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By McKesson

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ASH 2024:

# Transformations in Hemophilia & Sickle Cell Disease

**In our second installment of takeaways from the American Society of Hematology (ASH) 66th Annual Meeting and Exposition, we're sharing key insights on hemophilia and sickle cell disease, which generated excitement and showcased promising advancements in treatment and patient care.**

## Advancing Gene Therapy in Hemophilia:

### *Progress, Challenges, and Future Directions*

Gene therapy for hemophilia was a major topic of discussion at the ASH meeting, focusing on the potential to reduce bleeding episodes, eliminate prophylaxis, and improve quality of life.[1,2] For both Hemophilia A and B, hematology experts observed that a single infusion from a gene therapy enables the liver to produce clotting factors, with durable responses observed for at least 4 years in Hemophilia A and 8 years in Hemophilia B. Patients report significantly fewer bleeds, with many transitioning off prophylactic treatments and engaging in normal activities previously out of reach.

While these advancements are promising, challenges persist. Discussions highlighted the variability in factor VIII levels in Hemophilia A patients after gene therapy infusion, noting a steady decline over time. Additionally, it was noted that roughly 10% of Hemophilia A gene therapy patients derive no benefit, and approximately 25% return to prophylaxis within 5 years. Safety concerns, including liver inflammation, the potential for hepatocellular carcinoma (HCC), and the unknown long-term risks of insertional mutagenesis, underline the need for ongoing monitoring. Moreover, the high costs—$3-4 million per treatment—pose accessibility barriers.

Despite these challenges, gene therapy outcomes show reduced annual bleed rates and factor infusions for both types of hemophilia, with patients experiencing 7.6 and 5.6 fewer bleeds per year for Hemophilia A and B, respectively. Ultimately, gene therapy represents a monumental step toward a future where managing hemophilia does not dominate daily life. For patients seeking the opportunity to be factor-free with a reduced treatment burden, gene therapy provides a path forward. Tailoring treatment choices to align with each patient's

values and risk tolerance is crucial in this new era of medicine. As these innovations continue to evolve, the ability to personalize care empowers patients to choose the path that best fits their needs.

## Breaking Barriers in Sickle Cell Disease:

### *Expanding Access to Curative Therapies*

Abstracts at the meeting also made waves in sickle cell disease (SCD) and transfusion-dependent beta thalassemia (TDT), where curative treatments remain a pressing need.

- **BEAM-101 in SCD[3]**: Early results from a phase I/II trial showed all patients achieving endogenous fetal hemoglobin (HbF) of over 60% while reducing sickle hemoglobin (HbS) levels below 40%. This novel base-editing approach avoids double-stranded breaks, presenting a differentiated and highly targeted alternative to traditional gene editing.

- **Exagamglogene Autotemcel (Casgevy) in SCD and TDT[4,5]:** In SCD, 93% of evaluable patients were free from vaso-occlusive crises (VOCs) for at least 12 months, with a mean VOC-free duration of 30.9 months, while in TDT, 98% of evaluable patients achieved transfusion independence for at least 12 months, with a mean duration of 34.5 months. These findings highlight the therapy's potential to deliver durable clinical benefits for patients with significant unmet needs.

- **Lovotibeglogene Autotemcel (Lyfgenia) in SCD[6]:** Long-term follow-up data demonstrated that vaso-occlusive episodes (VOEs) and severe VOEs were eliminated or significantly reduced, with roughly 95% of evaluable patients achieving complete resolution of severe VOEs and 87% achieving resolution of VOEs, both sustained for a median of just over 42 months. Notably, all pediatric patients (10/10) achieved complete resolution of both VOEs and severe VOEs. These findings support the therapy's potential to provide durable and effective disease modification for patients with SCD.

However, barriers to access and capacity challenges in curative therapies for SCD emerged as significant themes in panel discussions.[1,7] Systemic challenges, such as limited treatment centers, high costs of therapies, and geographic disparities, continue to hinder widespread adoption. Only a fraction of the 100,000 U.S. patients with SCD receive curative treatments such as stem cell transplants or gene therapy, with many centers performing fewer than 10 procedures annually. Financial barriers also loom large, with costs exceeding $2 million per patient, compounded by geographic and resource disparities, particularly in pediatric care. Patients also face logistical hurdles, including travel, family responsibilities, fertility preservation, and mental health challenges.

Recommendations for addressing these gaps include establishing multidisciplinary teams to provide comprehensive care, developing standardized protocols for eligibility and follow-up, and increasing provider education to identify eligible patients early. Discussions focused on advocacy efforts to expand access to housing, transportation, and wraparound services for patients undergoing therapy. Additionally, mental health support is critical, with a need to optimize the integration of mental health referrals into care frameworks and help patients adjust to life without SCD.

Emerging curative options such as Lyfgenia and Casgevy offer hope but require systemic changes to maximize their potential. Efforts need to center on creating community-driven frameworks to ensure transformative treatments reach all patients in need. The speakers called for comprehensive solutions, blending medical innovation with advocacy and resource development, to bridge the gap in SCD care.

## Overcoming Barriers to Access a Major Theme Across Diseases

As in discussions surrounding CAR T-cell therapies, barriers to access emerged as a key topic in SCD and hemophilia treatments. With the potential to transform outcomes for patients, these therapies require collaboration across the healthcare ecosystem to meet demand.


1. American Society of Hematology. ASH-FDA Joint Symposium. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA.
2. American Society of Hematology. Gene Therapy and Hemophilia A: What Is the Future of Curative Therapy in the Age of Emicizumab? Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA.
3. Gupta A, Sharma A, Frangoul H, et al. Initial Results from the BEACON Clinical Study: A Phase 1/2 Study Evaluating the Safety and Efficacy of a Single Dose of Autologous CD34+ Base Edited Hematopoietic Stem Cells (BEAM-101) in Patients with Sickle Cell Disease with Severe Vaso-Occlusive Crises. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #513.
4. Locatelli F, Lang P, Meisel R, et al. Durable Clinical Benefits with Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #512.
5. Frangoul H, Locatelli F, Sharma A, et al. Durable Clinical Benefits with Exagamglogene Autotemcel for Severe Sickle Cell Disease. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #4954.
6. Rifkin-Zenenberg S, Kanter J, Kinney M, et al. An Update on Lovotibeglogene Autotemcel (Lovo-cel) Clinical Trials for Sickle Cell Disease (SCD) and Analysis of Early Predictors of Response to Lovo-Cel. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA. Abstract #511.
7. American Society of Hematology. Curative Therapies for Sickle Cell Disease: Option for Some but Not Quite All. Presented at: ASH 2024 Annual Meeting & Exposition. December 7-10; San Diego, CA.