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Hemophilia: review of the past and present

Abstract

Hemophilia is a hemorrhagic disorder with a sex-linked inherited pattern, characterized by an inability to amplify coagulation due to a deficiency in coagulation factor VIII (Hemophilia A or classic) or factor IX (hemophilia B). Sequencing of the genes involved in hemophilia has provided a description and record of the main mutations, as well as a correlation with the various degrees of severity. Hemorrhagic manifestations are related to the levels of circulating factor, mainly affecting the musculoskeletal system and specifically the large joints (knees, ankles and elbows). This document is a review and consensus of the main genetic aspects of hemophilia A and B, from the inheritance pattern to the concept of women carriers, physiopathology and classification of the disorder, the basic and confirmation studies when hemophilia is suspected, the various treatment regimens based on infusion of the deficient coagulation factor as well as innovative factor-free therapies and recommendations for the management of complications associated with treatment, development of inhibitors and/or transfusion transmitted infections.

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Introduction

Hemophilia A and B are the only sex-linked hereditary recessive hemorrhagic diseases, in 70% of cases (the rest of the cases are the consequence of spontaneous de novo mutations). The condition is almost exclusively of the male gender due to the XY genotype, since the genes that encode factors VIII and IX are located on the long arm of chromosome 23 (X chromosome) that determines sex, at positions Xq28 and Xq27, respectively. More than 4,000 pathogenic variants in these genes have been described, which cause a quantitative-qualitative decrease in the expression and protein activity of these clotting factors.[1,2]

Hemophilia is a hereditary hemorrhagic disorder caused by a quantitative deficiency of coagulation factor VIII, referred to as Hemophilia A (HA), representing 80% of cases; or of factor IX, known as Hemophilia B (HB), corresponding to the remaining 20%. The deficiency of these factors causes an inability to generate thrombin and amplify the fluid phase of coagulation, with subsequent hemorrhagic diathesis in persons with hemophilia (PWH).[3] Clinical manifestations of HA and HB are similar and depend on the amount of the deficient factor in circulation. In severe cases, the main site of bleeding is the joints (hemarthrosis), which without adequate integral therapy can develop into a chronic hemophilic arthropathy, which represents the main cause of morbidity in this population. The pattern of inheritance is sex-linked recessive (X chromosome).[4,5] This, males manifest the disease and women are asymptomatic carriers or present minimal hemorrhagic symptoms. The prevalence and genetic alterations of hemophilia are similar worldwide, with no influence of lineage or ethnic origin.[6]

Genetic defects in factor VIII can be divided into three groups: 1) genetic rearrangements, such as inversion of intron 22, which occurs in 45% of patients with severe hemophilia and is caused by homologous recombination between the 9.5 kb sequence and 2 extragenic homologous regions; additionally there may be an inversion of intron 1 that occurs in 1-2% of severe cases; 2) insertions or deletions of genetic sequences; and 3) single DNA base substitutions resulting in missense, nonsense or frameshift mutations.

Coagulopathy in the PWH is a consequence of the inability to magnify, control, and maintain thrombin generation due to FVIII or IX deficiency. Thrombin generation is positioned as an event of high biological-physiological value as it is an essential part of the molecular complex responsible for the fluid phase of hemostasis. When there is a tissue lesion, FIXa binds to FVIIIa on a lipid layer rich in tissue factor (TF), forming the "intrinsic Xase" complex, which has the ability to generate 90% of thrombin in the event of tissue damage, with 10^6 times greater efficiency than FVIII and FIX alone. This complex is 50 times more effective than the "extrinsic Xase" complex (with a high content of FVIIa) for the activation of FX to FXa, with the subsequent activation of factor II (prothrombin) into thrombin, which converts soluble fibrinogen (factor I) into fibrin (insoluble). This simple description of a specific segment of hemostasis explains how the absence of factors VIII and IX is clinically manifested with classic bleeding events in PWH.[7,8]

Diagnosis and classification

Hemophilia should be suspected in a male who presents with prolonged and excessive bleeding, unrelated to the magnitude of the trauma and/or hemorrhage that occurs hours after injury or is recurrent. In primary coagulation tests, platelet number, prothrombin time (PT), thrombin time (TT), and fibrinogen will be normal with a prolonged activated partial thromboplastin time (aPTT), which is described later. The hemorrhagic manifestations of PWH A or B are clinically indistinguishable, so it is necessary to identify the deficient factor in order to provide its specific replacement. The definitive diagnosis is based on the quantification of the coagulation factors. The World Health Organization (WHO) defined an international unit (IU) as the activity of the factor present in 1 ml of plasma, and depending on the nomenclature of each place, it can be equivalently expressed as: 1 IU/dl, 0.01 IU/ml or 1%. The severity of hemophilia is classified according to the activity of the circulating plasma level of FVIII or FIX without treatment, as severe, moderate or mild (Table 1).[9]

Table 1 Classification of hemophilia and correlation with hemorrhagic manifestations

Severity	Coagulation factor level	Hemorrhagic episodes
Severe	<1 IU/dL (<0.01 IU mL) or <1%	Spontaneous bleeding in joints or muscles.
Moderate	1-5 IU/dL (0.01-0.05 IU mL) or 1-5%	Occasional spontaneous bleeding; prolonged bleeding after trauma or surgery.
Mild	5-40 IU/dL (0.05-0.40 IU/mL) or 5 to 40%	Severe bleeding after trauma or major surgery. Spontaneous bleeding is rare.

Adapted from Blanchette and Srivastava, 2015.[4]

Laboratory studies

Hemostasis studies have a fundamental role in the diagnosis and monitoring of PWH. The quality assurance of these tests includes internal and external quality control, as well as the control of factors that can influence the different stages of test processing, such as the pre-analytical phase, where more than 70% of laboratory errors occur (requisition of studies carried out by the doctor, correct registration of the requested study, preparation, collection and sampling). This is relevant when considering that coagulation tests are exceptionally susceptible to temperature changes, particularly due to the thermolability of factor VIII.

The relevant aspects in processing laboratory studies of the PWH, and a brief description of the findings from screening, confirmatory studies, and for detection of inhibitors in hemophilia, are specified below.

General aspects

- Venipuncture: ensure an atraumatic sample with minimal use of the tourniquet, using 19 to 21G needles (23G gauge in pediatric patients).

- Collection tube with 3.2% sodium citrate anticoagulant: it must be filled with at least 90% of what is indicated (9:1 ratio between the sample obtained and the anticoagulant).

- Mix the sample completely with the anticoagulant, gently inverting the tip of the tube 4 to 6 times and ensuring that clots do not form.

- Sample transportation: at room temperature and centrifugation within the first hour of collection. If transporting to a laboratory, preferably freeze the plasma immediately at -20ºC or less and transport in dry ice.

- Fasting: not mandatory, although an excess of lipids can affect analytical analyzers.

Screening studies for suspected hemophilia

- Complete Blood Count: within the reference parameters if there is no other justifiable alteration.

- Normal prothrombin time (PT) and prolonged activated partial thromboplastin time (aPTT).

- Plasma correction: in congenital hemophilia the aPTT will be corrected by mixing the patient's plasma in a 1:1 ratio with normal plasma. If the mixture does not correct prolonged aPTT, it may indicate the presence of an inhibitor or the presence of an anticoagulant in the plasma.

Confirmatory studies for factor VIII and IX dosage

Factor VIII determination can be performed by chromogenic or clotting assay. Factor IX dosage is determined by a one-stage clotting test. Performing a comprehensive dosage determination of all the factors that can prolong aPTT (VIII, IX, XI and XII) during the initial evaluation is recommended. When there is a family history of hemophilia, FVIII or IX activity in umbilical cord blood of male newborns can be determined.[10,11]

Consensus recommendation: In patients without a hereditary history of hemophilia, with a clinical hemorrhagic profile and prolonged aPTT, perform plasma corrections and confirm the activity of the deficient coagulation factor by means of chromogenic or coagulation assay for FVIII and coagulation assay for FIX. In cases with a family history of hemophilia, carry out the deliberate search to determine the specific coagulation factor in the umbilical cord blood or peripheral blood of the newborn.

Detection of anti-factor VIII and anti-factor IX antibodies (inhibitors)

Anti-FVIII or FIX antibodies are IgG-type alloantibodies with neutralizing (inhibiting) or non-neutralizing activity of clotting factor activity, and represent a serious complication of clotting factor concentrate (CFC) replacement therapy, thus they are more frequent in severe PWH. They should be suspected in patients with an inadequate clinical response to the administration of the deficient factor, particularly if they had previously responded and/or there is a change in the hemorrhagic phenotype.

Confirmation of the inhibitor and titer quantification is carried out using the Bethesda assay or its Bethesda-Nijmegen modification, the latter having greater sensitivity and specificity. This consists of mixing equal volumes of the test plasma with normal plasma, incubation at 37ºC for 2 hours, and measuring the residual activity of the factor in the mixture, using a factor VIII or IX free plasma as a control. By definition, a Bethesda unit (BU) is the inhibitor titer that neutralizes 50% of factor activity in one milliliter of plasma.

If after incubation the residual factor equals 100% of the level in the control sample, then the inhibitor level is zero. If the residual factor VIII equals 50% or 25% of the control, the inhibitor level is 1 or 2 BU, respectively (Figure 9). In case of a result lower than 25%, the patient's plasma is subjected to various degrees of dilution until the result can be read in the graph and the result is multiplied by the dilution factor to be expressed in BU. For example, if a plasma mixture is diluted 1:5 before incubation, and the residual factor is 50%, or one unit, 1 x 5 = 5 Bethesda Units.[12]

Genetic diagnosis

Genetic information for PWH represents a useful tool for predicting the risk of inhibitor development and facilitates prenatal counseling in carriers. For PWH A, the initial genetic screening studies search for inversion of intron 22 and 1. If these alterations are not detected, the complete sequencing of the F8 gene is performed. For hemophilia B, the eight exons of the F9 gene are sequenced to detect mutations or deletions. The genetic study for carriers can be complex. About 80% of mothers of sporadic cases may be carriers of a mutation, in the remaining 20% of cases a mutation is not detected and may be secondary to mosaicism. Prenatal diagnosis is an integral part of care for hemophilia carriers and is relevant for completion of pregnancy.

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The studies include non-invasive techniques for the product, such as determining the gender of the product by analyzing fetal DNA in maternal blood (feasible in the first trimester of pregnancy) or by ultrasound from 15 weeks of gestational age (wGA), which are not conclusive.

Recommendation: Centers that have the diagnostic resources should carry out the genetic profile of the PWH, beginning with screening for inversion 1 and 22 in the case of HA. If negative, carry out the complete sequencing of the F8 gene. For HB, perform the sequencing of the F9 gene in the patient, as well as in the carriers and/or send the samples for research protocols.[13,14]

Treatment

Multidisciplinary management

Proper attention to the diverse needs of the PWH and their family is given through the intervention of a multidisciplinary team consisting of nursing, psychology, nutrition, orthopedics, rehabilitation, stomatology, occupational therapy, social work, and genetics, coordinated by the hematologist and in adherence to national treatment guidelines. All team members must have experience and ability to treat bleeding disorders and be available to care for patients in a timely manner. There must be the infrastructure of a hemophilia treatment center for emergency care at all times, with access to specific laboratory studies (determination of clotting factors and inhibitors), as well as the necessary drugs and clotting factor concentrates.

The multidisciplinary team will inform the patient and family members about the early symptoms of a hemorrhage with the goal of getting timely treatment, and will train them on conservation, preparation, and technique for applying coagulation factors, as well as care for venous accesses in the PWH, since they constitute vital access lines, thereby establishing an effective link between patients, family and members of the comprehensive care team that will promote adherence to treatment, based on the following recommendations:

a. Use butterfly needles caliber 23 or 25G.

b. Do not perform venous dissection, except in cases of emergency.

c. After venipuncture, apply pressure for 3 to 5 minutes. Avoid the use of permanent devices for venous access as much as possible, although they may be necessary for specific cases.[15–17]

Pharmacotherapy

The first-line pharmacological treatment in hemophilia is the application of the deficient CFC, either recombinant or plasma derived. Therapeutic application options can be on-demand or prophylactic, as outlined below.

On-demand treatment

This is the application of the CFC when there is clinical evidence of acute hemorrhage, calculating the dose to increase the activity of the factor based on the severity of the hemorrhage. On-demand treatment has been shown to decrease mortality and progression of arthropathy, but not prevent it. For life-threatening hemorrhage, the starting dose of CFC should be given immediately, even before completing the initial diagnostic evaluation, to obtain 80% to 100% activity, whereas in mild to moderate bleeding the goal is to maintain a factor activity between 35% and 50%. Maintenance doses for hemophilia A are generally administered every 12 hours, and every 24 hours for hemophilia B. The doses and duration of CFC treatment will depend on the site, severity of bleeding, and response to treatment.

Any acute bleeding in PWH should be treated as soon as possible, preferably within the first 2 hours of having occurred. When in doubt about the symptoms in a patient with hemophilia. The application of CFC in intravenous (IV) bolus is calculated considering the ideal weight of the PWH as follows:

Factor VIII

Patient weight in Kg x (% factor desired) x (0.5)

Factor IX

Patient weight in Kg x (% factor desired)

The half-life of the available factor, the purity, the presence of other components such as von Willebrand factor, or the use of recombinant factor should be considered. Recombinant FIX (rFIX) has a lower response than plasma-derived products, so that each unit of FIX infused per kilogram will raise FIX activity by approximately 0.8 IU/dl in adults and 0.7 IU/dl in children younger than 15 years. The reason for the lower rFIX response has not been fully determined.

If the type of hemophilia is not known, the administration of activated prothrombin complex concentrate (aPCC) is recommended at a dose of 50 to 100 U per kg of weight, without exceeding the daily dose of 200 U/kg/day.

The response to treatment in cases of acute hemarthrosis is determined according to the criteria in Table 2, which allows us to evaluate the response in a standardized manner, facilitate the comparison of results from different studies, and make therapeutic decisions.[18,19]

Table 2 Criteria for evaluating response to treatment in acute hemarthrosis.

Level of response	Response to treatment
Excellent	Complete disappearance of pain in 8 hours and/or disappearance of signs of bleeding after the first factor infusion and without subsequent dose requirements for relief of symptoms and signs in the same joint, in 72 hours.
Good	Significant improvement of pain or signs of bleeding at 8 hours after initial factor administration, but requiring subsequent doses in the following 72 hours for complete resolution.
Moderate	Partial improvement of pain or signs of bleeding at 8 hours after initial factor infusion and requiring subsequent doses in the following 72 h, but without complete resolution.
Poor	No or minimal improvement or worsening bleeding within 8 hours of initial factor administration.

Coadjuvant treatments

There are other therapeutic options that can help for the management of bleeding in PWH, which are highly relevant, especially in places where CFCs are limited or unavailable:

Desmopressin

Desmopressin (DDAVP) is a synthetic analogue of vasopressin that increases serum levels of factor VIII and von Willebrand factor, the expression of tissue factor, and stimulates platelet adhesion. Therefore, its use is reserved for patients with mild hemophilia A.

Dose:

- 0.3 µg/Kg of weight every 12 h, intravenous or subcutaneous use;
- 150 µg of nasal spray in each nostril for adults >40 kg in weight.

Due to liquid retention, DDAVP must be used carefully in young children, it is contraindicated for children under two years of age due to risk of seizures secondary to cerebral edema from water retention.[20,21]

Antifibrinolytics

Antifibrinolytic agents, such as tranexamic acid and epsilon aminocaproic acid, inhibit fibrinolysis, decreasing the activation of plasminogen to plasmin increasing clot stability. These drugs are useful in the management of bleeding in the mucosa (oral, nasal and menstrual cavities). Its use is contraindicated in case of hematuria, since it can prevent the dissolution of clots in the ureters, which would lead to severe obstructive uropathy.

Tranexamic acid: In Mexico there is a 650 mg tablet (Lysteda), which is administered orally 3 to 4 times per day. The injectable presentation of 500 mg/5 ml (Amchafibrin) is recommended 2 to 3 times per day intravenously. For pediatric patients, the recommended dose is 10 mg/kg weight per day, intravenously 3 to 4 times per day, or 15 mg/kg day in 3 oral doses, with a maximum of 4 grams per day.

Epsilon aminocaproic acid: The presentation in Mexico is as an injectable solution in a bottle, with a 5-gram ampule in 20 ml (Amicar). The recommended dose for intravenous infusion for adults is 4 to 5 grams in 250 ml of the diluent administered during the first hour, followed by a continuous infusion of 1 gram per hour in 50 ml of diluent until the hemorrhage has been controlled. The pediatric dose is 100 mg/kg 3 to 4 times a day. Fresh frozen plasma and cryoprecipitates.

Blood products containing clotting factors do not undergo viral or prion inactivation procedures, so their use is restricted exclusively for emergencies, when they are the only option available. The use of cryoprecipitates containing between 3 and 5 IU/ml of FVIII, or in general 100 IU of FVIII per unit, is preferred over fresh frozen plasma (FFP) for the treatment of hemophilia A. FFP and plasma devoid of cryoprecipitate contain FIX at a concentration of 1 IU/ml, so they can be used to treat hemophilia B. In addition to the coadjuvant therapies for the control of bleeding mentioned above, there are support measures for managing pain caused mainly by the musculoskeletal condition in PWH and/or during surgical interventions.[22]

Prophylaxis with bypassing agents

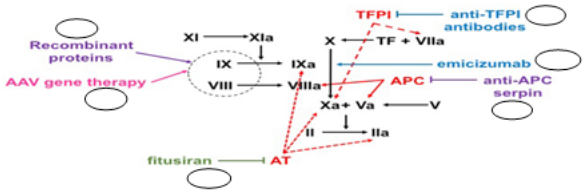
Prophylactic treatment with bypassing agents may be considered in patients with persistent inhibitors and a significant bleeding phenotype, which consists of: severe or life-threatening bleeding; three significant bleeds at the same site in a period of six months; or significant bleeding that requires bypassing agent therapy more than once a month. The main objective is to prevent or delay joint damage. There is no comparative study on the effectiveness of prophylaxis between the two bypassing agents. The Spanish and UK guidelines recommend prophylaxis with rFVII prior to ITI, other publications suggest that both agents can be used prophylactically before or during ITI. The suggested dose is rFVIIa 90 µg/kg once a day or aPCC 50 IU/kg on alternate days.[23]

Immune Tolerance Induction (ITI)

ITI treatment is aimed at inducing immune tolerance to the deficient factor against which the neutralizing antibody was developed, reducing bleeding events and allowing the prophylactic regimen to be reinstated. The principle of immune tolerance consists on repeated exposure of supra-physiological doses of CFC under non-inflammatory conditions, with or without the concomitant use of immunosuppressive agents. The first ITI therapy to eradicate inhibitor was performed in 1974 at the University of Bonn, Germany, using high doses of factor VIII of 100 IU/kg plus aPCC 2/day plus immunosuppressive treatment. To date, several ITI schemes have been described with different doses of FVIII with response rates of 100% for cases of low-responding inhibitor titers (>0.6-5 BU/ml) and between 60 and 90% for high-responding inhibitor (>5 BU/ml), internationally.[24]

New treatments

CFC replacement therapy has been effective for the control and/or prevention of bleeding in PWH for decades; however, it is limited by the accessibility and preservation of the products, the relatively short hemostatic duration and the development of complications such as appearance of neutralizing antibodies (inhibitors) against FVIII or FIX. The search for healing remains the ultimate goal. With the intention of normalizing the life of the PWH, new therapeutic tools are focused on improving the treatment of the PWH through: 1) CFCs with extended half-life (EHL); 2) gene therapy; 3) specific antibodies that simulate the function of FVIII, and 4) molecules that modify the action of natural anticoagulants. These are shown in Figure 1 and briefly described below:



Mechanisms of action for treatment of hemophilia. 1) rCFC with extended half-life; 2) gene therapy; 3) antibodies that simulate the function of FVIII (emicizumab), and 4) molecules that modify the action of natural anticoagulants: anti-TFPI antibodies (concizumab, BAY 1093884, BAX 499), anti-APC, AT blocking (fitusiran).
AAV= Adeno-associated virus, TFPI= Tissue factor pathway inhibitor, APC=Activated protein C, AT= antithrombin.
Taken and adapted from Arruda VR, 2018

Figure 1 Mechanisms of action of therapies in Hemophilia.

Extended half-life factor VIII

The benefit of EHL FVIII products has been limited, with an average half-life extension of 1.5 times, which has allowed prophylactic application in adults twice a week, but with a wide range in half-life between patients and shorter duration in the pediatric population. Therefore, the doses should be personalized according to the bleeding phenotype and the half-lives of the standard product and the EHL.

The first technology used to increase the half-life of FVIII was through fusion with IgG constant region (Fc). Efmoroctocog alfa is a FVIII factor analog bound to the Fc domain of human IgG1 lacking domain B.

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The second option to prolong factor half-life is through covalent binding of polyethylene glycol (PEG) to FVIII (pegylation). There are three FDA approved products with this technology:

a. Octocog alfa

b. Turoctocog alfa pegol

c. Damoctocog alfa pegol

The third mechanism to decrease FVIII clearance is by adding negative charges through polysialic acid (PSA), which interferes with receptor-mediated clearance.

Extended half-life factor IX

The traditional prophylaxis scheme for severe PWH B is by infusion of FIX twice a week. Structural modifications of FIX products with EHL include, like FVIII, pegylation and fusion with Fc or albumin. The first EHL rFIX on the market was fused to the Fc protein (rFIX-Fc) eftrenonacog alfa, with a half-life of 86.5 ±32.2 h. Patients who received 50 IU/kg weekly achieved minimum FIX levels of 1-3 IU/dl, with a rapid decrease in the first 24 to 72 h post-infusion, followed by a longer half-life. The second FDA-approved factor is albumin-bound rFIX (rFIX-FP) albutrepenonacog alfa, which has the advantage over rFIX-Fc pharmacokinetics of a gradual decrease following infusion, with a half-life of 104 h. The extended half-life of this product is based on its high molecular weight (above the renal threshold) and a pH-dependent interaction with the neonatal Fc receptor (FcRn), which prevents its intracellular degradation.[25]

Treatment strategies without substitute factor

The main advantages of this treatment modality are minimizing the risk of inhibitor development, subcutaneous administration, and prolonged weekly and/or monthly application intervals. These therapies attempt to amplify thrombin generation through different mechanisms of action, or to increase endogenous production of the deficient factor through gene therapy, as explained below.

Therapies that amplify thrombin generation:

a. Biospecific antibody that mimics factor VIII function

Emicizumab, authorized by the FDA is a bispecific humanized monoclonal antibody that simulates the biological function of FVIIIa, by establishing a procoagulant effect through its antigen binding fragment (Fab), joining FIXa and the coagulation substrate FX on a layer of phospholipids, generating thrombin with a dose-dependent effect and, therefore, shortening aPTT. Administration is subcutaneous, with a half-life of approximately 4-5 weeks. The authorized dose for the management of PWH A with inhibitors is 3 mg/kg weekly for the first 4 weeks, and subsequently 1.5 mg/kg weekly or 3 mg/kg biweekly or 6 mg/kg monthly. It does not share structural homology with FVIII, except for the binding sites, so the development of inhibitors against this molecule is not expected and it is not neutralized by FVIII inhibitors.

Studies evaluated PWH A with high-responding inhibitors, reporting a reduction in the annual bleeding rate with a significant difference of 87% with weekly application of emicizumab. Based on these studies, emicizumab was originally approved in 2017 as prophylaxis to prevent or reduce the frequency of bleeding episodes in PWH A with inhibitors directed against FVIII. It is pertinent to mention the possibility of thrombotic complications with the concomitant use of aPCC at therapeutic doses secondary to a synergism between the two substances. Since emicizumab increases the enzymatic action of the FIXa contained in CCP 20,000 times, therefore its use is recommended, if necessary, at low doses. No thrombotic events associated with the use of rFVIIa or emicizumab as monotherapy are reported.

Subsequently, clinical studies, which showed a reduction in the annual bleeding rate of between 96 and 97% compared to placebo, as well as a median of 0. In light of this indication, considering the use of emicizumab in patients without inhibitors, with difficult venous access, not candidates for use of central venous catheter, who require high doses of FVIII (with clinical behavior similar to patients with inhibitors) or at high risk of inhibitors has been suggested.

b. Agents that modify the function of natural anticoagulants such as tissue factor pathway inhibitor (TFPI), antithrombin, and activated protein C (APC)

- Tissue factor pathway inhibitor:

In PWH, the amplification of coagulation and thrombin generation is altered by FVIII or IX deficiency. Tissue Factor Pathway Inhibitor (TFPI) is a serine protease that plays an important role in the initial generation of thrombin by inhibiting tissue factor-factor VIIa complex (TF- FVIIa) and prothrombinase.[26,27]

Antithrombin inhibitor: Fitusiran is an interfering ribonucleic acid (RNAi), which binds to messenger RNA (mRNA) and interrupts its production, with the subsequent decrease in the synthesis of antithrombin (AT) in the liver. AT is the main natural anticoagulant that inactivates thrombin and FXa. Decreased AT levels in patients who have received different SC doses of fitusiran have reported an increase in thrombin generation and a decrease in average annual bleeding. For reasons of safety and efficacy, the ATLAS phase 3 clinical trial has been redesigned with the monthly application of fitusiran.

Gene therapy

Gene therapy consists of introducing the sequence of a specific gene into a target cell. The use of a virus as a vector for genetic material is called transduction, which can be carried out through two strategies: a) direct administration "in vivo" of the therapeutic gene through a vector, mainly associated with adenovirus (AAV, for its Adeno-Associated Virus), and/or b) transplantation of cells to which the "ex vivo" gene has been inserted, using Lentivirus-type vectors (LV).

Hemophilia gene therapy uses AAV to transduce the clotting factor gene directly into hepatocytes. Some clinical trials have obtained the sustained expression of therapeutic levels of FVIII and FIX. However, it has its limitations, since around 40% of the population has antibodies against the capsid of one of the AAV serotypes, which limits transduction, as well as the development of a cellular-type immune response characterized by transaminitis and/or a decrease in transgenetic expression. Current research in hemophilia gene therapy is focused on the administration of AAV vectors directly to the liver intravenously, with the immune response controlled by high doses of steroid. Recent studies in PWH B suggest a potential cure for this disease.[27,28]

Prophylaxis regimen

Evidence establishes that early prophylaxis (<36 months of age) is effective in terms of quality of life and in reducing the risk of joint damage. The ESPRIT study (Evaluation Study on Prophylaxis: a Randomized Italian Trial) used rFVIII at a dose of 25 IU/Kg 3/week and showed that patients who started prophylaxis ≤ 3 years of age had a lower incidence of all bleeding and Hemarthrosis of 0.35 and 0.12

events per patient per month, respectively, compared to patients who started after 3 years of age (0.62 and 0.25). The impact on joint health was important, since it was documented that none of the patients who started early prophylaxis presented radiological data of arthropathy using the Pettersson scale, compared to 46% who started after 3 years. Even in patients who received FVIII on-demand, a lower degree of arthropathy (57% vs. 85%) was demonstrated with the early start of substitution therapy in children under and over 3 years of age, respectively. The challenge is to identify patients who can benefit from low-dose CFC prophylaxis without compromising joint well-being and quality of life. Prophylactic treatment regimens are divided into two: 1) regimens with established doses of CFC (high, intermediate, low, or staggered doses), and 2) the regimens adapted to the needs of the patient. Table 3 lists the various primary prophylaxis regimens with their characteristics.[29]

Table 3 Lists the various primary prophylaxis regimens

Regimen	CFC Dose	Advantages	Disadvantages
Swedish (Malmő) High dose	FVIII: 25-40 IU/Kg/48 h FIX: 25-40 IU/kg/2 wks	ensures level of CFC ≥1% Reduces AJBR ~1 Ideal for patients with physical activity	High cost Low adherence; Need for central venous access
Dutch (Utrecht) Intermediate doses	FVIII: 15-25 IU/kg/2-3/wk FIX: 30-50 IU/kg/1-2 wks	Reduces AJBR 1-2 Lower cost than high doses Suitable for adults	Subtreatment in some patients Results slightly worse in MSS
Canadian Staggered doses*	FVIII: 50 IU/kg/1 wk 30 IU/kg/2 wks 25 IU/kg/48 h	Allows for infusion training intermediate cost	Depends on hemorrhagic events for dose adjustment Long-term effect on MMS
Low doses	10 – 15 IU/kg 1-2/wks	Lower cost Greater coverage of the number of PWH	Long-term effect on MMS unknown, probably worse than other regimens

Conclusion

As we have reviewed, hemophilia is a hereditary bleeding disorder caused by a quantitative deficiency of coagulation factor VIII, called, which represents 80% of hemophilia A cases; or factor IX, corresponding to the remaining 20%. The deficiency of these factors causes an inability to generate thrombin and amplify the liquid phase of coagulation, with the consequent hemorrhagic diathesis. Clinical manifestations depend on the amount of deficient factor in circulation. In severe cases, the main site of bleeding is the joints, which without adequate comprehensive therapy can evolve into chronic hemophilic arthropathy, which represents the main cause of morbidity in this population. The inheritance pattern is sex-linked recessive. The prevalence and genetic alterations of hemophilia are similar worldwide, without influence of lineage or ethnicity.

The mainstay of treatment is intravenous infusion of the deficient factor. This can be on demand (during bleeding episodes) or prophylactic (regular administration of the factor) with the main objective of avoiding spontaneous hemarthrosis, however, with considerable risk of developing inhibitors in severe hemophilia. This document has sought to update and review this entity in an objective and simple way and describe its most important aspects.

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None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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