This Week in Hemophilia

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Gene Therapy – Where Do the Viral Capsids Go?
Link:
https://ashpublications.org/bloodadvances/article/doi/10.1182/bloodadvances.2024013150/517075/Blood-biodistribution-and-vector-shedding-of

The study explores the biodistribution and vector shedding of valoctocogene roxaparvovec, a gene therapy for severe hemophilia A, in participants from the phase 3 GENEr8-1 trial. Hemophilia A is a genetic disorder where blood doesn't clot properly due to the lack of factor VIII. Traditional treatments involve regular infusions of clotting factor, but gene therapy offers a potential long-term solution by introducing a gene that helps produce factor VIII in the body.

This research is important because it addresses safety concerns about gene therapy, specifically whether the viral vector used to deliver the gene can spread to others (horizontal transmission) or be passed to future generations (germline transmission). The study monitored 134 men who received a single dose of the gene therapy, tracking how the viral DNA distributed in their bodies and how long it took to clear from various body fluids over three years.

The methods included using quantitative PCR (qPCR) to measure total vector DNA in blood, saliva, stool, semen, and urine. Additionally, immunocapture-based qPCR was used to detect encapsidated vector DNA (the active form of the virus that can infect cells) in plasma and semen. Multi-color digital PCR was used to assess the completeness of the vector genomes in blood cells.

Results showed that vector DNA levels peaked within the first week after infusion, highest in blood and followed by other fluids. Over time, the levels declined steadily. Encapsidated vector DNA cleared from plasma and semen within 12 weeks, indicating a low risk of transmission. The study found that the predominant forms of vector DNA in blood transitioned from fragmented to full-length forms, indicating stable gene incorporation in cells.

These findings contribute significantly to the understanding of gene therapy for hemophilia. They suggest that valoctocogene roxaparvovec is safe with minimal risk of transmitting the therapeutic gene to others or to future generations. This supports the potential of gene therapy to provide a long-term solution for managing severe hemophilia A, reducing the need for frequent treatments and improving patients' quality of life.

Arthropathy and miRNAs
Link: https://www.sciencedirect.com/science/article/pii/S0049384824002317

Hemophilic arthropathy (HArt) is a severe joint condition affecting many individuals with hemophilia, leading to chronic pain and disability. The primary problem in this study is identifying reliable biomarkers for early detection and monitoring of HArt. This is crucial because current diagnostic methods, like X-rays and MRIs, often detect joint damage only after significant progression, making early intervention challenging.

The study utilized a two-phase approach: a pilot screening phase and a validation phase. In the screening phase, blood plasma samples from hemophiliacs with and without arthropathy and healthy controls were analyzed to identify microRNAs (miRNAs) that were differentially expressed. miRNAs

are small molecules that help regulate gene expression, and their levels in blood can reflect underlying biological changes, including those associated with diseases. The researchers used quantitative real-time PCR, a technique to measure the levels of specific miRNAs, to pinpoint which miRNAs were linked to joint damage in hemophiliacs.

In the pilot phase, they identified 19 candidate miRNAs. The validation phase further examined these miRNAs in a larger, independent group of patients. They discovered that two miRNAs, miR-208a-3p and miR-524-3p, were significantly underexpressed in patients with advanced arthropathy compared to those without joint damage. This suggests these miRNAs could serve as biomarkers for detecting HArt. Additionally, three other miRNAs, miR-130a-3p, miR-335-5p, and miR-506-3p, showed significant changes in patients with moderate arthropathy, indicating their potential role in the early stages of joint damage.

These findings contribute significantly to the big picture of hemophilia management. By identifying miRNAs that correlate with joint damage, this research opens the door to developing non-invasive blood tests that can detect HArt early, allowing for timely intervention and better management of joint health in hemophiliacs. Early detection is crucial as it can lead to treatments that prevent further joint damage and improve the quality of life for those affected by hemophilia. This study represents a promising step towards integrating miRNA profiling into routine clinical practice for the benefit of hemophilia patients.

Inhibitors After 50 Exposure Days
Link: https://www.sciencedirect.com/science/article/pii/S247503792400150X

In this study, the researchers investigated the development of neutralizing antibodies, known as inhibitors, in patients with severe hemophilia A and B who had been treated with clotting factor concentrates for over 50 exposure days. This is important because these inhibitors can significantly reduce the effectiveness of treatment, making it challenging to manage bleeding episodes in people with hemophilia.

The study was conducted across 97 centers in Europe from 2008 to 2023, collecting data on patients who had received different types of factor concentrates, including plasma-derived and recombinant versions, both standard and extended half-life. The development of inhibitors was monitored, and incidence rates were calculated to compare the risk associated with each type of concentrate.

The findings showed that for severe hemophilia A, the inhibitor rate was low overall, with a significant reduction in risk observed for those treated with extended half-life recombinant factor VIII compared to standard half-life recombinant and plasma-derived versions. However, for severe hemophilia B, the number of patients with inhibitors was too small to make reliable comparisons among different factor IX concentrates.

These results contribute to a better understanding of how different treatments affect the risk of developing inhibitors in hemophilia patients. The lower inhibitor rates with extended half-life recombinant factor VIII suggest that this type of treatment might be a safer option for reducing the chances of inhibitor development. This information is valuable for making informed decisions about the best treatment approaches for individuals with hemophilia, aiming to enhance the quality of life and reduce complications associated with the disease.

Exome Sequencing of Hemophilia and Other Bleeding Disorders
Link: https://www.rpthjournal.org/article/S2475-0379(24)00166-3/fulltext

The study addressed a critical issue in hemophilia and other rare bleeding disorders (RBDs), which are genetic conditions that affect blood clotting. These disorders can lead to excessive bleeding, making even minor injuries potentially dangerous. Understanding the genetic basis of these disorders is crucial for improving diagnosis and treatment.

Researchers conducted a nationwide study in the Netherlands, involving patients from all six Dutch Hemophilia Treatment Centers. The study aimed to identify rare genetic variants linked to RBDs and explore how these genetic differences relate to the severity of bleeding symptoms. To do this, they used targeted exome sequencing, a method that analyzes specific regions of the genome known to be associated with blood clotting and bleeding disorders.

The study included 156 patients, and the researchers collected detailed clinical information, including bleeding history and laboratory measurements of clotting factors. The targeted exome sequencing focused on 156 genes related to thrombosis and hemostasis (the process of blood clotting and stopping bleeding). They identified 214 genetic variants, with 57% of these classified as clearly pathogenic (disease-causing), 19% as likely pathogenic, and 24% as variants of unknown significance (VUS).

One significant finding was that 85% of the patients had genetic variants corresponding to their specific RBDs. Additionally, in some patients, they found multiple genetic variants, suggesting that having more than one genetic alteration could influence the bleeding phenotype. Interestingly, in 15% of patients, no genetic variants were identified that could explain their bleeding disorder, highlighting the complexity of these conditions.

The results showed a strong correlation between the type of genetic variant and the severity of the bleeding disorder. For instance, patients with more severe genetic mutations had lower levels of clotting factors, which explained their increased bleeding tendency. This correlation is crucial as it can guide personalized treatment approaches, ensuring that patients receive therapies tailored to their specific genetic profile.

This study advances our understanding of the genetic underpinnings of RBDs and demonstrates the value of comprehensive genetic testing. By identifying the genetic causes of bleeding disorders, healthcare providers can improve diagnosis, predict disease severity, and tailor treatments more effectively. This personalized approach holds promise for better management and outcomes for patients with hemophilia and other RBDs.

Hemophilia and Quality of Life
Link: https://hqlo.biomedcentral.com/articles/10.1186/s12955-024-02267-6

Hemophilia A is a genetic disorder that prevents blood from clotting properly due to a lack of factor VIII. This leads to excessive bleeding, often into joints, causing chronic pain and joint damage. The study explores how the severity of Hemophilia A affects the quality of life of individuals in Europe. Understanding this relationship is crucial because managing Hemophilia A involves balancing treatment burden with improving life quality.

Researchers used data from the CHESS II study, which included 381 adults with varying severities of Hemophilia A. They employed a generalized linear regression model to analyze the relationship between disease severity and quality of life, measured using the EQ-5D-5L questionnaire. This questionnaire assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, scoring health on a scale from 0 (worst) to 1 (best).

The results revealed that individuals with mild Hemophilia A had a significantly higher quality of life compared to those with severe Hemophilia A. Specifically, those with mild Hemophilia A scored an average of 0.085 higher on the EQ-5D-5L index than those with severe Hemophilia A. Additionally, chronic pain was found to have a substantial negative impact on quality of life, with severe pain reducing the score by an average of 0.332.

These findings highlight the importance of effective pain management and advanced treatments to improve life quality for those with severe Hemophilia A. Emerging therapies like gene therapy, which

can provide long-term clotting factor production and reduce the frequency of treatments, show promise in significantly enhancing the lives of those affected.

By understanding how severity impacts daily living, healthcare providers can better tailor treatments to individual needs, ensuring that those with Hemophilia A receive the most effective care possible. This study underscores the critical need for ongoing research and development of new therapies that not only control bleeding but also enhance overall quality of life for patients.