickle cell disease. Let's go over these indications, the mechanism of action, and the indications for therapy

LYFGENIA is the longest-studied approved gene therapy for sickle cell disease. It's a one-time gene addition therapy, without the need for a donor, meaning that we collect stem cells from the patients themselves. It's an option for patients 12 years or older, with a history of vaso-occlusive events.

There is a limitation of use. Following treatment with LYFGENIA, patients with alpha thalassemia trait may experience anemia with erythroid dysplasia that may require chronic RBC transfusions. LYFGENIA has not been studied in patients with more than two alpha globin gene deletions.

So, how is LYFGENIA designed to treat the genetic cause of sickle cell disease?

Like we discussed earlier, sickle cell is caused by a single mutation in the beta globin gene, which leads to the production of hemoglobin S, rather than hemoglobin A.

LYFGENIA is manufactured by collecting autologous stem cells from the patient. They are then manufactured with a lentiviral vector, which carries the beta globin A-T87Q gene.

After production, those stem cells are infused back into the patient and allowed to grow, or engraft, in the bone marrow. They differentiate to produce red cells containing that modified beta globin. Following successful growth, or engraftment, the modified beta globin pairs with the alpha globin to produce that functional hemoglobin A.

Functional hemoglobin A is nearly identical to natural hemoglobin A, and the substitution is designed to inhibit polymerization of hemoglobin S, therefore limiting the sickling of red cells.

Now, let's review the important safety information.

Voiceover:
LYFGENIA has a boxed warning for hematologic malignancy, which has occurred in patients treated with LYFGENIA,

At the time of initial product approval, two patients treated with an earlier version of LYFGENIA using a different manufacturing process and transplant procedure developed acute myeloid leukemia.

One patient with α-thalassemia trait has been diagnosed with myelodysplastic syndrome.

Because of the risk of hematologic malignancies, patients should have lifelong monitoring with a complete blood count with differential at least every 6 months for at least 15 years after treatment with LYFGENIA, and integration site analysis at Months 6, 12, and as warranted.

In the event that a malignancy occurs, contact bluebird bio for reporting and to obtain instructions on collecting samples for testing.

Patients who intend to receive LYFGENIA are encouraged to enroll in the post-marketing long term follow-up study, as available, to assess the long-term safety of LYFGENIA and the risk of malignancies occurring after treatment. The study includes monitoring for clonal expansion.

Delayed platelet engraftment has been observed with LYFGENIA. Bleeding risk is increased prior to platelet engraftment and may continue after engraftment in patients with prolonged thrombocytopenia.

Two patients required more than 100 days to achieve platelet engraftment after LYFGENIA treatment.

Patients should be made aware of the risk of bleeding until platelet recovery has been achieved and you should monitor for thrombocytopenia and bleeding according to standard guidelines.

Additional Important Safety Information will be reviewed later in the presentation.

Dr. Shah:
So, Beth, I think this is a great opportunity to now go through some of the questions that often come up about viral vectors.

Dr. Krieger:
Yeah, absolutely.

Dr. Krieger:
Viral vectors have been studied for decades. The first clinical trials that used viral vectors were back in the 1990s, and they've now become the most common vehicle for FDA-approved gene therapies. The FDA has actually approved greater than 16 products using this viral vector form.

Dr. Shah:
One other specific question that often comes up is specific to the lentiviral vector that LYFGENIA uses. Tell me a little bit more in that regard.

Dr. Krieger:
Absolutely, it's important for patients to understand why we use lentiviral vectors in this therapy. Lentiviral vectors are used for their ability to integrate stably into the genome and to deliver a large volume of genetic material. LYFGENIA uses a traceable lentiviral vector that allows for monitoring of safety signals over time.

Dr. Shah:
And a final question that often comes up, and an important clarification is actually about HIV.

Dr. Krieger:
Absolutely. It's really important for our patients to understand that lentiviral vectors are developed from a modified HIV strain. It's important for them to understand that they do not contain any of the harmful viral genes that could cause the infection. What we do want them to understand is that patients who receive LYFGENIA should be advised to avoid PCR-based assays for HIV screening in the future, as they can result in a false positive test.

Dr. Shah:
So, at this point, let's change gears a little bit. Let's dive a little bit more into the LYFGENIA clinical trial design, the results, and probably a little bit more specifics of the efficacy and safety.

Dr. Shah:
Beth, why don't you give us a little bit more detail?

Dr. Krieger:
LYFGENIA is the longest-studied approved gene therapy for sickle cell disease. The key clinical trial, HGB-206, initiated in February of 2015. After completing the parent study, patients were invited to enroll in the long-term follow-up study, which is a 13-year follow-up safety and efficacy study. Over time, there were improvements made to the cell collection, transplant, and manufacturing process - which resulted in key protocol changes. These protocol changes resulted in three distinct study cohorts for group 1: study 1A, B, and C.

Safety of LYFGENIA was based on all of study 1 and long-term follow-up patients, whereas efficacy was based on study 1C, which used the same collection, transplant and manufacturing process that LYFGENIA uses today. In total, 45 patients had cells collected and LYFGENIA infused. 36 of those 45 patients with LYFGENIA infusions were part of study 1C. The median duration of follow-up for the patients in study 1C was 38 months post-LYFGENIA infusion. For the safety analysis, the median duration of follow-up for individuals treated with LYFGENIA was 42 months post infusion. The primary endpoints were complete resolution of VOEs, while the secondary outcomes include complete resolution of severe VOEs and globin response, and now, let's look at those definitions.

Dr. Krieger:
It's important to note that complete resolution of VOEs and severe VOEs was assessed in a window between 6 and 18-months post infusion with LYFGENIA. VOEs were only counted if they required evaluation at a medical facility and included episodes of acute pain and other complications, including acute chest syndrome.

Severe VOEs were defined as either priapism requiring any level of medical attention or as a VOE requiring hospitalization or multiple visits to an emergency care setting for more than 72 hours and received IV medication at each visit.

Globin response was defined as meeting the criteria shown on the slide for a continuous period of at least six months after infusion.

Dr. Krieger:
So, let's review. In study 1C, 36 patients were infused with LYFGENIA. 32 of those 36 patients had a history of at least four VOEs in the 24 months prior to enrolling on the study

Dr. Krieger:
The primary endpoint of the study was achieved by 88% of patients who had complete resolution of their VOEs.

Secondary endpoint was achieved by 94% of patients with complete resolution of their severe VOEs.

After the primary evaluation period to last follow-up, 4 patients who achieved complete resolution of VOEs experienced VOEs while maintaining their globin response.

Dr. Krieger:
It's important for me to point out, as a pediatric physician, there was no clinically meaningful difference in the efficacy or safety between the adult and pediatric subgroups.

In study 1C, five patients who were of adult age with a history of stroke or vasculopathy and were on chronic transfusion therapy prior to LYFGENIA infusion, who were followed to 44-60 months post therapy, all five of those patients remained transfusion independent, without recurrent stroke.

Dr. Krieger:
Here, we have a visual representation of what we just discussed. This is a swimmer's plot, with each lane representing a patient who was treated with LYFGENIA.

Each one of the dots represents either a VOE or a severe VOE that a patient experienced. On the left, you can see the 24 months prior to enrollment on therapy, and on the right, you can now see the drastic decrease in those events.

Dr. Krieger:
Nirmish, can you tell us more about how this looks for your patients in clinic?

Dr. Shah:
Yeah, I think it's always great to try and bring it back to the patient again, and I'm a big picture person so the swimmer's plot was a great opportunity to look at the differences from the left side versus the right side

Dr. Shah:
So, you can see that visually, but when you're talking to patients and actually have the patient experience, I really start to think about

one of my patients who actually went to the clinical trial and now is post therapy, several years out. He was actually enrolled in the study, because he did have VOEs. But now, he actually doesn't have VOEs, and he's actually able to get to work, and he is able to not miss work due to the VOEs, and I think that that's been a big difference for him. And he's really made sure that he's reminded me how happy he is, because he's able to be at work at and not miss it. Now, on top of that, the other thing that's really interesting, that's great to see, is that his hemoglobin - he comes in, and he gets his labs checked, and we monitor him closely as we should be - his hemoglobin's been consistently stable…

…and so, what we see here, with the data from the trial, is that LYFGENIA maintained a stable and durable hemoglobin A^{T87Q}, T87Q is the level that we can monitor over time. And so, from month six all the way up to month 48, you can see that we have a stable response in both the T87Q (the hemoglobin A) as well as the total hemoglobin, and I think that that's really something good to see.

Dr. Shah:
As Beth mentioned earlier, the safety of LYFGENIA was based on all the patients within study 1 as well as the long-term follow-up study. The table on the left includes grade three or higher adverse reactions, occurring in over 5% of patients. It's important to note that these adverse reactions included AEs associated with myeloablative conditioning.

The most common adverse reaction is listed here, grade three or higher were stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and finally, leukopenia.

I do want to also note that three patients died during the clinical trial, one from sudden cardiac death due to underlying disease, and two from AML, as we previously discussed, were treated with an earlier version of LYFGENIA.

Mobilization and apheresis triggered severe adverse events of sickle cell crisis in six patients. I wanted to call this out, as it reinforces the importance of the hematology team and the transplant team to work together, to partner throughout this process. And finally, as we discussed, participants in the clinical trial, were invited to enroll in a long-term follow-up study for an additional 13 years and will be monitored closely for both efficacy and safety.

Dr. Shah:
It's important to remember that LYFGENIA has a boxed warning for hematologic malignancy, which has occurred in patients treated with LYFGENIA.

Dr. Shah:
At the time of initial product approval, two patients treated with an earlier version of LYFGENIA developed AML. Additionally, one patient has been diagnosed with MDS in study 1C. This patient had dual alpha globin gene deletion, and as a reminder, there's a limitation of use for patients with alpha thalassemia trait.

And as discussed, LYFGENIA has not been studied in patients with more than two alpha globin gene deletions…

… and I think Beth would actually be appreciative of me testing for alpha thalassemia trait as I'm having these conversations with patients, their families, and as I'm collaborating with the QTC center as well.

I finally feel it's important too that we keep in mind that additional hematopoietic stress associated with mobilization, conditioning, and infusion may increase the risk of hematologic malignancies, and that patients with sickle cell disease have a higher risk, at baseline, compared to the general population.

Because of this risk of hematologic malignancies, patients need to be monitored closely, need to have a CBC at least every six months and for at least 15 years after treatment with LYFGENIA, and also have integration site analysis at months 6 and 12 and as warranted thereafter.

Voiceover:
Let's continue our review of the Important Safety Information.

There is a potential risk of neutrophil engraftment failure after treatment with LYFGENIA. Monitor neutrophil counts until engraftment has been achieved. If neutrophil engraftment failure occurs, provide rescue treatment with the back-up collection of CD34+ cells.

There is a potential risk of lentiviral vector-mediated insertional oncogenesis after treatment with LYFGENIA.

Allergic reactions may occur with the infusion of LYFGENIA. The DMSO or dextran 40 in LYFGENIA may cause hypersensitivity reactions, including anaphylaxis.

Additional Important Safety Information will be reviewed later in the presentation.

Dr. Krieger:
So, now that we've gone over the clinical data, let's look at the patient's treatment pathway. Nirmish, could you enlighten us on that?

Dr. Shah:
Absolutely. So, LYFGENIA must be administered at a Qualified Treatment Center, and you can see on this map here, there are a number of sites all around the United States at this point, but that can be updated. There's a nice QR code in the corner here. I encourage the audience to take use of that and look at what's actually active as a QTC around you at the moment that you're looking at this and trying to make a decision for your patient.

Now, in addition to that, the primary hematologist is going to be a huge, important role in trying to identify patients. So, I want the hematologist to understand their role and what the steps are to going through this process

Dr. Shah:
So, the pre-treatment begins with screening and preparation for the mobilization, and so, while preparing for the treatment, you want to confirm that your patient is appropriate for autologous transplant and do this before you initiate the mobilization, apheresis and the conditioning regimen. But once the important decision's actually been made, and you want to initiate LYFGENIA, the next steps are to screen for infectious diseases, prepare the patient that they're going to go through this mobilization and apheresis procedure, and I would absolutely encourage you to talk to your QTC center and talk to the transplanters and coordinate that effort together.

Dr. Shah:
So, here are the steps. There's six important steps I'd like to highlight here. The first we kind of went into, which can happen both at the doctor's office or at the QTC, and that's why that collaborative effort is really important. That's the pretreatment step, but once you've gone through that at the QTC, you're going to have that stem cell mobilization. You're going to take those stem cells. You're going to move them over to have that LYFGENIA production and have that while the patient's waiting at home for that production to complete. And then the patient's going to return. When they return to the QTC center, now they're going to go through the conditioning, the washout, and finally, the infusion. So, step five is that infusion process, but the after part here, step 6, is really important.

Dr. Shah:
So, post-infusion monitoring is a huge aspect, three to six weeks on average here at the QTC center as an inpatient, and then following that, for 15 years, we're going to monitor you very closely as an outpatient. This will be in coordination with the QTC, but not necessarily at the QTC. So, that long-term follow-up is also an important step.

And all these timeframes may vary, and I think that's also a good conversation to have with your patients, because you want to have appropriate expectations by the patients, and their families, to understand what each of these steps are and what timeframes might be expected.

Dr. Shah:
Now that we've gone through the process of getting LYFGENIA, let's turn now to identifying patients for getting LYFGENIA, and for that, I think we need to remember that the hematologist actually plays an active role in making that decision.

Dr. Shah:
Now, LYFGENIA's indicated for the treatment of patients 12 years of age and older with sickle cell disease and a history of VOEs.

What we've highlighted here on one side is the inclusion criteria from the clinical trial. On the other side, we have the exclusion criteria from the clinical trial, and I just wanted to call out a couple points.

The first is just to mention that, in the clinical trial, patients who were included had experienced at least four severe VOEs in the past 24 months, and on the exclusion side, I did want to just highlight that it does have a list that the patient was excluded if they had any history of severe cerebral vasculopathies but Beth knows that that's actually an evolved exclusion criteria.

Dr. Krieger:
That exclusion criteria has evolved over time, and there were five patients included who had a history of severe cerebral vasculopathy.

Dr. Krieger:
So, Nirmish, can you tell us more about what you look for when assessing potential patients for LYFGENIA?

Dr. Shah:
I'm so glad that we continue to root this conversation in our patients. We really need to understand who are potential patients, and for me, I think one big aspect is not just trying to understand how they're doing today, but where did they come from. If we look back, if they were a patient that were doing quite well for a good number of years, and then all of a sudden, has a change in their trajectory, they're

starting to have more vaso-occlusive episodes and they're in more pain crises, where they're coming to the hospital, a change in that is affecting every aspect of their life, of course, and that means it's a patient that I really should be considering for LYFGENIA as a potential patient, because things are changing, and I want to make sure that I try and address that as quickly as possible.

Dr. Krieger:
So, when you are talking to them, how do you describe LYFGENIA to your patients and their families?

Dr. Shah:
So, as the director of the transition program, talking to patients and educating them is a huge part of what I do. I take quite a bit of time, and actually I would advocate, for sure, number one, take several clinic visits to go through the process of educating your patients about something like LYFGENIA. It takes time for them to understand. So, start early and continue the conversation over several clinic visits…

…but the second thing I would do is to try and probably provide as many analogies and examples that you can really bring it down, so that they understand what you're saying. And so, when you're talking about a delivery system, a viral delivery system, use the analogy that you're using a delivery truck. A delivery truck has a bunch of packages inside, and you want make sure that package gets into your house, and so, whatever it is that you can do to get that patient to understand, really, kind of visually what's going on, so that they can make sure that, at the end of the day, they can have an informed decision about what to do next.

Dr. Krieger:
That's wonderful that you take the time to, on multiple visits, talk to your patients about LYFGENIA. One of the challenges I encounter when I see patients for the first time is their understanding of the magnitude of time that's required for this gene therapy. What challenges do you see when talking about LYFGENIA with your patients?

Dr. Shah:
So you reminded me, in regards to the timeline, it's absolutely true that patients don't really understand the timeline, and again, it takes time for them to understand that. I recently had a patient say, "I just graduated from high school in May - I'm going to go on a cruise in June, and I want to have my transplant, my gene therapy in July, so I can go to college in August". It's exciting that they're interested, but you want to give that time to have them understand...

...so the challenge comes down to have them understand not only the scope of the timeline, but the scope of what the intervention means. And so I, of course, will refer them to the transplanters like yourself, Beth, and I will refer them to other hematologists in our clinic to make sure that we're having back and forth conversation, because it's a bidirectional conversation to make sure that this is fair and balanced and making sure that we make the right decision.

Dr. Shah:
Beth, this has been a great conversation. We've gone through a good amount of information. It's been extremely valuable. At this point, let's go ahead and just summarize what we've gone through.

Dr. Shah:
LYFGENIA is the longest studied approved gene therapy for sickle cell disease, and what we've shown is that between 6 and 18 months after LYFGENIA infusion, almost all evaluable patients achieved complete resolution of both VOE and sVOE. Now, there is a box warning for hematologic malignancy, which did occur in patients treated with LYFGENIA, and therefore, we do have the advice to monitor patients closely throughout their therapies and following therapy. If a patient is an appropriate candidate for LYFGENIA, please consider referring them to the nearest QTC…

… and for that, we have, of course, a nice QR code here. I encourage the audience to scan this, to find the nearest QTC. Absolutely, consider discussing LYFGENIA with your patients, educating them. We spent a quite a bit of time about the questions that often come up. So, educate them about gene therapy, and if appropriate, refer them to the nearest QTC. And at the bottom you see, also, a website. We want to make sure we have resources for each and every one of us, mybluebirdsupport.com. You can find patient education resources, and a billing coding guide, a lot of really valuable information.

Voiceover:
Let's complete our review of the Important Safety Information.

Patients should not take prophylactic HIV anti-retroviral medications for at least one month prior to mobilization and until all cycles of apheresis are completed.

There are some long-acting anti-retroviral medications that may require a longer duration of discontinuation for elimination of the medication. If a patient is taking anti-retrovirals for HIV prophylaxis, confirm a negative test for HIV before beginning mobilization and

apheresis.

Patients should not take hydroxyurea for at least 2 months prior to mobilization and until all cycles of apheresis are completed. If hydroxyurea is administered between mobilization and conditioning, discontinue 2 days prior to initiation of conditioning.

Drug interactions between iron chelators, the mobilization process, and the myeloablative conditioning agent must be considered. Iron chelators should be discontinued at least 7 days prior to mobilization or conditioning.

Do not administer myelosuppressive iron chelators for 6 months post-treatment with LYFGENIA and non-myelosuppressive iron chelation should be restarted no sooner than 3 months after treatment. Phlebotomy can be used in lieu of iron chelation, when appropriate.

Patients who have received LYFGENIA are likely to test positive by PCR assays for HIV due to integrated BB305 LVV proviral DNA, resulting in a possible false-positive PCR assay test result for HIV. Therefore, patients who have received LYFGENIA should not be screened for HIV infection with a PCR-based assay.

Voiceover:
The most common adverse reactions grade 3 or higher occurring in at least 20% of patients were stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia.

Three patients died during the LYFGENIA clinical trials. One from sudden cardiac death due to underlying disease and two from AML who were treated with an earlier version of LYFGENIA.

Advise patients of the risks associated with myeloablative conditioning agents, including on pregnancy and fertility.

LYFGENIA should not be administered to women who are pregnant and is not recommended for women who are breastfeeding.

Pregnancy and breastfeeding after LYFGENIA infusion should be discussed with the treating physician.

A negative serum pregnancy test must be confirmed prior to the start of mobilization and re-confirmed prior to conditioning procedures and before LYFGENIA infusion.

Women of childbearing potential and men capable of fathering a child should use an effective method of contraception from start of mobilization through at least 6 months after administration of LYFGENIA.

Advise patients of the options for fertility preservation.

Dr. Krieger:
Thank you for joining us today, Dr. Shah and I hope that you found this to be an effective educational opportunity.