Developments in modern hemophilia care

Hassan, S.

Chapter 1
Introduction

General background

Hemophilia is an X-linked hereditary bleeding disorder. Hemophilia A is caused by a defect in the *F8* gene which leads to a deficiency in functional clotting factor VIII (FVIII) while hemophilia B is caused by a defect in the *F9* gene which leads to a deficiency in functional clotting factor IX (FIX). The prevalence at birth is 24.6 per 100,000 persons for hemophilia A and 3.8 per 100,000 for hemophilia B.[1] The severity of the disease is based on an individual's residual clotting factor activity. Severe hemophilia is defined as having ‹ 0.01 international unit (IU)/mL clotting factor activity, while patients with moderate and mild hemophilia have clotting factor levels of 0.01-0.05 IU/mL and › 0.05-0.40 IU/mL, respectively.[2]

In 1-4% of neonates with severe hemophilia, intracranial hemorrhaging can occur during the perinatal period, which can lead to permanent neurological damage. In children and adults with severe hemophilia, spontaneous bleeds in muscles and joints are common. In the long term, joint bleeds cause bleeding-induced arthropathy, leading to long-term disability. In patients with mild hemophilia, the disease primarily manifests as increased bleeding after trauma or surgery.[2]

Throughout history, references can be found to bleeding disorders similar to hemophilia. The earliest reference can be found in the Babylonian Talmud, which was compiled around the 2nd century AD. In these writings, warnings against circumcision in children with brothers that previously died due to excessive bleeding after this intervention can be found.[3] Usage of the actual term "hemophilia" to describe a hereditary bleeding disorder first appeared in 1828 in a text by Friedrich Hopff, a student at the University of Zürich.[3]

Assessment of the health status of the Dutch hemophilia population

Important developments in hemophilia care over time

Until the 1970s, patients suffering from hemophilia were treated with plasma or whole blood. Due to the low amount of clotting factor in these preparations, this was not effective at treating bleeds. Consequently, most patients died due to major bleeding in vital organs in adolescence or early adulthood. The introduction of cryoprecipitate in 1964 and freeze-dried clotting factor concentrates (which contain higher concentrations of FVIII or FIX) in the 1970s made effective treatment of bleeds possible and dramatically reduced mortality. The introduction of regular treatment with clotting factor concentrates to prevent the occurrence of bleeding episodes (also

called prophylactic treatment) during this period improved quality of life immensely as patients suffered from less joint bleeds and consequently, less bleeding-induced arthropathy. The introduction of desmopressin, which works by releasing endogenous FVIII from endothelial cells, added a treatment option for patients with mild hemophilia A that was safe and effective.[3]

This so-called 'golden era' of hemophilia ended when many patients were infected with the human immunodeficiency virus (HIV), or with the hepatitis C virus (HCV) through the infusion of contaminated blood products during the 1980s. This led to many deaths due to AIDS, as well as many cases of HCV-related liver disease. The adoption of new viral inactivation techniques as well as new screening methods have stopped transmission of HIV or HCV through blood products since 1992. In the early 1990s, the first clotting factor products produced through recombinant technology were introduced to the market. The supposed risk of transfusion transmitted diseases was further decreased by these new products (especially infections by as-yet-unknown pathogens), and production could be increased as the supply of blood donors was no longer a limiting factor. The first treatment options for patients infected with HIV and HCV became available in the 1990s which improved the survival of these groups.[3]

Previous studies confirmed that the average life expectancy of patients with hemophilia has been steadily increasing.[4] Consequently, age-related diseases are occurring increasingly among patients with hemophilia. Compared to patients without a bleeding disorder, managing age-related diseases might require a more personalized approach as certain treatment options might be contra-indicated in patients with an increased bleeding tendency. Furthermore, bleeding-induced arthropathy, which is cumulative and increases with age, may become even more of an issue as the population gets older.

Knowledge gap & aim

It is unknown how treatment- and non-treatment related factors (e.g. the higher uptake of prophylactic treatment, the introduction of more efficacious HCV-treatment options, demographic changes etc.) have impacted the current Dutch hemophilia population in terms of clinical- and psychosocial outcomes.

Furthermore, new treatment options for hemophilia have recently been introduced in the Netherlands or are in the process of obtaining market approval. About 28% of patients with severe hemophilia currently receive prophylactic treatment with emici-

zumab.[5] Since its introduction, emicizumab has been regarded as the treatment of choice by many physicians due to the ease of administration and its long half-life.[6] An accurate overview of the current health status of the Dutch hemophilia population will enable the assessment of the added value of emicizumab and other novel treatment modalities (such as gene therapy) in the coming years. Therefore, the first aim of this thesis was to describe the current health status of the Dutch hemophilia population.

In order to achieve this aim, we initiated the 6th Hemophilia in the Netherlands study (the HiN-6 study) that followed a series of nationwide studies that were held in 1972, 1978, 1985, 1992 and 2001. Broadly speaking, the previous studies explored important medical and psychosocial research questions in the Dutch hemophilia population. The HiN studies have always been organized in close collaboration with patients with hemophilia (represented by the Netherlands Hemophilia Patient Society) and physicians who are specialized in treating patients with hemophilia (represented by the Dutch Society for Hemophilia treaters), which has led to high study response rates for all studies. The previous HiN studies consisted of questionnaires that were sent out to all patients in the Netherlands known to have hemophilia at the time. In the current HiN-6 study, patients were asked to fill out a similar questionnaire, as well as provide a blood- and urine sample. In addition, clinical information was obtained from each patient's medical record. By combining information from previous HiN studies with the current HiN-6 study, it was possible to perform longitudinal evaluation of the health status of the Dutch hemophilia population over a span of almost 50 years.

Identifying patients at a high risk of inhibitor development and presenting an overview of anti-drug antibody prevention strategies used in other diseases

Inhibitor development

A major complication of replacement therapy with FVIII, is the development of anti-drug antibodies in response to infused FVIII. These polyclonal high-affinity IgG anti-FVIII antibodies (also called inhibitors) neutralize FVIII, rendering it ineffective. The incidence of inhibitor development is highest in patients with severe hemophilia A. In this group, 25%-30% of patients develop inhibitors.[7] In general, inhibitors tend to develop early in treatment, after a median of 10-15 days of exposure to FVIII treatment.[7] Furthermore, inhibitors almost always arise within the first 75 days of exposure to FVIII. The incidence of inhibitor development in patients with at least 150 days of exposure to FVIII is very low, about 2 per 1000 person-years, but increases with age.[8, 9]

Several characteristics have been identified that are strongly associated with inhibitor development. An important risk factor for inhibitor development is the type of *F8* mutation.[7] For example, the risk of inhibitor development in patients with a large deletion is around 38% while the risk associated with missense mutations is roughly 20%.[10] Other gene variants in genes that are involved in immune regulation such as the *IL-10* gene, the *CTLA-4* gene, and genes in the HLA locus may also play a role.[11]

There are also several important treatment-related risk factors for inhibitor development. Intensive treatment with FVIII for at least 5 consecutive days to treat major bleeding or after surgical interventions at the first moment of exposure to FVIII was associated with a twofold increased risk of inhibitor development.[12] Furthermore, recombinant FVIII products also seem to be more immunogenic, as patients using these products have almost double the risk of inhibitor development, compared to patients on plasma-derived FVIII products.[13]

In patients with inhibitor development, FVIII bypassing agents such as recombinant activated FVII (rFVIIa) or activated prothrombin complex concentrate (aPCC) are used[14] Unfortunately, both products have a lower efficacy than FVIII with regards to controlling bleeding. Frequent administration of FVIII over a long period of time, also known as immune tolerance induction (ITI) is currently the standard method to eradicate inhibitors. ITI protocols that are often used are the Bonn protocol (which consists of infusing 100–150 IU/kg FVIII twice daily)[15] and the "van Creveld" protocol (which starts with infusing FVIII at a dose of 25 IU/kg FVIII every other day, the dosage is then decreased when FVIII recovery exceeds 30%)[16]. The time needed to fully eradicate inhibitors using these protocols can vary anywhere from months to years and the treatment fails in about one-third of patients.[17] Patients with a persistent inhibitor that is refractory to ITI have higher mortality rates than patients without an inhibitor (which is mostly attributable to more deaths to bleeding-related complications).[18]

Knowledge gap & aim

Although hemophilia treatment has improved in many ways, inhibitor development continues to be a significant problem in patients treated with clotting factor products. Overall, much progress has been made in unraveling the pathophysiological mechanisms underlying inhibitor development. Despite this, accurately predicting the individual probability of inhibitor development is currently not possible for many patients. Furthermore, strategies to prevent inhibitor development in patients at high risk of inhibitor development are also lacking. Therefore, the second aim of this thesis was to identify patients at a high risk of inhibitor development and to present an

overview of anti-drug antibody strategies that could potentially be applied to these patients.

Thesis outline

In the first section of this thesis (***Chapters 2 and 3***), we analyzed the HiN-6 study to describe the current health status of the Dutch hemophilia population, focusing on the most important clinical and psychosocial outcomes:

- In ***Chapter 2***, we describe how treatment changes have influenced major clinical outcomes among patients with hemophilia from 1972 to 2019.
- Overall mortality and causes of death among patients with hemophilia from 1972 to 2018 are described in ***Chapter 3***.

Although hemophilia treatment has improved in many ways, inhibitor development continues to be a significant problem in patients treated with clotting factor products. Therefore, in the second section of this thesis (***Chapters 4-7***), we evaluated different strategies to identify patients at a high risk of inhibitor development and present an overview of anti-drug antibody strategies that could potentially be applied to these patients:

- In ***Chapter 4,*** we assessed the immunogenicity of several recombinant-derived FVIII products in patients with severe or moderately severe hemophilia A who were exposed to FVIII for at least 50 days.
- In ***Chapter 5***, we developed and evaluated a new clinical risk prediction tool for inhibitor development that incorporated several novel predictors.
- In ***Chapter 6***, we assessed if a novel high-throughput epitope mapping technique could be used to accurately assess the FVIII-specific IgG epitope repertoire of patients with severe hemophilia A and predict future inhibitor development.
- In ***Chapter 7*** strategies to prevent anti-drug antibodies in disorders other than hemophilia were reviewed and assessed with regards to their possible application in patients with hemophilia.

References

1. Iorio A, Stonebraker JS, Chambost H, et al. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-analytic Approach Using National Registries. *Ann Intern Med*. 2019;171(8):540-546. doi:10.7326/m19-1208.
2. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet*. 2016;388(10040):187-197. doi:10.1016/s0140-6736(15)01123-x.
3. Franchini M, Mannucci PM. The history of hemophilia. *Semin Thromb Hemost*. 2014;40(5):571-576. doi:10.1055/s-0034-1381232.
4. Darby SC, Sau WK, Spooner RJ, et al. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood*. 2007;110(3):815-825. doi:10.1182/BLOOD-2006-10-050435.
5. Taal E, Goedhart G, Driessens M, et al. Monitoring of emicizumab using a patient registry. In: *15th Annual Congress of European Association for Haemophilia and Allied Disorders*.
6. Mahlangu J. An update of the current pharmacotherapeutic armamentarium for hemophilia A. *Expert Opin Pharmacother*. 2022;23(1):129-138. doi:10.1080/14656566.2021.1961742.
7. Gouw SC, Van Den Berg HM. The multifactorial etiology of inhibitor development in hemophilia: Genetics and environment. *Semin Thromb Hemost*. 2009;35(8):723-734. doi:10.1055/s-0029-1245105.
8. Kempton CL, Soucie JM, Abshire TC. Incidence of inhibitors in a cohort of 838 males with hemophilia A previously treated with factor VIII concentrates. *J Thromb Haemost*. 2006;4(12):2576-2581. doi:10.1111/J.1538-7836.2006.02233.X.
9. Hay CRM, Palmer B, Chalmers E, et al. Incidence of factor VIII inhibitors throughout life in severe hemophilia A in the United Kingdom. *Blood*. 2011;117(23):6367-6370. doi:10.1182/BLOOD-2010-09-308668
10. Gouw SC, Van Den Berg HM, Oldenburg J, et al. F8 gene mutation type and inhibitor development in patients with severe hemophilia A: Systematic review and meta-analysis. *Blood*. 2012;119(12):2922-2934. doi:10.1182/blood-2011-09-379453.
11. Cormier M, Batty P, Tarrant J, Lillicrap D. Advances in knowledge of inhibitor formation in severe haemophilia A. *Br J Haematol*. 2020;189(1):39-53. doi:10.1111/bjh.16377.
12. Gouw SC, Van Den Berg HM, Le Cessie S, Van Der Bom JG. Treatment characteristics and the risk of inhibitor development: a multicenter cohort study among

previously untreated patients with severe hemophilia A. *J Thromb Haemost*. 2007;5(7):1383-1390. doi:10.1111/J.1538-7836.2007.02595.X

13. Peyvandi F, Mannucci PM, Garagiola I, et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. *N Engl J Med*. 2016;374(21):2054-2064. doi:10.1056/nejmoa1516437
14. Hay CRM, Brown S, Collins PW, Keeling DM, Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol*. 2006;133(6):591-605. doi:10.1111/J.1365-2141.2006.06087.X
15. Brackmann HH, Lenk H, Scharrer I, Auerswald G, Kreuz W. German recommendations for immune tolerance therapy in type A haemophiliacs with antibodies. *Haemophilia*. 1999;5(3):203-206. doi:10.1046/j.1365-2516.1999.00311.x
16. Mauser-Bunschoten EP, Nieuwenhuis HK, Roosendaal G, Van Den Berg HM. Low-dose immune tolerance induction in hemophilia A patients with inhibitors. *Blood*. 1995;86(3):983-988. doi:10.1182/blood.v86.3.983.983
17. Hay CRM, DiMichele DM. The principal results of the International Immune Tolerance Study: a randomized dose comparison. *Blood*. 2012;119(6):1335-1344. doi:10.1182/BLOOD-2011-08-369132
18. Walsh CE, Soucie JM, Miller CH. Impact of inhibitors on hemophilia A mortality in the United States. *Am J Hematol*. 2015;90(5):400-405. doi:10.1002/AJH.23957