

## HEMOPHILIA: A BIOGRAPHY ON THERAPEUTICAL APPROACHES

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### ABSTRACT

The history of hemophilia is ancient, with descriptions dated to the 2nd century AD. The first modern narratives appeared in 1800s, when total blood transfusion was the only available treatment and life expectancy was remarkably low. Advances occurred with the use of plasma and cryoprecipitate, but only the discovered of factor concentrates revolutionized the treatment. The implantation of prophylaxis allowed hemophilic patients to prevent bleeding and the development of chronic arthropathy, although with a significant burdensome with the regular infusions. In the past 20 years, this field has witnessed major improvements, including the development of gene therapy and other pharmacological approaches.

**Keywords:** *Hemophilia A; Hemophilia B; Biography*

### INTRODUCTION

Hemophilia is an inherited X-linked coagulopathy defined by a deficiency or abnormality in the clotting function of factor VIII (hemophilia A) or factor IX (hemophilia B). This name origins from the German *hämophile*, which is thereby derived from the Greek *haima* – blood or streams of blood – and *phila* – to love or tendency to. The term was coined in 1828 by the German physician Johann Lucas Schönlein (1793-1864)<sup>1</sup>.

This disease, notably the description of abnormal bleeding, is an ancient entity, that had played a crucial role in different moments of history. In the Talmud, a collection of Jewish rabbinical writings, dated from 2<sup>nd</sup> century AD, there is a decree that boys did not have to be circumcised if two of their brothers had previously died from the procedure<sup>2</sup>. The New Testament of the Bible mentions a woman who had bled for 12 years. Abu Khasim, a 10<sup>th</sup> century physician, described families whose males relatives had abnormal bleeding after trauma<sup>3</sup>.

The first scientific article describing an hemorrhagic disorder that primarily affected men, in certain families, was published in 1803, by John Conrad Otto, a physician from Philadelphia<sup>2</sup>. He was also able to traced the disease to a female ancestor, and called the males “bleeders”, already inferring the definition of carriers – women who inherit one affected X chromosome. Before Dr Otto’s description, two other possible cases were reported: one on a weekly local newspaper from Salem, USA – a 19-year-old boy, Isaac Zoll, that died from exsanguination like his five brothers – and other from Germany, described in 1793 from G. W. Consbruch of Bielefeld<sup>4,5</sup>.

Later, in 1813, John Hay proposed that men could pass the bleeding disorder trait to an unaffected daughter<sup>3</sup>. Thereby, in 1928, Dr Schonlein and his student Friedrich Hopff, coined the term, in a thesis entitled “About haemophilia or the hereditary predisposition to fatal bleeding”<sup>1</sup>.

The first genetic description of hemophilia was published by Nasse in 1820, which had coined “Nasse’s law”, that states that hemophilia is transmitted by unaffected females to their sons<sup>2</sup>. Just in 1947, in Buenos Aires, Argentina, the two types of hemophilia – A and B – were discovered by Dr. Alfredo Pavlovsky<sup>6</sup>.

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## A ROYAL DISEASE

Hemophilia is known as “the disease of Kings” or “Royal disease”, because it affected the royal families of England, Germany, Russia and Spain in the 19<sup>th</sup> and 20<sup>th</sup> centuries<sup>7,8</sup>. The most famous character is Queen Victoria of England, who ruled between 1837-1901, and was a carrier of Hemophilia B. She passed the trait to three of her nine children. Leopold died of brain hemorrhage when he was 31 years old. Her daughters Alice and Beatrice were carriers and passed to several children. Alice’s daughter Alix married the Tsar Nicholas of Russia, and their only son, Alexis, had severe hemophilia. His condition had an important impact on Russian modern history, and in the fall of the Romanov’s reign.

## TREATMENT THROUGHOUT HISTORY

In the early 1900s, storing blood was not a possibility. Therefore, hemophiliacs usually received total blood from a family member to treat bleeding. Life expectancy was 13 years old<sup>9</sup>.

In 1926, American physicians discovered that patients responded to plasma infusions when they were given promptly after joint and muscle bleeding. In 1937, Patek and Taylor described an anti-hemophilia globulin found in plasma<sup>10</sup>. In 1950 and 1960, hemophiliacs received plasma transfusions in hospital, but a big amount was necessary to reduce clotting time. By that time, life expectancy was about 20 years old<sup>11</sup>.

In 1964, a British hematologist called Robert Macfarlane described the coagulation cascade, which made possible several advances in this area<sup>12</sup>. In 1965, Dr Judith Graham Pool outlined cryoprecipitate, which is rich in factor VIII (fVIII), and it could be infused in smaller volumes to control bleeding<sup>13</sup>. By 1970, freeze-dried concentrates of fVIII and IX became available, and revolutionized the care.

Hemophilia’s treatment suffered a big calamity during 1980, with the confirmation that HIV/AIDS could be transmitted through blood products, and the contamination of half of the hemophilic population in the US<sup>14</sup>. Even more, the impact of hepatitis C virus was also remarkable.

By 1958, the concept of prophylaxis was introduced by Professor Inga Marie Nilsson, and radically changed hemophilia’s treatment and perspectives<sup>15</sup>. In the 1990s, treatment advanced, with the implementation of screening methods and viral inactivation. Still, synthetic factor products were manufactured using recombinant technologies.

## BRAZILIAN REALITY

In 1980, the Brazilian government approved the bases of the National Blood and Blood Components

Program (Pró-Sangue), with the intention of regularizing hemotherapy in Brazil. Among the objectives were the organization of a network for the supply and distribution of blood and its derivatives, the adoption of voluntary donation in a systematic way, and the regulation of production of blood products<sup>16</sup>. In 1988, the Brazilian Constitution prohibited the commercialization of blood and its derivatives. This initiative was partly the result of a campaign led by two hemophiliac brothers, the sociologist Herbert de Souza (known as Betinho) and the cartoonist Henrique de Souza (Henfil), both carriers of the human immunodeficiency virus, acquired through cryoprecipitate transfusions.

At that time, the state of Rio de Janeiro had a matrix for plasma fractionation, which produced enough factor fVIII to meet about 10% of the national demand. Most patients with hemophilia A were treated with cryoprecipitate transfusions, and some care centers or state governments acquired variable amounts of factor fVIII concentrates<sup>16</sup>. In the 1990s, the newly created SUS (Sistema Único de Saúde) began to acquire around 10,000 IU of fVIII/patient with hemophilia/year, while the recommended by the World Federation of Hemophilia was a minimum of 20,000 IU/patient/ year. Initially, this importation occurred irregularly, and there was no distribution criteria.

In 1994, the Ministry of Health implemented a national program for the treatment of hemophilia, with the objective of achieving the acquisition of the 20,000 IU/fVIII recommended as minimum for the maintenance of life, and organizing its distribution. Each Coordinating Blood Center was assigned to receive and dispense the product to Hemophilia Treatment Centers, which should offer it to patients free of charge<sup>16</sup>.

In 2001, fVIII’s importation by the Ministry of Health reached 30,000 IU/registered patient/year. Based on the product availability, and considering the associated risks of transmission of infectious diseases, the use of cryoprecipitate as a treatment for hemophilia was banned in 2002<sup>16</sup>.

The availability of reliable data regarding the affected population is of vital importance for the planning of public care policies. In Brazil, the national database is provided through the HEMOVIDA Coagulopathies Web system. This system was validated in September 2008 and started in clinical practice in January 2009. It consists of two modules, administrative and clinical. The administrative module includes: registration of new cases or transfer of a registered patient to another state of the federation, data extraction and issuance of reports, stock control, use and distribution of clotting factor concentrates. The clinical module includes sociodemographic data, diagnosis, clinical complications, laboratory tests and treatment<sup>17</sup>.

In 2009, a publication involving the Coordination of the National Policy on Blood and Blood Products



of the Brazilian Ministry of Health described the first compilation of data referring to the Brazilian registry of hereditary coagulopathies. In this study, it was emphasized that patients affected by these conditions, in the national territory, were treated with concentrates of plasma-derived coagulation factors, mostly, and imported in their entirety. Although treatment had made significant progress in the previous decade, it was still an episodic (on-demand) modality, with primary prophylaxis unavailable. It was also described that patients had low socioeconomic status, and were affected by chronic musculoskeletal complications<sup>18</sup>.

Primary Prophylaxis Protocol for severe hemophilia was implemented in Brazil in December 2011, according to Circular Letter No. 095/2011 of the CGSH/MS. Therefore, on May 6, 2014, through Decree Number 364, the Brazilian Ministry of Health, at the Health Care Department, approved the protocol for the use of primary prophylaxis for severe hemophilia<sup>16</sup>.

## NEW PERSPECTIVES

Replacement therapy – using prophylactic or therapeutic infusions of clotting factor concentrates – has so far been the mainstay of treatment for adult and pediatric patients with severe hemophilia A or B. Despite being more available and safer, the intravenous use of these concentrates is still burdensome for patients, who suffer from multiple venipunctures, episodes of breakthrough bleeding, eventual development of target joints and chronic arthropathy, and inhibitory neutralizing antibodies<sup>19</sup>.

The use of products of recombinant origin is already widespread. Genetically engineered modification of these factor concentrates, through the use of Fc-fusion, pegylation, or albumin-fusion technologies, has created a class of concentrates with an extended half-life compared to conventional products. This increase in drug circulation time is more substantial among factor IX concentrates, since the half-life of factor VIII also depends on its interaction with von Willebrand factor<sup>20</sup>. Furthermore, new recombinant factor VIII products have eliminated the most immunogenic epitopes, and are under study with the aim of reducing the inhibitors development<sup>19</sup>.

Emicizumab is a bispecific monoclonal antibody that provides binding between factors IX and X, replacing the function of deficient activated factor VIII. A phase III study with 152 patients over 12 years of age, with two different doses in weekly subcutaneous injections, and an unexposed group, found an annual bleeding rate of 1.5 for the weekly dose of 1.5 mg/day/kg, 1.3 annual bleedings for the dose of 3 mg/kg every two weeks, against 38.2 events for the group not exposed to this therapeutic modality, with statistical significance. The bleeding rate was 68% lower

than the one obtained with standard prophylaxis. No thrombotic or microangiopathy events or the development of inhibitors were found<sup>21</sup>. The same bispecific antibody was used in 109 patients with hemophilia A and affected by inhibitors, older than 12 years of age. In this phase 3 study, patients in the treated group received a weekly application of 3 mg/kg for 4 weeks, followed by 1.5 mg/kg weekly. The annual rate of bleeds was 2.9 versus 23.3 events, and 79% lower than that obtained with standard prophylaxis with bypass agents<sup>22</sup>.

The development of this new therapeutic modality makes the indication of prophylaxis simpler, since the subcutaneous application would allow a very early start, and would dispense the use of central venous access. This anticipation can protect children between 6 and 12 months from the risk of joint bleeding and even more critical ones, such as intracranial bleeding. However, safety data for emicizumab among very young children are still scarce<sup>23</sup>.

Strategies aiming to modify the balance of the hemostatic system, through the manipulation of procoagulant proteins and natural anticoagulants (antithrombin, tissue factor pathway inhibitor, or activated protein C) are also being evaluated. Blood hemostasis is finely regulated to promote its activation in case of injury, but not during homeostasis. In the deficiency of a clotting factor, as in hemophilia, this balance is shifted towards bleeding tendency. Evidence suggests that inhibition of natural anticoagulants in this context could restore the balance of hemostasis. This phenomenon is naturally found in patients with severe hemophilia who inherit some thrombophilia, such as protein C deficiency, and have their bleeding phenotype attenuated<sup>24</sup>.

It is postulated that reduced levels of antithrombin could increase thrombin production and promote hemostasis in hemophilia. In this context, fitusiram, an RNAi interference therapy that targets antithrombin messenger RNA, leading to suppression of hepatic antithrombin synthesis, is under development and evaluation. In the phase 1 study involving 4 healthy volunteers and 25 patients with moderate or severe hemophilia, outcomes were pharmacokinetic and pharmacodynamic as well as safety assessment. No thromboembolic events were observed during the study. The monthly subcutaneous application regimen led to a 70 to 89% reduction in baseline antithrombin levels. For the prevention of bleeding, suppression of 75% of antithrombin levels is considered effective. However, this initial study was extended to a longer follow-up, especially regarding the risk of thromboembolic events<sup>25</sup>.

Another target for balancing the hemostatic system is the tissue factor pathway inhibitor (TFPI). Multiple strategies are already being studied aiming at its inhibition, such as aptamers, monoclonal antibodies

and peptides. Concizumab, a humanized monoclonal antibody against TFPI, is at a more advanced stage of development. It has high affinity for the K2 domain of the TFPI molecule, inhibiting the binding to factor Xa, and reducing the inhibition of the TF-FVIIa complex (activated tissue factor-factor VII complex). Phase I data with healthy volunteers demonstrated a reduction in plasma TFPI concentrations, functional activity greater than 14 days, increased thrombin generation, and no significant adverse events<sup>26,27</sup>. Phase II studies in patients with hemophilia A, and A and B with inhibitors, administered subcutaneously daily, demonstrated the prevention of bleeding without significant adverse events in all groups of treated patients<sup>28</sup>.

Activated protein C acts through the degradation of activated factors V and VII, in addition to binding to the endothelial protein C receptor. By inhibiting the amplification of fXa, and consequently, the generation of thrombin by the intrinsic pathway, it acts as a natural anticoagulant. In addition, it has a cytoprotector effect through anti-inflammatory, anti-apoptotic and endothelial barrier protection mechanisms. Evidence supports that the signaling and anticoagulation functions of the activated protein C molecule are spatially diverse and have different kinetics as well. A phase I/II study is recruiting healthy volunteers, as well as people with hemophilia A and B, with and without inhibitors, to assess the use of structurally modified forms of this protein<sup>19</sup>.

New formulations, through pegylation or fusion technologies with proteins with longer half-lives, have considerably increased the stability of factor concentrates in plasma, especially factor IX. In patients with hemophilia B, these products with an extended half-life allow weekly or even biweekly applications, with factor IX levels above 5% maintained, even with a reduced frequency of applications. The new concentrates, and non-substitute therapies such as the antibody emicizumab, are changing the paradigm of hemophilia in developed countries, by decreasing the frequency of infusions, improving adherence to prophylaxis, offering alternatives to patients with inhibitors, and offering alternative routes of administration such as the subcutaneous. However, all these innovations do not impact the treatment of about 80% of people with hemophilia, who do not have access to these innovations. A therapy with curative intent, such as gene therapy, could offer an alternative treatment for these patients<sup>29</sup>.

Gene therapy offers potential healing for people with hemophilia, through the restoration of continuous endogenous expression of factors VIII or IX, obtained through the transfer of a functional gene. Among genetic diseases, hemophilia has a combination of characteristics that make it an excellent candidate for gene therapy. The clinical manifestation of this

condition is entirely attributable to the lack of a single gene product, which circulates in small amounts in plasma. Very fine control of gene expression is not essential, as small increments in clotting factors, even less than 5%, are associated with a significant improvement in the bleeding phenotype in patients with severe forms of the disease<sup>14</sup>.

Several approaches to promote the endogenous production of factors VIII and IX have already been evaluated. Therapy, or gene transfer using a modified adenovirus-like viral vector targeting hepatocytes, is the most consolidated modality, with some programs already in phase 3. Adenoviruses are present in the environment, and many individuals have already been exposed to them, with the development of neutralizing antibodies. The prevalence of these neutralizing antibodies against adenovirus is estimated at 20 to 60%, and their presence interferes with transduction and limits the effectiveness of the procedure<sup>20</sup>.

The longest follow-up in relation to factor VIII transfer concerns the valoctocogene roxaparvovec (BMN270), developed by BioMarin, and describes the results in 15 patients with hemophilia A, after 52 weeks (145) and three years of infusion (146) of a single dose of an AAV5 viral vector, with four different doses. After three years, two patients remained with factor VIII expression below 1 IU/dL, measured by chromogenic assay. Seven patients, all of whom received the highest dose of the product, maintained a median factor VIII expression of 20 IU/dL, a median annual bleed rate of 0, and a reduction of 138.5 concentrate infusions per year. The resolution of all target joints occurred in this group of patients. The group that received an intermediate dose had a two-year follow-up, maintained a median factor VIII expression of 13 IU/dL, a median annual bleed rate of 0, and a reduction of 155, 5 concentrate infusions per year. There was the resolution of the target joints in 5 of the 6 patients in this group. No development of inhibitors, thromboembolic events, deaths, or persistent changes in liver function tests were observed in all patients<sup>30</sup>.

In relation to hemophilia B, pioneering studies using AAV viral vectors targeting liver cells provided expression of factor IX at therapeutic levels, but not sustained. A common observation in the initial studies was the development of an immune response against hepatocytes infected by viral vectors, in a dose-dependent manner. Thus, in hemophilia B, low-dose administration of a variant, factor IX-r338L, was attempted. This corresponds to a naturally occurring gain-of-function mutation in the topography of the catalytic domain of factor IX, which results in an activity 8 to 12 times greater than that of unmutated factor IX. A phase 1-2a study evaluated 10 hemophilia B patients with factor IX activity of less than 2% (147). In this study, factor IX clotting activity was sustained in



all participants, with a mean of 33.7 + -18.5% (range 14 to 81%). After cumulative follow-up of 492 weeks among all participants, the rate of annual bleeds was significantly reduced from an average of 11.1 events before vector infusion (range 0 to 48), for 0.4 events per year (ranging from 0 to 4 bleedings per year). There was also a significant reduction in the consumption of factor concentrates, from 2,908 IU/kg/year (ranging from 0 to 8,090 IU/kg/year) prior to treatment, to 49.3 IU/kg/year (0 to 376 IU/year). kg/year). Eight of 10 participants had no need for factor concentrates, and 9 of 10 patients had no bleeding after vector infusion<sup>31</sup>.

Another study also used a vector with modified factor IX (AAV5-FIX Padua) in three patients with hemophilia B, factor IX activity below 2% and in whom the presence of neutralizing antibodies against adenovirus prior to infusion was detected. At week 36 after infusion, patients had factor IX activities of 54%, 30%, and 51%, no bleeding or no need for clotting factor replacement<sup>32</sup>.

The availability of clotting factor concentrates has allowed severe hemophilia to evolve from a life-threatening condition, with high and early mortality, to a chronic disease in several regions of the planet, including Brazil. This therapeutic approach, available for prevention and treatment of bleeding episodes, is demanding due to the need of frequent venipuncture to administer the concentrates. Even so, they are not capable of maintaining adequate and persistent levels of clotting factor activity, requiring the adjustment of daily activities to the moments of peaks and valleys associated with the moments of application. These considerations lead to variable adherence to prophylaxis protocols, even in developed countries. Permanent joint damage, although with a delayed onset and progression, is still a reality for people affected by severe hemophilia A and B under prophylaxis regimen.

Replacement therapies (such as emicizumab) and hemostasis balancing (such as antithrombin or activated protein C inhibitors) may constitute the therapeutic revolution in hemophilia, through their more comfortable application routes and the lack of association with the development of inhibitors. However, they bring a great challenge, since there are no laboratory tests available on a clinical scale that allow an effective assessment of their performance

in hemostasis. Assays such as thrombin generation and thromboelastography will possibly be necessary for the laboratory evaluation of these new therapies. Furthermore, the risk of thromboembolic phenomena linked to the use of these new therapeutic classes, alone or associated with factor concentrates for eventual breakthrough bleeding, is still a matter of concern.

Regarding therapies to increase the endogenous production of clotting factors, the individual variability of gene expression, and the uncertainty regarding the levels of activity of the clotting factors desired for acceptable outcomes, remain open questions. The duration of the endogenous response and longer-term safety issues require the follow-up of small populations of patients treated with these modalities. Perhaps, gene therapies offer long-term but temporary control rather than the intended definitive cure<sup>20</sup>.

The positive changes influenced by the dissemination of primary prophylaxis as a therapeutic strategy established a high degree of health perception among people with severe hemophilia, shifting the focus of therapy towards the individualization of life circumstances and personal aspirations, which vary from person to person, and also in the same person, throughout his life. However, from the patient's personal perspective, adherence may be better signified by how much, and to what extent, its execution allows the fulfillment of personal desires and aspirations. As annual bleed rates approach zero, differences between therapeutic approaches are perhaps best described using a patient-centered approach. Modern hemophilia treatment could therefore aim, in addition to bleeding control and joint damage mitigation, to the satisfaction of broader aspects of life, such as the development of adequate self-esteem, achievement in school and work, healthy relationships with the family and friends, career planning, leisure activities<sup>33</sup>.

Hemophilia has a fascinated history because of its huge impacts through world's modern history, despite being a rare disease. Even so, its treatment has evolved from the most "simple" blood transfusion to the current in investigation gene therapy, displaying the power of science in medical advances. Besides individualized approaches, treatment challenges rely on the dissemination of technological progress through the planet.

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