This Week in Hemophilia

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Invasive Procedures After Gene Therapy in Hemophilia B
Link: https://www.jthjournal.org/article/S1538-7836(24)00552-X/abstract

This study focuses on the impact of etranacogene dezaparvovec gene therapy in people with hemophilia B (HB) who later underwent invasive procedures, such as surgeries or dental work. Hemophilia B is a genetic disorder where the blood doesn't clot properly due to low levels of factor IX (FIX), a protein necessary for normal blood clotting. Typically, people with HB need frequent FIX infusions to prevent excessive bleeding, especially during surgeries. However, gene therapy, like etranacogene dezaparvovec, aims to provide a longer-lasting solution by introducing a modified gene that helps the body produce its own FIX at higher levels.

The problem addressed in the study is how individuals who received this gene therapy manage during surgeries or other invasive procedures. This is important because surgeries can trigger bleeding risks in people with hemophilia, and ensuring safe management of these procedures post-gene therapy is critical.

The study analyzed data from participants in two clinical trials who had received the gene therapy and then underwent invasive procedures within two to three years post-treatment. Researchers collected information on the participants' FIX levels before the procedures, the use of additional FIX infusions during the procedures, and whether there were any postoperative bleeding incidents.

The results were encouraging. In most cases, participants had FIX levels high enough to perform minor surgeries or dental procedures without the need for additional FIX infusions. Major surgeries required some additional FIX, but in much smaller amounts and for shorter durations than what would be typical for people without gene therapy. Notably, there were very few cases of postoperative bleeding, and no severe complications like FIX inhibitor development or blood clots were observed.

These findings are significant for the hemophilia community. They suggest that gene therapy could significantly reduce the need for FIX infusions around surgeries, making life easier and safer for people with hemophilia B. This could lead to fewer medical interventions and a better overall quality of life, especially during critical situations like surgery.

Genetics of Inhibitor Development
Link: https://www.sciencedirect.com/science/article/abs/pii/S1473050224001733

This study examines the relationship between genetic mutations and the development of inhibitors in patients with severe Hemophilia A (HA). Hemophilia A is a genetic disorder caused by a deficiency of clotting Factor VIII (FVIII), which can result in frequent and severe bleeding episodes. One of the biggest challenges for individuals with severe HA is the potential development of inhibitors—antibodies that neutralize the effect of FVIII treatment. This makes managing bleeding episodes much harder and can lead to increased complications and reduced quality of life.

The study was conducted on 480 patients, analyzing genetic profiles to understand why some develop inhibitors while others do not. Researchers focused on specific mutations, particularly an inversion in a part of the gene called intron-22 (Inv-22), which is found in about 41.5% of these patients. They collected demographic and clinical data over a 23-year period to assess patterns in

inhibitor development. They used advanced techniques like inverse-shifting PCR and Sanger sequencing to identify genetic mutations and evaluate their association with inhibitor formation.

Results revealed that the presence of the Inv-22 mutation, a family history of inhibitors, and a history of intense Factor VIII treatments were strongly associated with a higher risk of inhibitor development. Among those who developed inhibitors, 73.6% were classified as having a high-titer, meaning their antibodies were particularly effective at neutralizing FVIII. This connection between genetic factors and inhibitor risk helps explain why some patients are more vulnerable than others.

In the broader context of hemophilia, these findings are essential. By identifying which patients are at higher risk of developing inhibitors, doctors can tailor treatment strategies more effectively. It also highlights the importance of genetic testing in early diagnosis and management planning. This study helps to improve our understanding of hemophilia treatment challenges and contributes to developing more personalized, preventative care approaches for patients with severe Hemophilia A.

Joint Health in Hemophilia
Link: https://bmjopen.bmj.com/content/14/9/e082204

This study focuses on joint health, pain, and quality of life in people with hemophilia A, a bleeding disorder where the blood doesn't clot properly. Patients with moderate to severe forms of hemophilia A are especially prone to joint damage because of repeated bleeding into the joints, known as hemarthrosis. Over time, these joint bleeds can lead to a condition called hemophilic arthropathy, which is a form of arthritis specific to people with hemophilia. The study is important because even though many people with hemophilia are treated with prophylaxis (preventative clotting factor infusions to reduce bleeding), joint problems still occur frequently, affecting the quality of life and causing chronic pain.

The researchers used surveys to gather real-world data from both patients and their doctors across five European countries. They asked about joint health, pain, and overall well-being in adults with moderate or severe hemophilia A who were on prophylactic treatment. The main focus was to compare those who had hemophilia-affected joints (HAJs) to those who did not.

The results showed that 60% of the 351 patients studied had HAJs, despite being on prophylaxis. People with HAJs reported more pain, needed more pain medication, and had lower overall health-related quality of life than those without HAJs. Specifically, patients with HAJs were more likely to have synovitis (joint inflammation) and arthropathy. Many had already undergone joint surgery, showing the severe impact of these joint issues. The study highlights that while prophylaxis is beneficial, it doesn’t always prevent joint damage or pain.

These findings are significant because they underline the ongoing challenge of managing joint health in people with hemophilia A. Although treatments have improved, there is still a large burden of joint disease that can severely affect daily activities and quality of life. This suggests the need for more effective prevention strategies or better use of current treatments to reduce joint complications in people with hemophilia A.

Gene Therapy vs Standard Treatment for Hemophilia B
Link: https://onlinelibrary.wiley.com/doi/10.1111/hae.15096

The study focuses on the use of etranacogene dezaparvovec (ED), a gene therapy designed for treating moderately severe and severe hemophilia B (HB). Hemophilia B is a genetic disorder where patients lack sufficient clotting factor IX (FIX), which leads to frequent bleeding episodes, especially into joints, causing pain and long-term joint damage. Traditional treatments include regular infusions

of FIX, but these therapies, though helpful, are not curative and still leave patients vulnerable to spontaneous bleeds and other complications.

The importance of this research lies in exploring whether gene therapy with ED offers better outcomes than current extended half-life recombinant factor IX (rFIX) therapies. These treatments have improved patient care, but unmet needs remain, especially the hope for a more permanent solution. ED aims to offer a potential one-time gene therapy that can modify the disease, significantly reducing or even eliminating the need for regular FIX infusions.

The study utilized multi-criteria decision analysis (MCDA), which is a structured way to evaluate treatments based on various factors, not just efficacy and safety. Experts rated ED on criteria such as effectiveness, patient quality of life, safety, costs, and the quality of evidence. They compared ED to the current leading treatments: rIXFc, rIX-FP, and N9-GP.

Results showed that experts rated ED as more effective than these alternatives, particularly because of its potential to improve the patient's quality of life by reducing bleeding and the need for frequent treatments. However, safety concerns were raised, especially around potential liver toxicity, which would require ongoing monitoring and could impact long-term use. Despite these concerns, experts agreed that ED could lead to cost savings over time by reducing the need for continuous treatment with FIX.

In the bigger picture of hemophilia treatment, ED represents a promising step toward a more sustainable and effective therapy. While it's not without its uncertainties—particularly regarding long-term safety—it could eventually transform how hemophilia B is managed, moving closer to a potential cure.