
Article:
Hermans, C. and Makris, M. orcid.org/0000-0001-7622-7939 (2021) Disruptive technology and hemophilia care : the multiple impacts of emicizumab. Research and Practice in Thrombosis and Haemostasis, 5 (4). e12508.

https://doi.org/10.1002/rth2.12508

Received: 17 December 2020 | Revised: 19 February 2021 | Accepted: 26 February 2021

DOI: 10.1002/rth2.12508

rpth research & practice in thrombosis & haemostasis

FORUM

Disruptive technology and hemophilia care: The multiple impacts of emicizumab

Cedric Hermans MD, PhD, FRCP[1] | Mike Makris MA, MBBS, MD, FRCP, FRCPath[2,3]

[1]Hemostasis and Thrombosis Unit, Division of Hematology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain (UCLouvain), Brussels, Belgium

[2]Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK

[3]Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK

Correspondence
Cedric Hermans, Haemostasis and Thrombosis Unit, Division of Adult Hematology, Cliniques Universitaires Saint-Luc, Université catholique de Louvain (UCLouvain), Avenue Hippocrate 10, 1200 Brussels, Belgium.
Emails:cedric.hermans@uclouvain.be; hermans.cedric@gmail.com

Handling Editor: Pantep Angchaisuksiri

Abstract

Emicizumab, a bispecific antibody mimicking the action of factor VIII (FVIII), is currently the first and only approved and increasingly accessible disruptive treatment option for hemophilia A, a disease so far mainly treated with frequent intravenous infusions of FVIII concentrates or bypassing agents in case of inhibitor development. Other disruptive treatments are expected to follow, such as agents that rebalance coagulation and gene therapy with the ambition of curing hemophilia. While these treatment options represent major achievements or expectations, their adoption and implementation should consider their multiple direct and indirect, immediate or delayed, consequences on hemophilia care globally. It is these multiple changes, present and future, already visible or hypothetical, that this article intends to review and explore.

KEYWORDS
care, disruptive technology, emicizumab, hemophilia, inhibitor, nonreplacement therapy

Essentials

- Emicizumab is a bispecific antibody mimicking the action of factor VIII and administered subcutaneously.
- Emicizumab represents a disruptive treatment of hemophilia.
- Beyond its mode of action and route of delivery, its adoption and implementation could impact on many aspects of hemophilia care.
- These multiple changes, present or future, already visible or hypothetical, are reviewed and explored.

1 | INTRODUCTION

A disruptive technology is a new emerging technology that replaces the established one. Many disruptive technologies are regularly reshaping our societies and the way we live. Examples include what email has done for personal communications or what the mobile phone has done for the telecommunications industry.[1]

These technologies are also relevant to hemophilia. Beyond the classic substitutive treatment by intravenous administration of factor VIII (FVIII) concentrates, markedly improved over the past decades, a revolutionary alternative has recently become available.[2-5] This is the bispecific antibody (emicizumab), administered subcutaneously, which mimics the hemostatic action of FVIII without its immunogenicity and lability.[6] Emicizumab, however, only partially

corrects the FVIII deficiency typical of severe hemophilia A, so that coadministration of FVIII is required in certain circumstances.[7]

Emicizumab represents a disruptive technology that can change many aspects of hemophilia care that have hitherto been mainly based on the availability and administration of intravenous FVIII. It is these multiple changes, present or future, already visible or hypothetical, that this article intends to review and explore.

2 | DISRUPTION IN THE MODE OF ACTION

Over the past decades, the standard treatment for hemophilia A has been the complete or partial FVIII substitution, initially prepared from human plasma and more recently using recombinant DNA technology.[2,8] Regardless of the source, FVIII treatment suffers from three issues inherent to its characteristics: (i) the need to administer FVIII intravenously, (ii) its short half-life, and (iii) its immunogenicity.[9] Hemophilia treatment relies on repeated intravenous infusions to maintain a residual FVIII activity in the circulation effective to protect against spontaneous or provoked bleeding. The patient with hemophilia treated on a regular basis experiences FVIII fluctuations, with a lot of interindividual variability, alternating concentration peaks just after infusion, and troughs before the next infusion. In addition to these challenges, FVIII is particularly immunogenic, resulting in the development of neutralizing antibodies (inhibitors) in a significant proportion of mainly severely affected patients, especially when replacement therapy is initiated early in life. The development of these inhibitors represents a major complication and can be particularly difficult to control in many patients, even with the approved classical bypassing agents (activated recombinant factor VII [rFVIIa] or FEIBA [FVIII inhibitor bypassing activity]).[10]

Emicizumab represents the first approved and widely available nonsubstitutive therapy for hemophilia. Taking advantage of the cofactor function of FVIII in coagulation, this bispecific antibody binds to activated factor IX [FIX] and factor X, present in high concentrations at sites of clot formation, and brings the two molecules together, as FVIII does physiologically.[11] Emicizumab has the inherent properties of antibodies and, unlike FVIII, can be administered subcutaneously at infrequent intervals.[4,6-11] With emicizumab, the peaks and troughs seen with intravenous FVIII administrations are replaced by a more constant level of hemostatic activity. Since its structure is unrelated to FVIII, emicizumab does not induce the formation of anti-FVIII antibodies and allows the treatment of patients with hemophilia A with and without inhibitors. The advantages of emicizumab include ease of administration, constant hemostatic activity, and the possibility of treating patients irrespective of inhibitor presence with high hemostatic efficacy. Compared to rFVIIa or FEIBA, prophylaxis with emicizumab results in much fewer breakthrough bleeding episodes in both adults and children with inhibitors. In patients without inhibitors, emicizumab prophylaxis also leads to a significantly lower bleeding rate than previous FVIII prophylaxis. Emicizumab, however, has some potential weaknesses. The most important is that the correction of the coagulation defect is only partial, which leaves the patients treated with emicizumab at risk of bleeding complications in certain situations such as trauma or invasive procedures.[7] Emicizumab cannot therefore be considered as a monotherapy that cures severe FVIII deficiency, since adjunctive intravenous FVIII or bypass therapy is necessary in certain circumstances. Unlike endogenous FVIII, emicizumab does not undergo regulation during hemostasis (activation and inactivation), which raises concern about potential risk for thrombotic complications, particularly when used in conjunction with certain bypassing agents. Other disadvantages include the difficulty in assessing and monitoring the hemostatic effect of emicizumab (although the relevance of such laboratory monitoring has not been established),[12] the limited long-term experience, and the rare development of neutralizing anti-emicizumab antibodies.[6]

3 | REMODELING OF TREATMENT MODALITIES TODAY

The treatment and prevention of bleeding complications in patients with FVIII inhibitors are typically based on two conventional bypassing agents: rFVIIa and/or FEIBA. Like FVIII, these agents must be administered intravenously and have a short half-life, two major obstacles against their prophylactic use. It is therefore not surprising that emicizumab has emerged as an at least as effective alternative to rFVIIa and FEIBA. Emicizumab is recommended for patients with persistent inhibitors, with or without prior attempts at eradication through immune tolerance induction (ITI); it is currently being studied as a preventive bypass agent during ITI.[13] Emicizumab is able to replace FVIII concentrate for prophylactic use in patients with severe hemophilia A without inhibitors.[14] The potential for use in this indication is enormous. Emicizumab can indeed be used as a preventive treatment in patients with severe hemophilia A not treated prophylactically for various reasons (poor adherence, difficult vascular access, unfavorable pharmacokinetics). Emicizumab can also replace FVIII prophylaxis in adherent patients by providing them with a less burdensome treatment option associated with nonfluctuant coagulation status. Finally, emicizumab offers the prospect of starting preventive treatment early in life, well before any hemorrhagic event in newborns with severe hemophilia A, an option that is currently being validated.[15] Although the modalities of use in these various indications have yet to be confirmed by clinical trials and large-scale real-life data, emicizumab has already revolutionized the treatment of many patients with hemophilia A with and without inhibitors. Administered in a fixed weight-based dose, infrequently and subcutaneously, emicizumab also offers many advantages: fixed dose for prolonged periods in the absence of significant weight changes, easily calculated, almost no risk of over- or underuse, avoidance of training for intravenous infusions and use of central venous access, and easier stock management and delivery, especially for patients treated every 4 weeks.[16]

4 | MUTATION IN HEMOPHILIA TREATMENT AND FUTURE CARE

The rapid and large-scale use of emicizumab could in the near future have major consequences for the management of hemophilia, some of them, although hypothetical, negative or possibly disastrous. Very young children treated early with emicizumab could grow up without developing or recognizing the symptoms of hemarthrosis and without acquiring the skills necessary for intravenous administration of concentrate. The delay in obtaining intravenous treatment could potentially lead to more joint damage than in patients able to treat themselves. The fact that administration of emicizumab is increasingly started in early childhood, including in patients <1 year of age, could mean that inhibitors after a FVIII exposure may appear at a much later age and can go undetected because emicizumab is effective in patients with inhibitors. However, if these patients develop an inhibitor and require an invasive procedure or urgent surgery, the lack of knowledge of the presence of an inhibitor could be disastrous. The lack of laboratory monitoring of emicizumab means that some laboratory facilities are likely to downgrade their hemophilia sections. The limited availability of highly specialized tests such as chromogenic assays using bovine FVIII reagents[17] could impact the care of patients with hemophilia in emergency situations in many places. Some patients may not want to visit hemophilia treatment centers (HTCs), and this is all the more problematic when one considers countries that do not have a nationalized system, such as the United States. Telemedicine could alleviate this problem, but the need for blood monitoring will always be there.

5 | SHIFT IN RATE OF ADOPTION

With unusual speed and stimulated by promising results of clinical studies and a variety of consensus and expert opinions,[13,18-20] emicizumab has rapidly replaced conventional bypassing agents for patients with inhibitors and is recognized as the prophylactic agent of choice for these individuals. In a recent survey performed by the European Association for Haemophilia and Allied Disorders involving 32 European HTCs, emicizumab was found to be the prophylactic agent of choice used in 69% of patients with hemophilia A with inhibitors (unpublished). Also in many countries where reimbursement has been approved for both indications, emicizumab is increasingly emerging as a major or even leading therapeutic agent in patients without inhibitors replacing both standard and extended half-life (EHL) FVIII concentrates. The percentage of patients with severe hemophilia A without inhibitors on emicizumab is currently 25% in Israel (G. Kenet, personal communication), 30% in the United Kingdom (M. Makris, personal communication), and 35% in Belgium (C. Hermans, personal communication). As it can be self-administered by noncandidates for regular intravenous infusions of bypassing agents or FVIII concentrates, emicizumab increases the number of patients on prophylaxis with no marketing competition. There are currently no peer-reviewed or freely accessible data[21] available on the impact of emicizumab on the market shares of the different treatment options for hemophilia A in countries where emicizumab is reimbursed in both indications.

Although the hemophilia community has seen many innovations in recent decades, few single products have been adopted as quickly or as widely. This is all the more important when one considers that there is currently no alternative approved product with the same profile. In this context, there is a real risk that emicizumab could acquire a monopolistic position in certain HTCs, jeopardizing the wide diversity of treatments previously available with impact on product competition systems.

6 | REVOLUTION IN INNOVATION

For decades, FVIII has been the common and unique platform for the therapeutic innovations in hemophilia A,[8] undertaken and supported by several pharmaceutical companies. These include plasma-derived FVIII concentrates of increasing purity, multiple generations of recombinant FVIII ultimately devoid of any human or animal protein and products with extended half-life using technologies such as Fc or albumin fusion and pegylation.[10] Emicizumab marks a break in this sequence by offering the first therapy, with a totally new mode of action, distributed by a single company with no current direct competitor. Despite its advantages, therapy with emicizumab remains dependent on conventional treatments (bypass and FVIII agents) in certain circumstances such as trauma and invasive procedures.[7] As of today, it is difficult to anticipate what the next major innovations in the field of hemophilia will be, how they will be adopted, and how and whether conventional treatments (FVIII concentrates and classical bypassing agents) and the nonsubstitutive approach using bispecific antibodies will coexist. Other bispecific antibodies are being developed, as well as a recombinant FVIII with an ultra-extended half-life (BIVV001) and subcutaneous formulations of FVIII.[22] It is also difficult to assess the impact that emicizumab will have on the further development and adoption of gene therapy and nonsubstitutive therapies such as the coagulation rebalancing agents in patients with hemophilia A.

Assuming that these treatment options are successfully developed, it is highly unlikely that they will modify the hemophilia landscape to the same extent and with the same magnitude as emicizumab. BIVV001 will likely position in the continuity of EHL FVIII concentrates and have a similar impact on hemophilia A to that of EHL FIX concentrates in hemophilia B while competing with emicizumab. Given their mode of action and uncertainties regarding their thrombotic risks, it is unlikely that coagulation rebalancing agents will largely replace FVIII and FIX concentrates. As for gene therapy, it seems increasingly attractive for severe hemophilia B but its disruptive impact should be limited, at least in the near future.

7 | TRANSFORMATION OF THE PHARMACEUTICAL INDUSTRY

National plasma collection services, initially solely responsible for the production of stable blood products and supply of plasma-derived

FVIII, have gradually been replaced by international companies. These companies have specialized in the large-scale collection and fractionation of plasma and the production of plasma-derived FVIII concentrates distributed in several countries. The development of recombinant FVIII was initiated by companies already involved in the production of plasma-derived concentrates or who were completely new to the field of hemophilia therapy. There is no other rare disease that has attracted so much pharmaceutical investment in recent years. Several companies of varying size, some of which combine the production of plasma and recombinant FVIII, are currently competing in the global hemophilia market. The recent development of synthetic FVIII with a prolonged half-life has seen the emergence of new players that are challenging the supremacy of some historical pharmaceutical leaders. The success of emicizumab could totally change the pharmaceutical landscape for hemophilia. The consequences of such an evolution are difficult to assess but could impact the availability of certain treatments, either derived from plasma or recombinant, in low- and middle-income countries as well as countries with more well-developed health care systems.

A striking example of this worrying development is the recent interruption in the production of a plasma-derived FIX concentrate (Mononine, CSL Behring, Marburg, Germany), which did not survive the success of EHL-FIX.[23] This decision exposes many patients worldwide to the risk of not having access to a treatment that is certainly less sophisticated and more burdensome but equally effective in terms of bleeding control.

8 | A NEW ERA IN EDUCATIONAL AND FUNDING SUPPORTS

The explosion of innovations over the past 2 decades, initiated and supported by a growing number of pharmaceutical companies, has created an environment highly beneficial to hemophilia treatment. Educational initiatives have never been as prominent in the form of congresses, symposia, preceptorships, and multiple other activities. These have made a significant contribution to improving knowledge and multidisciplinary care of hemophilia, a discipline that is little taught in medical schools and in the curricula of future hematology specialists. Furthermore, this stimulating landscape has motivated the pharmaceutical companies to try and stand out and position themselves. This is how joint ultrasound,[24] personalized treatment with pharmacokinetic tools,[25] and the management of comorbidities in older patients[26] were brought to the forefront and aroused unprecedented interest. In addition, scientific societies, patients' associations, lay hemophilia organizations, and many HTCs have benefited from the financial support of pharmaceutical companies, a support that is sometimes critical and whose loss could jeopardize the sustainability of certain structures. Ideally, all these organizations should function without industry support, but this is quite difficult to achieve in the field of rare diseases. Clearly, the quickly changing hemophilia therapeutic landscape will have consequences on many of the initiatives described above. This impact is difficult to assess, but the possible repercussions of a redistribution of resources in the field of hemophilia should be anticipated.

9 | NEW CHALLENGES IN ACCESS TO CARE GLOBALLY

On a global scale, hemophilia treatments are currently accessible to only a limited number of patients. This is reflected by the results of the World Federation of Hemophilia (WFH) annual global survey that found that 51% of the captured population with access to FVIII concentrates are in high- and upper-middle-income countries. These countries use 94% of the total international units of FVIII.[27] Only persons with hemophilia residing in the most developed countries have routine access to standard treatments and innovations. In these countries, treatments are largely or totally reimbursed by effective social security and solidarity systems. Worldwide, the majority of persons with hemophilia either have no access to treatment or have access to very limited quantities, often obtained through humanitarian donation programs.[28] These programs have experienced tremendous growth in recent years, stimulated by the dynamism of the WFH and the generous support of several pharmaceutical companies. In many countries, it is now possible to treat young children with prophylactic regimens, including EHL FVIII and FIX concentrates used in reduced doses. So while most patients in more developed countries have access to a wide range of increasingly ambitious treatment options, patients in less developed countries can only expect to have access to donated factor concentrates for minimal prophylaxis, and only in children.[29] Although there is a major gap between developed and less developed countries, the management of hemophilia is gradually and constantly improving in both worlds. The revolution of the therapeutic landscape in the developed world should not be at the expense of the less developed countries. Emicizumab is indeed ideally suited for long-duration subcutaneous treatment of patients in low-income countries who do not receive training for intravenous injections and live great distances away from HTCs. To make this ambition a reality, it was announced in 2019 by the WFH that prophylactic treatment with emicizumab would be provided by the Roche Company to as many as 1000 people with hemophilia A in developing countries over the course of 5 years.[30] It is hoped that emicizumab will become increasingly accessible and that the global FVIII production capacity will benefit less developed countries, a totally hypothetical scenario today.

10 | CONCLUSIONS AND PERSPECTIVES

Emicizumab is currently the first and only approved disruptive treatment option for hemophilia A. Other disruptive treatments are expected to follow, such as agents that rebalance coagulation and gene therapy with the ambition of curing hemophilia.[31] While these treatment options represent major achievements or expectations, their adoption and implementation should consider their multiple direct or indirect, immediate or delayed, consequences on hemophilia care.

Divestment in hemophilia, deterioration in the quality of multidisciplinary care provided by HTCs, trivialization of hemophilia, loss of expertise, ignorance of certain possible complications in the future, and regression of donations and education programs are just some of the potential side effects that must be anticipated and proactively avoided. As long as treatments that cure all patients with hemophilia worldwide are not available, it seems important to remain vigilant and preserve everything that contributes to giving all patients the best possible care.

RELATIONSHIP DISCLOSURE

CH has provided consultancy and received invitations to give lectures from Shire, Pfizer, Bayer, Octapharma, LFB, CAF-DCF, Roche, Novo Nordisk, CSL Behring, SOBI Bioverative, Biomarin and Kedrion. MM has provided consultancy to Grifols, Sanofi, NovoNordisk, and CSL Behring. He is also the project lead for the EUHASS project, which receives support from Bayer, BPL, CSL Behring, Kedrion, NovoNordisk, Octapharma, Pfizer, Roche, Sobi, and Takeda.

AUTHOR CONTRIBUTIONS

Both authors contributed to the writing and approved the final version of the manuscript.

ORCID

Cedric Hermans https://orcid.org/0000-0001-5429-8437
Mike Makris https://orcid.org/0000-0001-7622-7939

TWITTER

Cedric Hermans @HermansCedric
Mike Makris @ProfMakris

REFERENCES

1. Christensen CM. *The Innovator's Dilemma: When New Technologies Cause Great Firms to Fail*. Boston, MA: Harvard Business Review Press; 1997. Ref Type: Online Source.
2. Mannucci PM. Hemophilia therapy: the future has begun. *Haematologica*. 2020;105(3):545–53.
3. Shima M. New hemophilia treatment employing a bispecific antibody to factors IXa and X. *Rinsho Ketsueki*. 2015;56(6):623–31.
4. Shima M. Bispecific antibodies and advances in non-gene therapy options in hemophilia. *Res Pract Thromb Haemost*. 2020;4(4):446–54.
5. Shima M, Hermans C, de Moerloose P. Novel products for haemostasis. *Haemophilia*. 2014;20(Suppl 4):29–35.
6. Blair HA. Emicizumab: a review in haemophilia A. *Drugs*. 2019; 79(15):1697–707.
7. Susen S, Gruel Y, Godier A, et al. Management of bleeding and invasive procedures in haemophilia a patients with inhibitor treated with emicizumab (Hemlibra((R))): proposals from the French network on inherited bleeding disorders (MHEMO), the French Reference Centre on Haemophilia, in collaboration with the French Working Group on Perioperative Haemostasis (GIHP). *Haemophilia*. 2019;25(5):731–7.
8. Sankar AD, Weyand AC, Pipe SW. The evolution of recombinant factor replacement for hemophilia. *Transfus Apher Sci*. 2019;58(5):596–600.
9. Raso S, Hermans C. Recombinant factor VIII: past, present and future of treatment of hemophilia A. *Drugs Today (Barc)*. 2018;54(4):269–81.
10. Franchini M, Mannucci PM. Past, present and future of hemophilia: a narrative review. *Orphanet J Rare Dis*. 2012;7:24.
11. Lenting PJ, Denis CV, Christophe OD. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? *Blood*. 2017;130(23):2463–8.
12. Tripodi A, Chantarangkul V, Novembrino C, et al. Emicizumab, the factor VIII mimetic bi-specific monoclonal antibody and its measurement in plasma. *Clin Chem Lab Med*. 2020;59(2):365–71.
13. Escuriola-Ettingshausen C, Auerswald G, Konigs C, et al. Optimizing the management of patients with haemophilia A and inhibitors in the era of emicizumab: recommendations from a German expert panel. *Haemophilia*. 2020. https://doi.org/10.1111/hae.14010. Online ahead of print.
14. Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. *Lancet Haematol*. 2019;6(6):e295–305.
15. Pierce GF, Hart DP, Kaczmarek R. Safety and efficacy of emicizumab and other novel agents in newborns and infants. *Haemophilia*. 2019;25(5):e334–5.
16. European Medicines Agency (europa.eu) 2021. Hemlibra. https://www.ema.europa.eu/en/medicines/human/EPAR/hemlibra. Accessed April 12, 2022.
17. Jenkins PV, Bowyer A, Burgess C, et al. Laboratory coagulation tests and emicizumab treatment A United Kingdom haemophilia centre doctors' organisation guideline. *Haemophilia*. 2020;26(1):151–5.
18. Holstein K, Albisetti M, Bidlingmaier C, et al. Practical guidance of the GTH haemophilia board on the use of emicizumab in patients with haemophilia A. *Hamostaseologie*. 2020;40:561–71.
19. Coppola A, Castaman G, Santoro RC, et al. Management of patients with severe haemophilia a without inhibitors on prophylaxis with emicizumab: AICE recommendations with focus on emergency in collaboration with SIBioC, SIMEU, SIMEUP, SIPMeL and SISET. *Haemophilia*. 2020;26(6):937–45.
20. Hermans C, Giangrande PLF, O'Mahony B, et al. European principles of inhibitor management in patients with haemophilia: implications of new treatment options. *Orphanet J Rare Dis*. 2020;15(1):219.
21. *Hemlibra (Emicizumab-kxwh) - Drug Insight and Market Forecast – 2030*; 2021. https://www.researchandmarkets.com/reports/5135476/hemlibra-emicizumab-kxwh-drug-insight-and?utm_source=GNOM&utm_medium=PressRelease&utm_code=93n2zf&utm_campaign=1483655+-+Hemlibra+(Emicizumab-kxwh)%3a+A+Bispecific+Factor+IXa-+and+Factor+X-directed+Antibody+-+Global+Drug+Insight+and+Market+Forecasts+2017-2030&utm_exec=chdo54prd. Ref Type: Online Source. Accessed April 12, 2021.
22. Konkle BA, Shapiro AD, Quon DV, et al. BIVV001 fusion protein as factor VIII replacement therapy for hemophilia A. *N Engl J Med*. 2020;383(11):1018–27.
23. *Hemophilia B Therapy to be Discontinued*; 2021. https://www.hemophilia.org/news/hemophilia-b-therapy-to-be-discontinued. Ref Type: Online Source. Accessed April 12, 2021.
24. Martinoli C, Di Minno MN, Pasta G, Tagliafico A. Point-of-care ultrasound in haemophilic arthropathy: will the HEAD-US system supplement or replace physical examination? *Haemophilia*. 2016;22(1):20–1.
25. Alvarez-Roman MT, Fernandez-Bello I, Corte-Rodriguez H, et al. Experience of tailoring prophylaxis using factor VIII pharmacokinetic parameters estimated with myPKFiT((R)) in patients with severe haemophilia A without inhibitors. *Haemophilia*. 2017;23(1):e50–4.
26. Holme PA, Combescure C, Tait RC, Berntorp E, Rauchensteiner S, de Moerloose P. Hypertension, haematuria and renal functioning in haemophilia - a cross-sectional study in Europe. *Haemophilia*. 2016;22(2):248–55.
27. Stonebraker JS, Bolton-Maggs PHB, Brooker M, et al. The World Federation of Hemophilia annual global survey 1999–2018. *Haemophilia*. 2020;26(4):591–600.

28. Pierce GF, Haffar A, Ampartzidis G, et al. First-year results of an expanded humanitarian aid programme for haemophilia in resource-constrained countries. *Haemophilia*. 2018;24(2):229–35.
29. Lambert C, Meite N, Sanogo I, Lobet S, Hermans C. Feasibility and outcomes of low-dose and low-frequency prophylaxis with recombinant extended half-life products (Fc-rFVIII and Fc-rFIX) in Ivorian children with hemophilia: two-year experience in the setting of World Federation of Haemophilia humanitarian aid programme. *Haemophilia*. 2020;27:33–40.
30. *Roche joins the WFH Humanitarian Aid Program*; 2021. https://news.wfh.org/roche-joins-the-wfh-humanitarian-aid-program/. Ref Type: Online Source. Accessed April 12, 2021.
31. Butterfield JSS, Hege KM, Herzog RW, Kaczmarek R. A molecular revolution in the treatment of hemophilia. *Mol Ther*. 2020;28(4):997–1015. Accessed April 12, 2021.

How to cite this article: Hermans C, Makris M. Disruptive technology and hemophilia care: The multiple impacts of emicizumab. *Res Pract Thromb Haemost*. 2021;00:e12508. https://doi.org/10.1002/rth2.12508