

Hemophilia: past, present and future

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Purpose and Overview: Hemophilia A and B are rare X-linked recessive bleeding disorders. Prior to the availability of safe and effective clotting factor concentrates, hemophilia resulted in early mortality from catastrophic bleeding and poor quality of life due to hemophilic arthropathy. The goal of this program is to describe the advances in hemophilia management over the last 50 years, and discuss novel therapies that are easing the burden on patients and paving the way for a possible cure in the future

Educational Objectives: At the conclusion of this lecture, attendees should be able to...

- Understand why hemophilia A and B lead to a bleeding diathesis.
- Understand the concept of prophylaxis and how this has changed the natural history of severe hemophilia.
- Describe strategies for managing inhibitor development.
- Explain the rationale behind novel therapies targeting natural anticoagulants.
- Describe the progress made in gene therapy that may eventually lead to a life-long cure.

This is to acknowledge that Dr. Siayah Rambally has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Rambally will not be discussing off-label uses in her presentation.

Hemophilia: past, present, and future

Overview of Hemophilia A and B

Hemophilia A and B are inherited bleeding disorders resulting from deficiency of clotting factors VIII and IX, respectively. Hemophilia is an X-linked recessive disorder, therefore, females are typically asymptomatic carriers and the disease is passed on from the mother to the son. In some cases females may be symptomatic due to skewed lyonization. There is a wide range of genetic heterogeneity, with >2000 genetic mutations identified in the Factor VIII gene and >1000 mutations in the Factor IX gene. With current molecular diagnostic testing we are able to identify >90% of causative mutations [1]. It is estimated that approximately 30% of cases are the result of de novo mutations, and thus these patients have no family history of a bleeding diathesis [1].

The incidence of Hemophilia A is approximately 1/5,000 males births. Hemophilia B is less common, affecting 1/30,000 male births. There are an estimated 400,000 people living with hemophilia worldwide. There is no predilection for a certain race or ethnicity. [2]

Bleeding manifestations are largely based on the amount of residual clotting factor activity. Severe hemophilia is classified as <1% factor activity, and results in spontaneous joint and muscle bleeds. Intracranial, abdominal, and other soft tissue hemorrhages may also occur. Moderate hemophilia is defined as factor activity between 1-4%, and bleeding manifestations are variable with patients on the lower end of the spectrum having occasional spontaneous bleeds, and all patients having prolonged bleeding after minor trauma or invasive procedures. Mild hemophilia is defined as factor activity between 5-40%, and usually only results in clinical bleeding with major trauma or surgery.

Classification of Hemophilia	Residual Factor activity	Clinical manifestations
Severe	<1%	Spontaneous bleeding into joints and muscles
Mild	1-4%	Variable degree of spontaneous bleeding Prolonged bleeding after minor trauma or surgery
Moderate	5-40%	Bleeding only after major trauma or surgery

Hemophilic Arthropathy

Joints are the most common site of bleeding in hemophilia, accounting for 70-80% of events [2]. Hemophilic arthropathy shares features with both rheumatoid arthritis (inflammation and synovitis) and osteoarthritis (articular cartilage destruction). The most commonly affected joints are the ankles, knees, and elbows. Recurrent bleeding into the joints results in chronic pain, muscle atrophy, and crippling structural deformities.

Iron released from red blood cells within the synovial tissue is toxic, resulting in inflammatory synovitis with hypertrophy of the synovial tissue and recruitment of inflammatory cells and vascular growth factors. Inflammatory cytokines, activated monocytes, matrix metalloproteinases and hydroxyl radicals induce chondrocyte apoptosis. Molecular markers of bone turnover are skewed to favor osteoclastic activity, resulting in subchondral bone destruction. Recruitment of vascular growth factors, including VEGF, lead to neoangiogenesis. These friable vessels are susceptible to re-bleeding, resulting in a vicious cycle with the development of “target joints”. [3].

Treatment of target joints includes synovectomy to remove the friable hypertrophied synovium. This can be accomplished via synoviorthesis, with injection of either a chemical sclerosing agent or radioactive material into the synovial space. If these less invasive measures are not effective, open or arthroscopic surgical synovectomy can be undertaken with a prolonged period of intensive rehabilitation to preserve joint function. Severe cases of chronic hemophilic arthropathy with debilitating pain or functional impairment may require joint replacement.

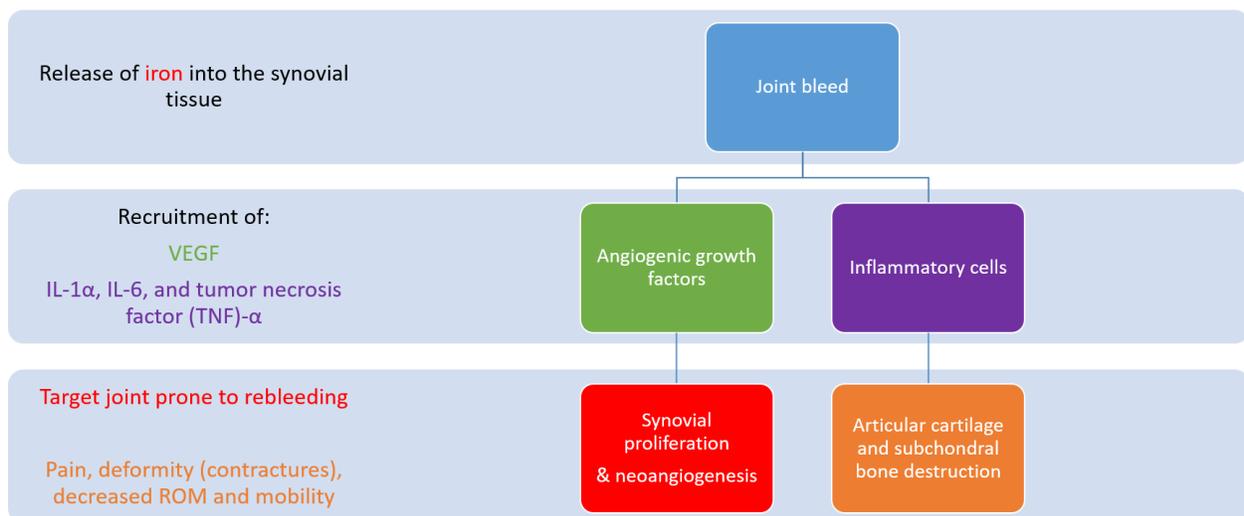


Figure 1: Pathophysiology of hemophilic arthropathy

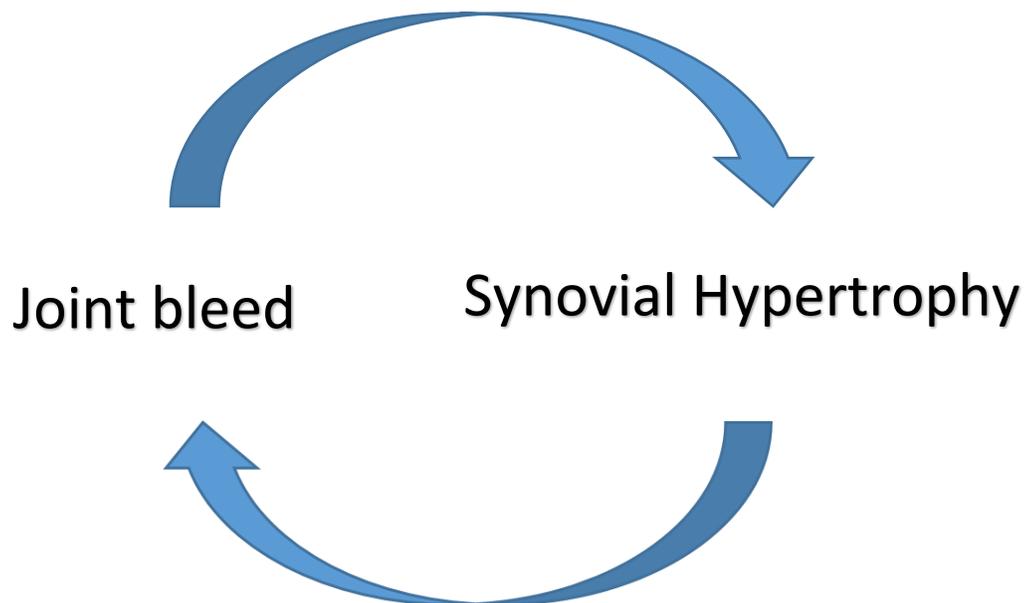


Figure 2: Vicious cycle of hemophilic arthropathy leads to the development of “target joints” that are susceptible to re-bleeding due to friable neovascularization in the hypertrophied synovium.

A Timeline of Discovery and Therapy

In the late 18th century, Otto described “a hemorrhagic disposition existing in certain families” and astutely noted that it was passed from the mother to the son, despite the females being asymptomatic. In 1840, Samuel Lane, a surgeon practicing at St. George’s Hospital Medical School in London, successfully performed the first case of transfusion of whole blood to treat a hemophiliac suffering from post-operative hemorrhage [2].

In 1947, Pavlovsky transfused blood from one hemophiliac to another, leading to normalization of the coagulation defect. This led to the realization that there are 2 types of Hemophilia with deficiencies of different coagulation factors.

In the 1950s, transfusion of fresh frozen plasma was the only available treatment for bleeding events. This required hospitalization and transfusion of large volumes of plasma due to the low concentration of factor in plasma. It was difficult to obtain factor levels >25-30%, and often the risk of volume overload would prohibit adequate treatment. The life expectancy during the 1950s was only 11 years old.

In 1964, Judith Graham discovered a process of obtaining concentrated Factor VIII from plasma [3]. If fresh frozen plasma was thawed slowly at 2-4 degrees Celsius, cryoprecipitate rich in fibrinogen, FVIII, VWF, and FXIII could be isolated after centrifugation. This allowed for hemostatic levels of FVIII activity after administration of smaller volumes. Patients with Hemophilia A were finally able to receive adequate treatment for bleeding events and undergo invasive surgical procedures.

Lyophilized plasma derived factor VIII and IX concentrates became available in the 1970s, allowing for accurate dosing and effective factor replacement at home. This became known as the “golden age of hemophilia”. The Hemophilia Act of 1973 designated federal funding to hemophilia treatment centers in order to provide comprehensive care.

However, this period of hope would soon end in tragedy for many patients. These concentrates were made from plasma that was pooled from thousands of whole blood donations with no virucidal methods in place. In the 1970s, physicians began to notice that it was not uncommon for patients with hemophilia to have elevated liver enzymes. By the early 1980s there was evidence that nearly 100% of previously untreated patients developed hepatitis after they began regular infusions with plasma derived factor concentrates. The etiology of this was not apparent at the time, but over the next decade it would become clear that this was due to a non-A, non-B viral hepatitis that was identified as Hepatitis C in 1989. By the early 1980s, cases of HIV in the hemophilia community were detected. Approximately 50% of the hemophilia community was infected with HIV, leading to increased mortality, social stigmatization and economic burden.

The tragedy of the HIV and hepatitis epidemics in the hemophilia community ignited a flurry of innovation and discovery. In the early 1980s, the Factor VIII and IX genes were cloned. Recombinant DNA technology led to the production of recombinant FVIII and FIX products. Shortly after the completion of the first clinical trials in the 1990s, recombinant factor concentrates were FDA approved.

In addition, the safety of plasma derived products has improved significantly with better donor screening and selection processes, the development of viral inactivation/removal steps, and nucleic acid testing of blood products. Currently, 2 virucidal methods are used in the manufacturing process of factor concentrates, including heating, solvent-detergent methods and nanofiltration. There has not been a reported case of transfusion associated HIV or hepatitis since the early 1990s with the adoption of these new safety measures.

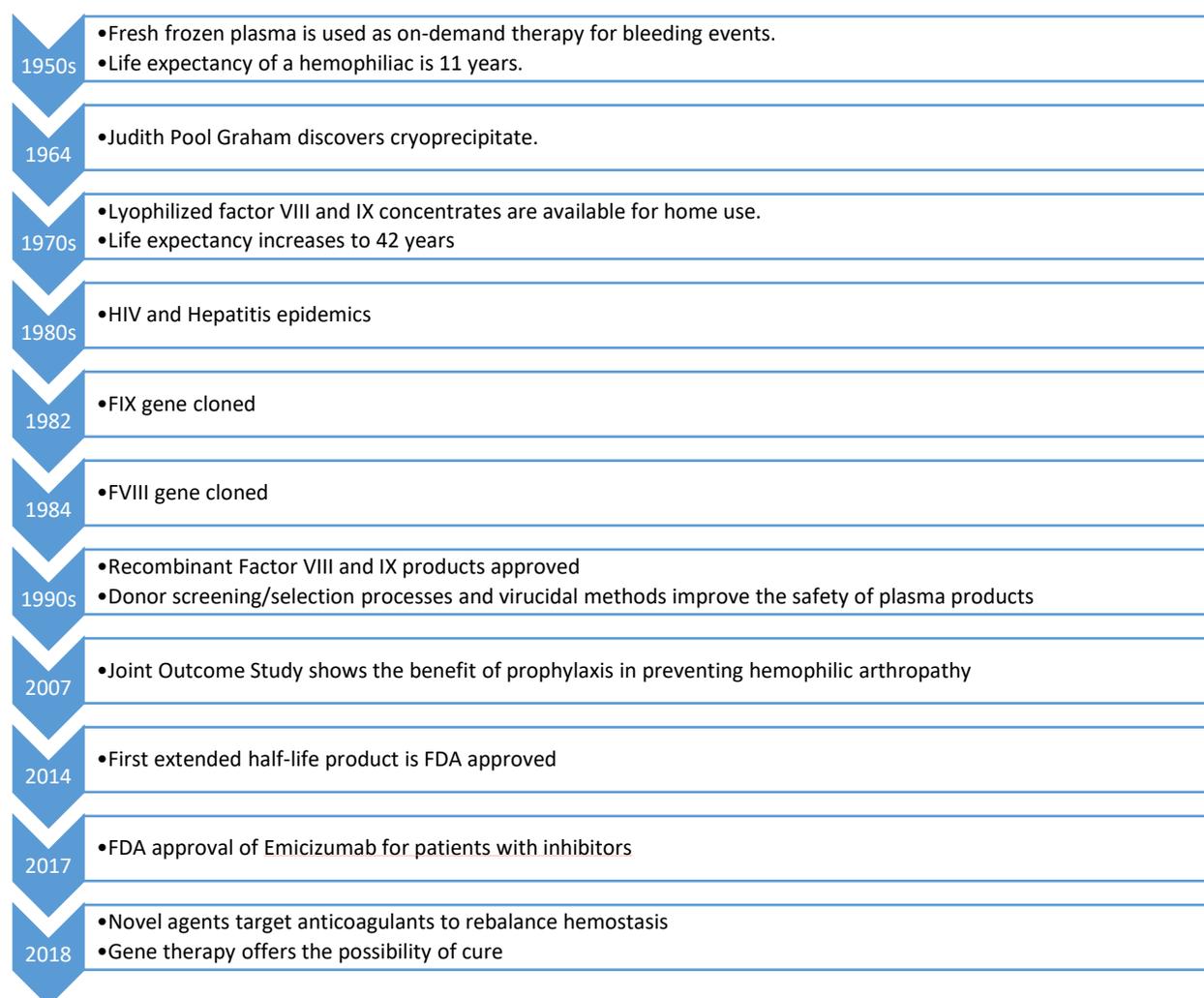


Figure 3: Timeline of hemophilia discovery and management

Modern Treatment of Hemophilia

Primary, Secondary, and Tertiary Prophylaxis

Clinicians observed that patients with moderate hemophilia had less joint damage and better overall quality of life compared to individuals with severe hemophilia. This led to the concept of prophylactic factor replacement to decrease the risk of bleeding and improve joint health. Prophylactic regimens were initiated in Sweden for severe hemophiliacs in the late 1960s. Compared to historical controls, they were able to show that men who started prophylactic factor infusions early in life had a lower incidence of hemophilic arthropathy [6]. In 2007, Manco-Johnson et al. published the Joint Outcome Study, a randomized controlled trial of children <2.5 years of age with baseline normal joints to prophylaxis with recombinant FVIII every other day versus on-demand therapy for bleeding events. At 6 years of age, joint evaluation by MRI revealed the absence of hemophilic arthropathy in 93% of those boys who received prophylaxis versus 55% of those who received on-demand therapy [7]. The ESPRIT

study (Evaluation Study on Prophylaxis: a Randomized Italian Trial) confirmed that prophylaxis in children resulted in less bleeding events, less joint damage on imaging, and improved quality of life [8].

After proving the benefit of prophylaxis in young children with minimal or no baseline joint damage, investigators set out to determine if there is a benefit in adolescents and adults, most of whom already have significant hemophilic arthropathy and target joints. The SPINART trial [9] is a randomized controlled trial of tertiary prophylaxis in males with severe hemophilia A, aged 15-20 years, with established joint damage. Patients on prophylaxis had 94% reduction in bleeding events, improvement in activity level, pain, and quality of life. However, joint damage as assessed by imaging was not significantly different between the 2 groups, indicating that prophylaxis should be started early prior to recurrent joint bleeds to prevent irreversible damage.

Given these data, the current recommendations from the Medical and Scientific Advisory Council of the US National Hemophilia Foundation (MASAC) are to start prophylaxis in all boys before the onset of recurrent bleeding (usually before age 2) to maintain trough levels $>1\%$. For those adolescents and adults who did not receive prophylaxis during childhood, it is recommended to start prophylaxis regardless of pre-existing joint damage.

Despite the proven benefits of prophylaxis in severe hemophilia, adherence remains an issue. Life-long prophylaxis is burdensome, requiring frequent self-infusions. Studies have shown that compliance is best in early childhood when the parent is infusing, but decreases during adolescence and adulthood. Up to 50% of adults abandon prophylaxis. The 2 most important aspects of the patient's ability to maintain adequate prophylaxis are their acceptance of the disease and ability to carry out the demands of self-infusion, maintaining appropriate supplies of factor, communication with the hemophilia team, insurance companies, and pharmacy [10]. Dedicated social workers in hemophilia treatment centers routinely assess psychosocial barriers to compliance, which are greatest in adolescence and early adulthood when patients tend to have a strong desire to be like their peers and are learning how to handle their independence.

Various cost effectiveness analyses have found significant gains in quality adjusted life years for prophylaxis versus on-demand therapy. The cost of prophylaxis, which can be up to several hundred thousand dollars per year, is offset by decrease in health care utilization and the patient's ability to maintain employment and productivity.

Extended Half-life Factor Products:

The usual half-life of Factor VIII is $\sim 8-12$ hours. Therefore, prophylactic factor infusions are required 3-4 times weekly to maintain trough levels $>1\%$. The usual half-life for FIX is $\sim 18-20$ hours, thus requiring twice weekly intravenous infusions.

There are now 3 proven techniques to extend the half-life of recombinant factor products: pegylation, fusion to the Fc fragment of IgG1, and albumin fusion.

Polyethylene glycol (PEG) results in a longer circulating half-life of the recombinant factor due to steric hindrance of the hydrophilic polymers surrounding the protein, which decreases proteolytic degradation.

Fusion to the constant region (Fc) on IgG1 utilizes the natural mechanism of the neonatal Fc receptor (FcRn) for prolonging the half-life of proteins. Binding to the FcRn protects the protein from lysosomal degradation by re-directing it toward the plasma membrane and recycling it back into the circulation. This is the same pathway that is responsible for recycling both IgG and albumin, resulting in their long half-lives of 21 days and 19 days respectively.

The first extended half-life product was FDA approved in 2014. These products have increased the half-life of recombinant FIX by ~5 times, thus allowing for dosing once every 7-14 days.

EHL products have not been as successful for FVIII products. The half-life has only been extended by ~1.5 fold, allowing for decreased dosing from every other day to twice weekly. The modest increase in half-life is likely due to the role that von willebrand factor plays in the clearance of factor VIII. VWF circulates with FVIII and protects it from proteolysis. Thus, the recombinant product only affects the half-life of the small amount of “free factor VIII”, while the majority is still cleared by VWF dependent mechanisms.

The extended half-life products allow for less frequent dosing (especially with the FIX product), which could potentially decrease the need for venous access devices and improve compliance. The ability to maintain higher trough levels has led to decreased bleeding episodes and allowance for a more active lifestyle. Finally, >80% of bleeding events can be controlled with a single infusion. There has been no indication that any of these products lead to increased rate of inhibitor development in previously treated patients. [11-15] Studies with previously untreated patients are ongoing.

Adjunctive therapies

Desmopressin (DDAVP)

DDAVP is a synthetic peptide derived from the antidiuretic hormone vasopressin. It releases Factor VIII that is stored in the Weibel-pallade bodies of endothelial cells, and can be helpful in the management of mild bleeding events or low risk invasive procedures for mild or moderate Hemophilia A. Levels of factor VIII activity can be expected to increase up to 3-6 times baseline values. It will not work for severe hemophilia A, as these patients do not produce any Factor VIII. DDAVP is only effective for 3 consecutive days at most due to tachyphylaxis, given the limited supply of FVIII stored in endothelial cells. Hyponatremia is a potential side effects, so water intake should be limited during its use.

Antifibrinolytic agents

Antifibrinolytic agents are useful in both Hemophilia A and B to help stabilize the fibrin clot. This can be especially helpful for mucosal bleeding or dental procedures as there is a high degree of endogenous fibrinolytic activity in the oropharynx. The use of antifibrinolytic agents should be avoided in the case of hematuria given the risk of ureteral obstruction and subsequent renal failure.

Inhibitors

The most severe complication of hemophilia in the current age is the development of neutralizing alloantibodies to the deficient factor. The development of inhibitors renders coagulation factor concentrate ineffective, and leads to increased bleeding risk, functional impairment due to hemophilic arthropathy, decreased quality of life, and significant increase in healthcare costs. Data collected by the Centers for Disease Control and Prevention found the odds ratio of death to be 70% higher in inhibitor

patients compared to those without an inhibitor in multivariable analysis ($p < 0.01$), and these deaths were significantly more likely to be attributed to bleeding complications [16].

Inhibitors develop in 30-35% of patients severe Hemophilia A, most often in young patients within the first 50 exposure days. It is less common in mild or moderate hemophilia A (5-10%), and usually occurs after intensive factor replacement therapy for a traumatic bleed or surgery. Inhibitors are rare in Hemophilia B, affecting approximately 2-5% of patients, possibly due to the more frequent expression of the mutant Factor IX protein [1].

There are patient-related and treatment-related risk factors for developing an inhibitor. The strongest predictor of inhibitor development is the type of genetic mutation, with null mutations (such as large deletions and nonsense mutations) portending a greater risk than missense mutations.

In 2016, the first randomized controlled trial comparing plasma derived versus recombinant factor concentrates in previously untreated patients with severe hemophilia A was reported in the New England Journal of Medicine. The SIPPET study (Survey of Inhibitors in Plasma-Products Exposed Toddlers) [17] found an 87% risk reduction in inhibitor formation in those subjects receiving plasma derived products. The reduced immunogenicity of plasma derived factor concentrates is thought to be secondary to protective immunomodulatory effects of von willebrand factor, which may decrease uptake of FVIII by antigen producing cells [18].

Risk Factors for Inhibitor Formation	
Patient related factors	Treatment related factors
Type of gene mutation	Greatest risk in the first 50 exposure days
Hemophilia severity (severe >> mild or moderate)	Intensity of first exposure to factor (high dose, intensive treatment increase risk 2 fold)
Race (Hispanics and African Americans > Caucasians)	Factor product source (plasma derived vs recombinant)
Family history	

Inhibitors are measured in Bethesda Units (BU), with 1 BU being the amount of inhibitor required to neutralize 50% of the coagulation factor activity. High titer inhibitors are defined as >5 BU. Low titer inhibitors have a higher chance of spontaneously resolving, and in case of bleeds may be overcome by administering high doses of factor concentrate to saturate the inhibitor and provide adequate hemostasis. The management of bleeding episodes in patients with high titer inhibitors is more complicated as they will not respond to factor replacement. Treatment of bleeding events requires the use of “bypassing agents”, either recombinant activated Factor VII (rFVIIa) or plasma derived activated prothrombin complex concentrate (aPCC). rFVIIa directly activates FX on the platelet surface, thus “bypassing” the tenase complex and allowing for thrombin generation. aPCC contains plasma derived vitamin K dependent clotting factors (II, VII, IX, and X) in both zymogen and activated states. The addition of activated factors that are downstream of the coagulation defect allow for thrombin generation. A randomized controlled trial found the efficacy of rFVIIa to be equivalent to aPCC, with control of ~80% of bleeding events [19]. However, the efficacy of the bypassing agents are suboptimal and unpredictable compared to factor concentrates. In addition, there are no laboratory tests that are

validated to monitor the efficacy or safety of these agents. Thrombotic complications are a rare adverse event with the use of bypassing agents; the risk increases with higher doses, longer duration of treatment, use of both agents concurrently, and the presence of other thrombotic risk factors such as immobility, surgery, and active infection. Finally, the short half-lives of these agents requires frequent intravenous infusions (every 2 hours for rFVIIa and every 8 hours for aPCC).

There is now data from 3 randomized controlled trials supporting prophylactic use of bypassing agents to prevent bleeding in hemophiliacs with high responding inhibitors and frequent bleeds, with a reduction in bleeding events of 45%–74% [20-22]. However, this requires frequent infusions and is on the order of 5-10 times more costly than routine prophylaxis in non-inhibitor patients.

Given the suboptimal efficacy, high cost, and inconvenience of the bypassing agents, the goal is to eradicate the inhibitor. Immune tolerance induction (ITI) involves the infusion of high frequent doses of factor replacement to restore normal pharmacokinetics and efficacy with regular factor concentrate replacement. ITI is successful in eradicating the inhibitor in up to 60-80% of hemophilia A patients [20]. Those rare patients with Hemophilia B who develop inhibitors have less chance of responding to immune tolerance induction and have difficulty tolerating this treatment due to anaphylactic reactions that occur in approximately half of patients upon exposure to factor IX containing product. The etiology of these allergic reactions remains unclear, but these allergic reactions seem to be more common in those patients with large deletions and missense mutations [1].

Factors associated with improved response to ITI
Historic peak inhibitor titer <200 BU/ml
Inhibitor titer <10 BU/ml prior to initiation of ITI
Peak inhibitor titer (due to anamnestic response) while receiving ITI <200 BU/ml
<5 years between development of inhibitor and initiation of ITI
Interruption in ITI < 2 weeks

Novel Therapies

Novel therapies in the pipeline for hemophilia address barriers to standard factor prophylaxis by providing more convenient modes of administration with longer half-lives. Most importantly, these novel therapies are effective in patients with inhibitors and do not have the potential to promote the development of inhibitors. Current strategies include factor mimetics, targeting the natural anticoagulants to rebalance hemostasis, and gene therapy.

Emicizumab

Emicizumab is a recombinant, humanized, bispecific monoclonal antibody that bridges activated factor IX and factor X, thereby mimicking the function of the missing factor VIII. Advantages over standard factor replacement include subcutaneous administration, long half-life of 4-5 weeks, efficacy in patients with inhibitors, and lack of potential for alloantibody formation. The Haven-1 trial, a phase 3 open label randomized controlled trial in Hemophilia A with high titer inhibitors, showed an 87% reduction in bleeding events with Emicizumab compared to on-demand therapy with bypassing agents ($p < 0.001$) [24]. 63% of patients receiving the bispecific antibody had no bleeds, compared to only 6% in the control

group. In an intra-individual assessment of patients receiving Emicizumab who were on prior bypassing agent prophylaxis, there was a 79% reduction in annual bleeding events ($0 < 0.001$). There were 5 thrombotic severe adverse events (2 thromboses and 3 thrombotic microangiopathies); all of these patients received concurrent high doses of activated prothrombin complex concentrate (>100 U/kg) for >24 hours to treat a breakthrough bleed. No patients receiving Emicizumab alone or with rFVIIa had a thrombotic event. It is thought that accumulation of activated and non-activated FIX and FX in aPCC leads to synergistic thrombin generation while receiving Emicizumab. Therefore, aPCC should be avoided while on Emicizumab and breakthrough bleeds should be treated with rVIIa. The FDA approved Emicizumab for patients with severe hemophilia A and inhibitors in November 2017.

The HAVEN-3 study for patients with severe Hemophilia without inhibitors was recently reported in the New England Journal of Medicine [25]. Not surprisingly, this showed $>95\%$ reduction in annualized bleeding events compared to on-demand dosing of FVIII concentrate. Over 55% of subjects on Emicizumab had no bleeding events, compared to 0% of patients treated with on-demand factor replacement. Patients who were previously on Factor VIII prophylaxis were treated with weekly Emicizumab and an intraindividual comparison of annualized bleeding rates showed a 68% reduction during the time that they were on Emicizumab versus standard factor prophylaxis ($p < 0.001$). There were no thrombotic complications, even with concomitant administration of Factor VIII for breakthrough bleeds. This is thought to be due to the fact that endogenous Factor VIII has a higher binding capacity to Factor IXa and X, and thereby competes with Emicizumab rather than resulting in synergistic thrombin generation. Emicizumab is currently undergoing review by the FDA for use in non-inhibitor patients, and will likely revolutionize the treatment of hemophilia A.

Targeting Antithrombin with small interfering RNA (siRNA) technology

Antithrombin is a natural anticoagulant produced by the liver that inhibits thrombin and other circulating activated coagulation factors (IXa, Xa, XIa). Endothelial cells contain proteoglycans on the external membrane surfaces which enhance the anticoagulant effect of antithrombin. Similarly, heparin takes advantage of the antithrombotic properties of AT by enhancing its action 1000-4000 fold for therapeutic purposes of anticoagulation in clinical practice.

Antithrombin deficiency is a hypercoagulable state that can lead to pathologic thrombosis. Clinical data suggest that hemophilia patients with co-inherited antithrombin deficiency have a decreased tendency toward bleeding. This observation led to the hypothesis that decreasing levels of this natural anticoagulant in hemophilia patients can be used as a therapeutic modality. Fitusiran is a small interfering RNA that inhibits posttranscriptional antithrombin production by the liver. [26] In a phase 1 dose escalation study in Hemophilia A and B patients without inhibitors, monthly doses of Fitusiran resulted in a dose-dependent reduction in antithrombin activity with corresponding increases in thrombin generation. A reduction in the antithrombin level by more than 75% from baseline resulted in median peak thrombin values at the lower end of the range observed in healthy volunteers [27]. A post-hoc analysis of efficacy revealed a lower bleeding frequency compared to bleeding rates in individuals in the 6 months prior to study initiation, but it was not powered to detect this difference and we must keep in mind that this was a small trial with only 25 hemophilia patients enrolled. There are ongoing phase 3 studies in Hemophilia A and B with and without inhibitors to assess efficacy and safety.

Targeting Tissue Factor Pathway Inhibitor

Tissue factor pathway inhibitor (TFPI) is a kunitz-type serine protease produced by endothelial cells, megakaryocytes, and smooth muscles cells. It regulates the coagulation pathway by inhibiting the TF/FVIIa complex through a Factor Xa dependent feedback mechanism. Concizumab is a humanized monoclonal antibody that binds to the K2 domain of TFPI to prevent its anticoagulant activity. In a phase 1b study, a dose-dependent decrease in TFPI level and concomitant increase in thrombin generation was reported [28]. There are ongoing phase 2 studies evaluating the efficacy and safety of this once monthly subcutaneous injection for treatment of both hemophilia A and B, with and without inhibitors.

Gene Therapy

Hemophilia is an ideal disease for gene therapy given that all clinical manifestations are attributable to the deficiency of a single gene product and small increases in production of the deficient protein can lead to significant clinical improvement. The current approach to gene therapy in hemophilia involves gene delivery to hepatocytes via viral vectors.

In 2009, an Italian group reported a case of a 23 year old man with an unprovoked lower extremity DVT and Factor IX activity levels that were elevated 8 fold above normal values. He was found to have an activating mutation in the Factor IX gene caused by substitution of leucine for arginine at position 338. This is currently known as Factor IX Padua, after the hospital in which he was treated [29]. This knowledge has been used to manufacture a highly active Factor IX transgene that was transduced into hepatocytes of 10 severe hemophilia B patients via adeno-associated viral vector [30]. Results after an average of 49 weeks follow up are very encouraging with average vector derived factor IX activity of 33.7%. All patients were able to stop prophylaxis, and 9/10 patients had no further bleeding events despite a high prevalence of target joints in the study population. The estimated cost savings due to reduced consumption of factor IX concentrate was \$3.6 million. Only 2 patients had transient elevations of transaminases, thought to be secondary to T cell mediated immune response against the viral capsid, which resolved with a short course of steroids. These 2 patients were able to maintain sustained levels of Factor IX activity once steroids were discontinued.

Gene therapy is more complex for Hemophilia A due to the large size of the Factor VIII gene. A recent study by Rangarajan et al, reported in the NEJM in 12/2017, reported results of a single infusion of a codon-optimized adeno-associated virus serotype 5 (AAV5) vector encoding a B-domain–deleted human factor VIII (AAV5-hFVIII-SQ) into 9 patients with severe hemophilia A. 6/7 patients in the high dose cohort maintained normal factor levels for 1 year after the infusion. All patients were able to stop prophylactic factor infusions and there was a significant decreases in annualized bleeding rates from 16 to 0. [31]

There are ongoing studies of gene therapy in both Hemophilia A and B. A lasting cure is now a realistic goal for this devastating disease.

Conclusion

There have been significant advances in the treatment of hemophilia over the last 50 years. The HIV/hepatitis epidemic in the hemophilia community due to contamination of blood products in the 1980s ignited a wave of research that led to safer plasma derived products and recombinant DNA technology. Prophylactic factor infusions decrease the risk of hemophilic arthropathy and enables patients with severe hemophilia to live a normal life-span. Extended half-life recombinant factor concentrates enable patients to maintain higher trough levels with fewer infusions, thus improving adherence and allowing for a more active lifestyle. The most serious complication of hemophilia treatment is the development of inhibitors, which neutralize the activity of clotting factor replacement. The standard of care has been the use of “bypassing agents” such as recombinant factor VII and activated prothrombin complex concentrate. However, these agents are not as effective as standard factor replacement, are more expensive, and have short half-lives requiring frequent infusions. A factor VIII mimetic, Emicizumab, has recently been FDA approved for treatment of patients with inhibitors. Advantages include significantly decreased rates of bleeding compared to bypassing agent prophylaxis, subcutaneous dosing, and long half-life. Emicizumab is currently under FDA review for treatment in patients without inhibitors given recent data showing decreased bleeding rates compared to standard factor concentrate prophylaxis [25]. This will certainly revolutionize the treatment of hemophilia. Future endeavors include inhibiting natural anticoagulants as a way of rebalancing hemostasis. With promising advances in gene therapy, a future cure is a realistic possibility.

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