Received: 15 May 2020 | Revised: 12 June 2020 | Accepted: 15 June 2020

DOI: 10.1111/hae.14097

REVIEW ARTICLE

Haemophilia WILEY

Haemophilia care in Europe: Past progress and future promise

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Abstract

Haemophilia care has experienced unprecedented advances over the past 50 years, with the promise of a functional 'cure' being within reach in the not so distant future. This review outlines the challenges the haemophilia community in Europe has faced over the decades since the 1970s and how it has overcome them to steadily advance care. It will also look towards the future and anticipate the hurdles to accessing the next wave of innovation and apply how past experience can help reduce or eliminate these hurdles. The lessons we can learn from the past can inform not simply treatment decisions, but shape the policy, advocacy and access environment needed to make the future promise a reality. The future is bright, but only through active participation across the haemophilia community will we be able to achieve it. We need to work together, to ensure progress will not only be realized by those with haemophilia in Western Europe, but by all those with haemophilia and other inherited bleeding disorder throughout Europe.

KEYWORDS

Europe, haemophilia

1 | INTRODUCTION

In the present era of unprecedented progress in haemophilia care in Europe, growing innovation will be accompanied by both opportunities and challenges in access to healthcare. To envision the future, it is worthwhile to examine the past. This review provides a historical perspective on the evolution of haemophilia care over the past 50 years and the challenges faced during those decades. It also examines the current access to treatment in Europe, and future aspirations within the haemophilia community.

2 | HISTORIC PERSPECTIVE (1970-2010)

2.1 | 1970s: A decade of promise and progress

Treatment for severe haemophilia progressed significantly during the 1970s. Widespread use of cryoprecipitate or fresh frozen plasma enabled some measure of treatment for many people with haemophilia (PwH), breaking the vicious cycle of painful joint bleeding, treatment and resolution. Both offered improvements over no treatment but were unsuitable for rapid treatment of bleeding episodes and unable to prevent long-term joint damage.

Significant improvements came with the availability of plasma-derived coagulation factor concentrates (CFCs). Factor VIII (FVIII) concentrates of intermediate purity and prothrombin complex concentrates were available. There were no purified FIX concentrates. Although limited, availability of these concentrates meant that, for the first time, target factor levels could be achieved. More effective treatment could be infused without the volume constraints imposed by plasma. Crucially, these concentrates allowed at-home treatment instead of travelling to a hospital or haemophilia treatment centre (HTC). This was a major advance, not simply in convenience, but in maximizing the benefits of CFC to immediately treat a bleed, resulting in significantly decreasing joint damage. Pain and immobility were also decreased, and less time was missed from school or work.[1,2]

The 1970s also saw the beginning of the development of HTCs and comprehensive care, the concept of registries and national patient organizations. Without strongly established HTC networks and low acceptance of the budget needed for adequate haemophilia treatment, prophylaxis was unavailable in most countries.[3] For the first time, haemophilia became visible within national health systems. Availability of CFCs and acceptance of home treatment were major advances in haemophilia care. By controlling bleeding episodes, survival improved and pain and suffering decreased.[4] A normal life seemed attainable for the first time.

2.2 | 1980s: A decade of despair

A sense of hope and optimism carried forward into the early 1980s, when organization of HTCs grew, and prophylaxis gained wider acceptance. This edifice of hope and optimism began its crash back to reality with the first case reports of pneumocystis pneumonia in the United States in 1981[5] after which it became apparent that many thousands of PwH had been infected by human immunodeficiency virus (HIV) through contaminated blood products and factor concentrates pooled from tens of thousands of donors.

The clinical impact was initially slow, with hope that only a small minority of infected PwH would eventually develop AIDS. Testing for the virus from late 1984 revealed that a significant proportion of those with severe haemophilia were infected, and by 1996, up to 70% of those infected had died. AIDS became the leading cause of mortality in PwH in many Western European countries. Trends towards increased factor use and prophylaxis were reversed, as PwH grew fearful about treatments, experienced anxiety and prejudice due to the stigmatization of HIV and AIDS, and guilt was experienced by parents who had injected contaminated CFCs into their children. HTCs had to include new expertise in infectious diseases, in addition to providing counselling and other services. Haemophilia patient organizations became more active, advocating and assisting HIV-infected PwH in coping with the added clinical, emotional, psychological and financial burdens.

The vast majority of PwH who were infected with HIV were infected prior to 1985, the year virally inactivated CFCs became commercially available. After infections were largely halted, clinical consequences, including growing numbers of opportunistic infections and deaths from AIDS, became more apparent each year. Many patient organizations changed and became more active. Advocacy campaigns developed focused on securing a safe and adequate supply of blood and plasma products in Europe and, separately, for providing financial support and assistance for HIV-affected PwH. In 1989, haemophilia societies from 12 European countries came together to form the European Haemophilia Consortium (EHC). Collectively, haemophilia societies and treatment centres worked to manage HIV, political change with the fall of the Berlin Wall presaging major political change in Eastern Europe, and, ominously, the discovery and characterization of yet another blood-borne virus—hepatitis C virus (HCV).

2.3 | 1990s: A decade of restored hope and renewal

To counter HCV, virally inactivated CFCs treated with solvent detergent were first available in 1988, but in limited quantities. Europe continued to see transmission of HCV to PwH until 1990, when adequate supplies were finally established.[6] Infections continued to occur in some European countries after 1991.

The impact of HCV on the haemophilia population was not initially appreciated, as the virus did not generally cause acute illness, having a more insidious impact. Many infected PwH eventually developed chronic infection and varying degrees of liver fibrosis or cirrhosis. Early HCV treatments with interferon monotherapy did little in achieving sustained virologic response (SVR). The problems associated with HCV were exacerbated by the fact that almost all of those who had been infected with HIV were now co-infected with HCV.

From 1990 to 1996, the mortality rate of PwH from HIV continued to increase annually, decreasing from 1996 when highly active anti-retroviral therapy became available in many countries. From that point onward, mortality from HCV became greater than from HIV. Emergence of variant Creuzfeldt Jacob Disease (vCJD) associated with Bovine Spongiform Encephalopathy in cattle led to major fears about potential exposure to prions via plasma-derived CFCs. Plasma from UK and Ireland was no longer used for manufacture of CFCs, and blood donor restrictions were imposed. As it transpired, the number of clinical cases of vCJD was very small in proportion to the worst-case scenario, with no clinical cases of vCJD reported in haemophilia (except detection of prions in the spleen of one PwH who died of other causes).[7]

Following political changes in Europe, the decade saw greater activity among haemophilia patient organizations in many Eastern European countries and the development of a real European haemophilia patient community. Regarding treatment, the 1990s were a decade of promise and progress. CFC use increased again, and HTCs were more willing to initiate prophylaxis for some individuals. However, lower yields of CFCs due to viral inactivation processes led to supply constraints. In 1992, a European White Paper concluded that rational use of FVIII was 1.9 IU per capita—which is low compared with current use, but reflected the reality of depressed utilization, non-aggressive treatment of bleeding episodes and total lack of prophylaxis in many countries.[8]

In 1994, the first recombinant FVIII (rFVIII) was licensed. This development, along with other rFVIII and recombinant FIX (rFIX) products, helped break the dependency on plasma-derived FVIII and FIX in many countries. Until then, the mantra of self-sufficiency in blood and plasma had been widely promulgated to avoid viral contamination. Several countries developed a mindset where FVIII or FIX CFC use depended on the amount of plasma that could be collected nationally and fractionated by contract fractionation

with a pharmaceutical company. The view was also expressed in 1994 at the WFH Congress that, as recombinant CFCs could be manufactured on a large scale without the need for human plasma, they would be available in large quantities at a relatively low cost. The quantities did increase over the years, but the cost remained high. Initially, recombinant CFCs were priced at a premium compared with plasma-derived CFCs, likely due to a perception of greater safety.[9,10]

This price differential was widely maintained until recent years, changed only by competition from more products and newer generations of products such as extended half-life (EHL) CFCs.

The 1990s also saw the licensing of rFVIIa as a second option for the treatment of PwH with inhibitors following the licensing of activated prothrombin complex concentrate (aPCC) in the 1980s.

2.4 | 2000s: A decade of incremental progress and stagnant innovation

The first decade of the 21st century saw little innovation in haemophilia treatment and only incremental progress in some areas. We saw the development of second- and third-generation rCFCs manufactured without the addition of human or animal proteins, partially in response to fears linked to vCJD. And with SVR rates increasing up to 70% for the most common HCV genotype, treatment for HCV improved with the availability of pegylated interferon with ribavirin.

Publication of the European Principles of Haemophilia Care by a diverse group of haemophilia clinicians led to a set of ten principles against which progress could be measured.[11] This led to the formation of the European Association for Haemophilia and Allied Disorders (EAHAD) in 2009. In the same year, the European Directorate of Quality and Medicine in Healthcare (EDQM) published recommendations on optimal use of clotting factors, and EHC initiated the first systematic data collection across 19 European countries to examine the extent to which the principles of haemophilia care were achieved.[12]

2.5 | 2010s: A decade of innovation and constructive engagement

Development of direct-acting antivirals (DAA) delivered the potential for HCV to be effectively eradicated in PwH. This has been achieved in some European countries, but access to DAA therapy and an appreciation of the urgency in treating Hepatitis C continue to require active advocacy.

2.5.1 | Development of novel therapies

The development of EHL CFCs was the first major innovation in haemophilia treatment since rCFCs were introduced in 1994. To date, we have seen the licensing of 5 EHL FVIII concentrates and 3 EHL FIX concentrates in Europe. These long-acting CFCs enable PwH to be treated less frequently or at the same frequency but to a higher trough level, thereby increasing protection from bleeding. For EHL FIX CFCs, both objectives are achievable. Frequency of infusion could decrease from twice weekly to once every 1-2 weeks, reaching FIX trough levels up to 27%.[13] For PwH on FVIII prophylaxis, treatment could now be infused twice instead of 3 times weekly. Alternatively, the same infusion frequency could be maintained, and trough levels started to move from 1% to between 3% and 5%. Clinical trials are progressing for improved EHL FVIII, such as BIVV-001 where coupling of FVIII to both the Fc fragment of immunoglobulin and the DD3 fragment of von Willebrand factor (VWF) may lead to significant prolongation of half-life to ~33 hours.[14]

Non-replacement therapies (NRTs) have also emerged, including emicizumab, a bispecific antibody which mimics the action of FVIII. Licensed in 2019 by the European Medicines Agency (EMA), emicizumab may be used for prophylaxis in PwH with and without inhibitors providing a level of protection akin to FVIII trough levels of 10%-15%.[15,16] In clinical trials, emicizumab significantly lowered annual bleed rate (ABR) and significantly increased the percentage of PwH with zero ABRs. Subcutaneous delivery significantly reduces treatment burden for those with poor venous access, needle phobia or children. Bypassing agents for those with inhibitors and FVIII CFCs for those with haemophilia A are still required for bleeding episodes. Innovative re-examination of the coagulation cascade has led to development of NRTs that, instead of replacing missing factor, reduce the effectiveness of natural anti-coagulants within the cascade. Fitusiran, an antithrombin inhibitor, and several anti-Tissue Pathway Factor Inhibitor (TFPI) antibodies are in clinical trials. These products can theoretically be used subcutaneously for either haemophilia A or B, with or without inhibitors, and may also have some utility in rarer bleeding disorders. None of these rebalancing agents are currently licensed, and development of 2 of the 4 anti-TFPI agents has been halted due to reports of unexpected thrombosis. Improved understanding of the complex coagulation cascade will be useful in addressing future issues.

Gene therapy (GT) clinical trials are demonstrating exciting potential. The first patient dosed in the longest running FIX trial has now passed the 8-year mark with steady levels of factor expression.[17] Many clinical trials for FVIII and FIX GT are now underway with 8 phase 3 trials for FVIII and 6 phase 3 trials for FIX. Several have been prioritized by the FDA and the EMA.[18] The first FVIII GT is expected to be licensed later this year, and the first FIX GT to follow in late 2021. GT offers the prospect of changing severe haemophilia into mild haemophilia or even normal, offering the prospect of a phenotypic or functional cure.

Collection of outcomes data is vital to demonstrating the impact of new therapies and promoting continued investment in haemophilia. Haemophilia-focused outcome tools have also been developed by patient leaders (eg, Patient Reported Outcome Burden and

Experience [PROBE] survey tool) and produced unique disease-specific insights and evidence.[19]

2.5.2 | Constructive engagement and principles of haemophilia care

EDQM-organized meetings in 2013, 2016 and 2019, along with EHC-implemented surveys of progress in each preceding year, have led to implementation of recommendations that provide benchmarks against which haemophilia care can be measured.[20–22] Utility of these recommendations was strengthened by their acceptance by the Committee of Ministers on two occasions in resolutions: Resolution CM/Res (2015) 3[23]Resolution CM/Res (2017) 43.[24] Consequently, national haemophilia societies have been equipped with powerful and effective tools for clinicians and patient organizations, both jointly and separately, to advocate for recommended treatment and care, as well as incremental progress towards their achievement. For example, based on clinical evidence and changes to recommended treatment regimens, EDQM recommended an increased minimum per capita FVIII use in 2009 from 1 to 2 IU, in 2013 to 3 IU and in 2016 to 4 IU. For FIX, no minimum use was recommended until 2016 (0.5 IU per capita). No increase in minimum use for FVIII or FIX was recommended in 2019, as availability of EHL FVIII and FIX CFCs rendered the concept meaningless in the absence of a system for comparing standard and EHL units. In 2019, the recommended minimum trough level for prophylaxis also increased from 1%, which historically reduced ABR and delayed but did not prevent joint damage, to 3%-5%, a level expected to offer greater protection to joints. Combined with a recommendation of prophylaxis for all severe PwH, real clinical improvement became possible.[25]

Recommendations on the organization of European haemophilia care have included strengthening and harmonizing existing national registries by pooling and comprehensively evaluating data to properly assess the medium- and long-term beneficial effects of new therapies. EDQM has also recognized that PwH, particularly those using non-replacement therapies and GT, should be supervised by CCCs (eg certified European Haemophilia Comprehensive Care Centres [EHCCC]). This echoes an earlier joint recommendation by EAHAD and EHC and gives recognition to the informal system of certification of centres (eg EHCCC or European Haemophilia Treatment Centres [EHTC]), which has been in place since 2015 with active oversight from EUHANET, EAHAD and EHC.

Other important EDQM recommendations have included the establishment of a formal body for haemophilia in each country (2013), prioritized access to HCV treatment (2016), collection of outcomes data (2016), and national or regional tender boards which include both haemophilia clinicians and patient organization representatives for haemophilia medicines. National Haemophilia Councils or committees, now established in many European countries, provide a forum where doctors, patient advocates, and healthcare officials, together with payers, collaborate on haemophilia policy at a national level, thereby agreeing to a clear and united approach towards interactions with governments and officials.[26]

2.5.3 | Procurement, tenders and access to treatment

In this era of unprecedented innovation, economics will play a critical role. The recommendation for national or regional procurement of relatively expensive, complex medicines for haemophilia should consider that products are not interchangeable, and decisions should be informed by safety, efficacy and expertise—which may not be readily available to many hospitals or insurance companies in small fragmented procurement systems.[27]

European Haemophilia Consortium data have demonstrated beneficial economic impacts of national tender or procurement systems in which patients and doctors are involved, significantly lowering costs, improving scientific and clinical assessment of product options, avoiding the potential for divisive, suboptimal decisions and obtaining economy of scale in purchasing larger, country-wide quantities for extended durations.[28] For example, in Ireland, per capita use of FVIII increased threefold in the past 16 years, and, by 2019, only EHL formulations of FVIII and FIX were used, despite a national budget which had not significantly increased in the past 17 years. This was achieved due to an effective national approach to tenders which formally includes clinicians, patient leaders and payers.[29]

Data collected by EHC from 2009 to 2016 demonstrated a trend of increased access to CFCs in many Western and central European countries.[30-32] During that time, access to treatment increased significantly, sometimes linked to increased home treatment, prophylaxis for adults, and availability of immune tolerance therapy. In a group of mostly Eastern European countries, economies grew but without a parallel improvement in access to treatment and use of replacement therapy remained stubbornly below EDQM recommendations. In total, fourteen countries were below the minimum standard of care, not meeting some or all of the following criteria: minimum FVIII use of 4 IU per capita, minimum FIX use of 0.5 IU per capita, access to prophylaxis for all children with severe haemophilia, and establishment of a national or regional tender or procurement board including doctors and patient organization leaders. These criteria were used to create the EHC PARTNERS (Procurement of Affordable Replacement Therapy Network of European Relevant Stakeholders) programme to encourage sustainable access to replacement therapies through purchasing on a multi-year national basis while not negatively impacting the national budget. The programme has led to a significant improvement in access to treatment.

Innovation is happening at a rapid pace in haemophiliaa. Affordability may be the main barrier to access. In an EHC survey of tender systems in Europe in 2015, there was a fourfold difference in cost per unit of rCFC and a sevenfold difference for plasma-derived CFCs, neither relating to a country's wealth. Instead,

countries with the most organized and effective purchasing systems often paid a lower unit cost.[28] Cost of such therapies will depend on several factors, including the economic size of a country and its healthcare budget, purchasing systems, reference pricing between countries, and option for economy of scale through multi-year commitments. Cost also depends on competition where competitive tendering including several products has a distinct advantage. Some emerging economies in Europe who currently purchase small volumes of CFCs pay higher prices because very few products are licensed nationally. Additional costs may include high mark up by distributors, handling fees or taxes such as value-added tax.

Inefficient procurement systems are exemplified in Romania whose low utilization of FVIII and FIX is a consequence of 33 separate tenders resulting in multiple low volume purchases at higher unit costs. The knowledge and expertise needed to optimally assess each product are diluted among many ineffective tender systems. Until such systematic problems are addressed, existing disparities will continue to be exacerbated with the availability of new therapies, which should instead provide impetus to procure therapies in a more effective manner.

Novel therapies also will require novel access strategies. Decision-making between standard half-life (SHL) and EHL CFCs, NRTs and GT will necessitate new pricing and reimbursement models based on compared annual costs per patient. SHL and EHL CFCs can be compared within the same tender process using correction factors to calculate the number of required units of each product. NRTs can be included in this calculation to compare cost of prophylaxis, based on estimates from clinical trial and real-world data but would need to consider CFC use for treatment of breakthrough bleeds. Other approaches could include cost per patient for prophylaxis per year, cost to treat to a defined ABR or defined trough level, or a subscription model where as much product as required up to a reasonable ceiling can be consumed for a fixed annual cost.

2.6 | 2020s and beyond: A future of promise fulfilled?

The level of innovation we are now seeing in haemophilia is unprecedented. The limiting factor may be access. In most European countries, particularly those with national healthcare systems, the relatively high cost of paying for GT on a one-off basis may be prohibitive, even if the proposed payment assessed by health technology assessments is found to be cost-effective. In this scenario, reimbursement may be refused or a small number of PwH may be eligible for treatment, resulting in ethical challenges for clinicians, patient organization and payers. The most practical system may be an agreed annual payment for a predefined timeframe based on a given range of factor expression, with payment linked to factor expression levels or decrease in CFC use. Variations could include a larger initial payment followed by smaller annual payment, or open-ended payments for longer durations. There is considerable divergence of opinion on the number of eligible PwH in Europe for GT who will be treated in the next 5-10 years.[33] Estimates have ranged from 10% to up to 50% of PwH. When licensed, GT will almost certainly be limited initially to adults with severe haemophilia and will exclude those with inhibitors. Mechanisms allowing for an annual payment for a single treatment may have to be added in many countries.

In the future, the importance of HTCs and CCC's will be greater than ever. The 20-year trend of combining treatment of haemophilia and thrombosis patients in the same centre has growing relevance with ageing PwH and potential for thrombotic events from raised factor levels with constant expression. Assessment of activity, optimized laboratory assays, interpretation of results and management of new therapies are best undertaken by such centres. As GTs become licensed, some centres may become GT delivery centres, while routine follow-up can take place in others. The current informal system of certification may develop into a more formal accreditation system. Peer-reviewed audits may become more established in many countries, and a pilot audit programme for centres is underway from EAHAD. Development of new therapies, along with changes in clinical practice wrought by the current Covid-19 pandemic will accelerate the move towards telemedicine and development of patient portals. Innovative use of technology will form part of the solution to the requirement for increased levels of patient and parent education on the changing therapeutic environment. People with severe haemophilia who have higher trough levels or expression in the mild/normal range will want to limit visit frequency, yet long-term follow-up for GT and other therapies will remain vital. Centres will have to adapt their practice to these new realities.

There is a growing perception that haemophilia is solved, and doctors may be unmotivated to work in this area. We must engage medical students via lectures on haemophilia and thrombosis and undergraduate placement opportunities at HTCs to increase their level of interest before they choose alternative career pathways. Technology will improve monitoring of outcomes data. Wearable devices, artificial intelligence, and predictive treatment algorithms will all play important roles. Most of the innovation is directed at those with severe haemophilia. We must redouble our efforts to provide treatment, services and support to the underserved in our community—those with von Willebrands, rare bleeding disorders, women and those with mild haemophilia. In Eastern Europe, the same progress has not generally been made but progress in the west can provide a road map for acceleration in treatment and care hopefully in a shorter time span.

3 | CONCLUSION

The future for haemophilia in Europe is exciting. It is important that we take full advantage of the coming wave of innovation. Progress in Western Europe must be matched by greater access to treatment and care in central and eastern European countries. EHC and EAHAD must continue their effective collaboration and

joint initiatives. We must ensure that the next decade results in increased access for more people, that care is truly comprehensive for all with bleeding disorders and that those who are currently underserved in our community are fully integrated into services and support. This can be a golden age for haemophilia treatment, but only if the promise is matched by a golden age of access to treatments.[34]

ACKNOWLEDGEMENTS

Ingrid Koo, PhD, provided writing support during manuscript development.

DISCLOSURES

Brian O Mahony has been a consultant to Biomarin, Freeline and Uniqure.

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How to cite this article: O'Mahony B. Haemophilia care in Europe: Past progress and future promise. *Haemophilia*. 2020;00:1–7. https://doi.org/10.1111/hae.14097