This Week in Hemophilia

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From Emicizumab to Gene Therapy

Link: https://onlinelibrary.wiley.com/doi/10.1111/hae.15086

The study discusses the transition of a patient with severe hemophilia A from emicizumab prophylaxis to a novel gene therapy called valoctocogene roxaparvovec. Hemophilia A is a genetic disorder where the blood doesn't clot properly due to a lack of factor VIII (FVIII), leading to excessive bleeding. Managing this condition often requires regular injections of FVIII or treatments like emicizumab, which mimics FVIII to prevent bleeding. However, these treatments can be burdensome, requiring frequent injections.

Valoctocogene roxaparvovec represents a breakthrough because it involves a one-time gene therapy that aims to correct the underlying genetic issue by introducing a functional copy of the FVIII gene directly into the liver cells, allowing the body to produce FVIII on its own. The importance of this study lies in exploring how to safely transition patients from the established emicizumab treatment to this new gene therapy, ensuring they remain protected from bleeding during the switch.

The study's approach involved transitioning a patient without a washout period, meaning they did not stop emicizumab before starting the gene therapy. This was possible because emicizumab has a long half-life, meaning it stays in the body at protective levels for several weeks even after stopping the injections. The patient, who had been managing his condition with emicizumab since 2021, successfully switched to the gene therapy without any significant issues. His FVIII levels significantly increased after the gene therapy, reducing the need for ongoing prophylactic treatment and showing no bleeding events in the following five months.

This real-world experience contributes to the broader understanding of how gene therapy can be integrated into the treatment of hemophilia A. It shows that transitioning from traditional prophylaxis like emicizumab to gene therapy can be done safely, offering patients a more convenient and potentially more effective long-term solution. This study provides valuable insights for clinicians considering gene therapy for their patients, indicating that such transitions can be managed effectively without compromising the patient's safety or care.

Immune tolerance induction in hemophilia B

Link: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ccr3.9312

This study discusses a significant challenge faced by patients with severe hemophilia B (SHB), a condition where blood doesn't clot properly due to a lack of factor IX (FIX). SHB patients sometimes develop inhibitors—antibodies that attack the FIX treatments meant to help them. This makes managing the condition extremely difficult, especially when these inhibitors lead to severe allergic reactions, including anaphylaxis, when FIX is administered. These complications not only worsen the disease but also limit treatment options and drastically affect the patient's quality of life.

The article presents a case where a young child with SHB and a history of anaphylactic reactions to FIX was treated with a novel approach aimed at inducing immune tolerance—essentially "teaching" the body to accept FIX without launching an immune response. Traditional immune tolerance induction (ITI) methods often involve high doses of FIX and immunosuppressive drugs, which can

have serious side effects and are not always effective. Given the child's severe reactions, the medical team used a more cautious approach. They administered very low and slowly increasing doses of a specialized FIX product with an extended half-life, meaning it stays in the body longer, allowing for less frequent dosing.

The results were promising. The child gradually became tolerant to FIX without needing additional immunosuppressive drugs. Over time, his inhibitor levels dropped, and he no longer experienced allergic reactions to FIX. This approach allowed him to move to a maintenance treatment with FIX, reducing the risk of bleeding and improving his overall quality of life.

This case contributes valuable knowledge to the treatment of hemophilia B, particularly for those who develop inhibitors. It suggests that with careful dosing and the use of extended half-life FIX products, it may be possible to manage such cases without the risks associated with traditional ITI methods. This could pave the way for safer and more effective treatments for other patients facing similar challenges.

How Emicizumab and APCC Interact to Increase Thrombosis in Hemophilia A Patients
Link: https://www.rpthjournal.org/article/S2475-0379(24)00168-7/fulltext

The study tackles an important issue for those with hemophilia A, especially when it comes to managing bleeding episodes. Hemophilia A is a genetic disorder where blood doesn’t clot normally due to a deficiency in factor VIII (FVIII). For patients with inhibitors—antibodies that neutralize FVIII—managing bleeding can become even more complex. Treatments like emicizumab, a new therapy that mimics FVIII, and activated prothrombin complex concentrates (APCC), a commonly used bypassing agent, have been successful. However, when used together, they might increase the risk of dangerous blood clots, known as venous thromboembolic events (VTEs).

The problem this study addresses is the unclear mechanism behind why patients taking both emicizumab and APCC are at higher risk for these clots. The researchers suspected that something might be interfering with the body's natural defenses against clotting, particularly the functions of activated protein C (APC) and antithrombin (AT), both of which help prevent excessive clot formation.

To explore this, the researchers conducted experiments using blood plasma samples. They mixed these samples with emicizumab and various clotting agents, including APCC, and then observed how well APC and AT could still do their job of regulating clot formation. They used a test called a thrombin generation assay to measure how much thrombin—a key protein in blood clotting—was produced in different conditions.

The results were revealing. While AT seemed to function normally, the presence of emicizumab and APCC together made the plasma resistant to the effects of APC. This resistance means that once clotting starts, the body’s usual checks and balances aren't as effective at stopping it, which could lead to the formation of clots.

This discovery is significant for the hemophilia community because it helps explain the previously observed risks associated with combining emicizumab and APCC. Understanding these interactions can lead to better guidelines and safer treatment options for managing hemophilia A, particularly for those with inhibitors. This research highlights the need for careful monitoring and possibly adjusting treatment strategies to minimize the risk of VTEs in these patients.