This Week in Hemophilia

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Subcutaneous FIX Injection?
Link: https://www.sciencedirect.com/science/article/pii/S1538783624004240

Hemophilia B is a genetic disorder where blood doesn't clot properly due to mutations in the factor IX (FIX) gene. This results in prolonged bleeding episodes, which can be life-threatening if they occur in critical areas such as the brain. Current treatments involve regular intravenous (IV) injections of FIX, but these can be challenging and inconvenient for patients, impacting their quality of life.

The study explored a potential new treatment approach using recombinant FIX fusion proteins (rIX-FP) that can be administered subcutaneously (under the skin), rather than through the more invasive IV method. This would make the treatment less cumbersome and more accessible. The researchers focused on two variants of rIX-FP, known as R338L and R338L/E410K, which were expected to have enhanced specific activity. Specific activity refers to the effectiveness of a protein in promoting a biochemical reaction, in this case, blood clotting.

In their methods, the researchers used both in vitro (test tube) and in vivo (live animal) experiments. They tested the FIX activity and pharmacokinetics (how the drug moves and is processed in the body) of these variants in FIX-deficient mice. They also conducted a tail-clip bleeding test to evaluate the hemostatic (bleeding control) efficacy of these variants after IV and subcutaneous administration.

The results showed that both variants had significantly higher specific activity compared to the wildtype (WT) rIX-FP. However, the R338L variant demonstrated a higher FIX activity exposure and comparable efficacy to the WT variant when administered subcutaneously. This variant was able to reduce bleeding time and blood loss in mice with hemophilia B using a lower amount of protein compared to the WT variant.

The study's findings suggest that the R338L variant of rIX-FP is a promising candidate for subcutaneous administration in hemophilia B patients. This could potentially reduce the frequency and invasiveness of treatments, improving patient compliance and quality of life. It represents a significant step towards more convenient and effective management of hemophilia B, aligning with ongoing efforts to enhance therapeutic options for this condition.

Good Results for a Novel Hemophilia A Drug
Link: https://www.nejm.org/doi/full/10.1056/NEJMoa2312611

Hemophilia A is a genetic disorder where blood doesn't clot properly, leading to excessive bleeding even from minor injuries. Standard treatments involve frequent injections of clotting factors, which can be challenging, especially for children. This study focuses on a new treatment, efanesoctocog alfa, aimed at making life easier for children with severe hemophilia A by reducing the frequency of these injections.

The study involved 74 boys under 12 years old who had previously been treated for hemophilia A. They received once-weekly injections of efanesoctocog alfa for a year. The main goal was to see if any developed inhibitors, which are antibodies that can make the treatment less effective. Other goals included measuring how often they had bleeding episodes, the safety of the treatment, and how the drug behaved in their bodies (pharmacokinetics).

The results were promising. No children developed inhibitors, indicating the treatment's effectiveness and safety. Most side effects were mild and not serious. Impressively, many children had no bleeding episodes at all. The average annualized bleeding rate (how often bleeding episodes occurred in a year) was very low. Additionally, the treatment was very effective in stopping bleeds quickly when they did occur, with most bleeding episodes resolving after just one injection.

This new treatment allows for maintaining higher levels of the clotting factor in the blood for longer periods, reducing the number of injections needed. This is significant because frequent injections are burdensome, particularly for children. Efanesoctocog alfa has a longer half-life, meaning it stays active in the body longer than traditional treatments.

In the big picture, this study suggests that efanesoctocog alfa can significantly improve the quality of life for children with severe hemophilia A. By reducing the frequency of injections and effectively preventing bleeding episodes, this treatment can help manage hemophilia more efficiently and comfortably. This advancement represents a significant step towards more manageable and effective long-term treatment options for hemophilia patients.

Making FVIII and von Willebrand Factor Last Longer in Blood
Link: https://ashpublications.org/blood/article/doi/10.1182/blood.2024024055/517007/Aptamer-BT200-blocks-interaction-of-K1405-1408-in

BT200, also known as Rondaptivan pegol, is a PEGylated RNA aptamer, which means it’s a small piece of RNA that has been chemically modified to improve its stability in the bloodstream. It specifically binds to a region on the von Willebrand factor (VWF) protein called the A1 domain. This binding helps prevent the clearance of VWF from the blood, thereby increasing the levels of VWF and factor VIII (FVIII) in the plasma. This is important because VWF and FVIII are crucial for blood clotting, which is especially relevant for individuals with bleeding disorders like hemophilia.

A protein domain is like a specific section of a protein that has a unique structure and function, much like a room within a house that serves a particular purpose. In the context of VWF, the A1 domain is one of these “rooms” that plays a critical role in how VWF interacts with other molecules and cells in the blood.

Platelets are small cell fragments in the blood that are essential for clotting. When you get a cut, platelets gather at the site of injury and stick together to form a plug that helps stop bleeding. They work alongside VWF and FVIII to ensure that blood clotting happens efficiently and effectively.

The study focuses on understanding how BT200 helps to prevent the clearance of VWF from the bloodstream. This is crucial because VWF plays a significant role in blood clotting, and its rapid clearance can lead to bleeding problems, particularly in individuals with hemophilia or von Willebrand disease (VWD).

The researchers hypothesized that BT200 could reduce the clearance of VWF by blocking its interaction with certain receptors on macrophages (a type of white blood cell). They tested this by observing how BT200 affects the binding of VWF to these receptors in various experiments. They used techniques like flow cytometry to measure how well VWF binds to macrophages and specific cell receptors when BT200 is present.

The results showed that BT200 significantly reduced the binding of VWF to macrophages and specific receptors called LRP1 and MGL. By blocking these interactions, BT200 effectively prolonged the presence of VWF in the blood. This finding is significant because it supports the potential use of BT200 as a therapeutic approach to increase VWF and FVIII levels in patients with bleeding disorders, thereby improving their clotting ability and reducing bleeding episodes.

In summary, BT200 appears to be a promising treatment that can help manage bleeding disorders by increasing the levels of crucial clotting factors in the blood, addressing a significant challenge in the treatment of hemophilia and VWD.

Roctavian (Gene Therapy): Results from Clinical Trials
Link:
https://ashpublications.org/bloodadvances/article/doi/10.1182/bloodadvances.2023011847/516942/Roctavian-Gene-Therapy-for-Hemophilia-A

Interesting results about the development and clinical trials of Roctavian, a gene therapy for Hemophilia A (HA). Hemophilia A is a genetic disorder where the blood doesn't clot normally due to a lack of factor VIII (FVIII), leading to excessive bleeding. Traditional treatments involve regular infusions of FVIII or other medications to prevent bleeding episodes, but these require lifelong administration and can still result in joint damage.

Roctavian represents a new treatment approach by using an adeno-associated virus (AAV) to deliver a functional copy of the FVIII gene directly to the patient's liver cells. This gene addition aims to enable the liver to produce FVIII, potentially reducing or eliminating the need for regular infusions.

The clinical trials of Roctavian included both Phase 1/2 and Phase 3 studies. In the Phase 1/2 trial, different doses of the gene therapy were tested to determine the optimal dose that balances safety and effectiveness. Participants were selected based on criteria like a history of FVIII usage, absence of inhibitors against FVIII, and no significant liver disease. The highest dose cohort showed promising results, with some participants achieving FVIII levels in the mild to normal range, significantly reducing their annual bleeding rates. However, there were challenges such as elevated liver enzymes (a sign of liver stress) and the need for immunosuppressive drugs to manage these side effects.

In the larger Phase 3 trial, which led to Roctavian's approval, the results showed a significant reduction in bleeding episodes and a marked improvement in FVIII levels in most participants. However, a consistent decline in FVIII levels over time was observed, which raises questions about the long-term durability of the treatment. Additionally, some participants experienced adverse effects like elevated liver enzymes and required prolonged use of steroids.

Despite these issues, the development of Roctavian is a significant milestone in HA treatment. It demonstrates the potential of gene therapy to provide long-lasting FVIII production, reducing the need for frequent treatments and improving the quality of life for those with HA. Ongoing research aims to address the decline in FVIII levels and improve the safety and efficacy of gene therapies. This breakthrough opens the door for future advancements in gene therapy, offering hope for a more stable and effective treatment for hemophilia and other genetic disorders.

New Technique to Detect FVIII Inhibitors
Link: https://pubmed.ncbi.nlm.nih.gov/38992344/

Inhibitors are antibodies that attack Factor VIII, a protein essential for blood clotting, making it inactive. This can complicate the management of hemophilia, especially since the current methods for detecting these inhibitors, such as the Nijmegen and Bethesda assays, are labor-intensive, time-consuming, and often imprecise, particularly at low inhibitor levels.

To solve this, researchers developed a new rapid, fully automated assay for detecting Factor VIII inhibitors that remains unaffected by the drug emicizumab, commonly used in hemophilia treatment. Emicizumab can interfere with traditional assays, leading to inaccurate results. The new assay utilizes a full-length recombinant Factor VIII (rFVIII) as the target for inhibitors instead of plasma-derived Factor VIII, which binds more quickly and effectively due to the absence of von Willebrand Factor (VWF). This feature reduces the assay time significantly.

The assay operates on an advanced coagulation analyzer, which automates the entire process, including sample preparation and multiple dilution steps, producing results in about 20 minutes. The core principle involves mixing patient plasma with rFVIII, incubating for 10 minutes, and then measuring the remaining FVIII activity using a chromogenic method. The difference in FVIII activity between the patient sample and a reference allows for the calculation of inhibitor levels.

The results of the study showed that this new assay could detect inhibitors with a high degree of sensitivity and specificity. It performed reliably in various conditions and maintained accuracy even in the presence of emicizumab. Additionally, the assay demonstrated excellent reproducibility across different laboratories.

This advancement is significant for the hemophilia community. A faster, more reliable, and automated method to detect inhibitors means better management of hemophilia, as it allows for timely and accurate adjustments in treatment plans. This could lead to improved outcomes and quality of life for patients by reducing bleeding episodes and preventing complications associated with ineffective clotting.

In summary, the new automated Factor VIII inhibitor assay represents a promising development in hemophilia care, offering precise, rapid, and reliable inhibitor detection, crucial for effective patient management and treatment optimization.