Published in final edited form as:

Haemophilia. 2020 January ; 26(1): e23–e25. doi:10.1111/hae.13896.

Excessive Breakthrough Bleeding in Hemophilia B Patients on Factor IX-Albumin Fusion Protein Prophylactic Therapy: A Single Center Case Series

B Kleiboer^{1,3}, B Nielsen³, AD Ma^{2,3}, Y Abajas^{1,3}, DM Monroe², NS Key^{2,3}

¹Department of Pediatrics, University of North Carolina at Chapel Hill, USA

²Department of Medicine, University of North Carolina at Chapel Hill, USA

³Department of Hemophilia and Thrombosis Center, University of North Carolina at Chapel Hill, USA

Keywords

Hemophilia B; Factor IX; Pharmacokinetics; Hemostasis; Half-Life; Coagulation

Persons with hemophilia B (HB) suffer from impaired health-related quality of life both because of the disease and its associated treatment burden. Severe HB patients with baseline FIX activity <1% are at risk for spontaneous joint bleeds, which can result in debilitating arthropathy. Until recently, the mainstay of prophylaxis in patients with severe HB was intravenous injection of plasma-derived or recombinant FIX (rFIX), typically administered twice weekly. Recent therapeutic advances have included the development of recombinant FIX-Fc (rFIX-Fc, Alprolix™) and recombinant FIX-albumin (rFIX-FP, Idelvion™) fusion proteins. These molecules confer plasma half-lives three- to five-fold greater than standard half-life products, which in clinical practice translates to intravenous dosing once every 7 to 14 days. The pivotal clinical trials reported excellent bleed control [1], with considerably reduced infusion treatment burden. The combination of improved disease control and lower treatment burden should result in improved quality of life for patients with severe HB.

However, in three patients on prophylactic rFIX-FP therapy at our institution, we have observed unexpectedly poor bleed control. We describe these cases and review the relevant FIX physiology that may underlie these observations.

Patient 1 is a 71-year old white man with severe HB who had been maintained on 50 U/kg of rFIX twice weekly with no breakthrough bleeds for more than a decade, and no target joints.

Address correspondence to: Nigel S. Key, MD, 8008B Mary Ellen Jones Building, CB #7035, 116 Manning Drive, Chapel Hill, NC 27516, USA, Tel: 919-966-3311, nigel_key@med.unc.edu.

Department of Pediatrics, 130 Mason Farm Rd, Chapel Hill, NC 27514

Department of Medicine, 125 MacNider Hall, Campus Box #7005, Chapel Hill, NC 27599

UNC Hemophilia and Thrombosis Center, University of North Carolina at Chapel Hill Campus Box #7016 Chapel Hill, NC 27599

B. Kleiboer made substantial contributions to the conception, design and drafting of the manuscript; N. Key, A. Ma, and B. Nielsen provided clinical care for the patients and critically revised the manuscript for important clinical and intellectual content. Y. Abajas provided clinical insights and revisions to the intellectual content. D. Monroe provided substantial contributions and revisions to the intellectual content and interpretation of data. All authors gave final approval of the version to be published.

To reduce injection frequency, he transitioned to rFIX-FP, 60 U/kg every 14 days in January 2018. Pharmacokinetic data by a 1-stage FIX assay demonstrated trough factor IX activity of 12% fourteen days after administration. Between April and November 2018, however, he reported four separate spontaneous right elbow bleeds, each occurring between six and eight days after dosing. In November 2018, he was evaluated for a bleed which occurred seven days after dosing, and on evaluation, had a measured FIX activity of 15%. An inhibitor was ruled out. He switched to a weekly regimen of rFIX-FP, 60 U/kg, at that time. He had one further breakthrough right elbow bleed three months later, but has since done well with no breakthrough bleeds in the subsequent six months.

Patient 2 is a 32-year old African American man with severe HB who initiated prophylaxis with rFIX-FP, 60 U/kg every two weeks, in March 2018. At time of starting rFIX-FP prophylaxis, he had no active target joints and no hemophilic arthropathy. He had previously been on prophylactic rFIX twice weekly, but reported challenges with adherence. In May 2018, he developed a spontaneous bleed in his right elbow, 10 days after his most recent dose of rFIX-FP. At the onset of pain, he self-administered two additional doses of rFIX-FP at 35U/kg over two days, per his emergency plan, but did not experience relief in the pain and swelling. On presentation to the Emergency Department, he had a measured plasma FIX activity of 82% and no evidence of inhibitor, but persistent evidence on exam of hemarthrosis. He was admitted to hospital for continuous rFIX infusion to achieve hemostasis. After this hospitalization, he was switched to a regimen of rFIX-FP 40 U/kg every seven days, with no subsequent breakthrough spontaneous bleeds reported since.

Patient 3 is a 56-year old white man with severe HB who, in order to reduce injection frequency and because of difficult venous access, transitioned from a rFIX regimen of 35 U/kg twice per week to rFIX-FP 65 U/kg every two weeks in March of 2018. At that time he had no target joints, and despite known hemophilic arthropathy in his right elbow, had not experienced any spontaneous breakthrough bleeds in the past year. Within three months on the rFIX-FP regimen, however, he reported eight spontaneous joint bleeds involving shoulders, leg, wrist, and toe (laterality not specified in phone calls). Although he did not present for pharmacokinetic evaluation after starting rFIX-FP, while being evaluated in clinic for a spontaneous right elbow bleed five months into his regimen, a trough FIX level (seven days after 65 U/kg of rFIX-FP) was 46%, with no laboratory evidence of FIX inhibitor. After a 65 U/kg dose of rFIX-FP in clinic, he had a measured peak FIX activity of 140%. Due to concern for inadequate bleed control on every-two-week dosing, he was advised to shorten the dosing interval to 65 U/kg every week, with complete resolution of breakthrough bleeding.

These cases represent a troubling pattern of unexpected and excessive spontaneous breakthrough bleeding in patients with severe HB taking rFIX-FP for prophylaxis. The bleeds occurred in the absence of known trauma, in the absence of active inhibitors, and despite seemingly adequate plasma FIX activity levels. For the periods of observation on rFIX-FP, these patients were on pace to have annualized bleeding rates (ABR) of as low as four, and in one case as high as 32. This experience is quite disparate from the reported outcomes in the phase 3 clinical trial evaluating rFIX-FP, in which the median AsBR (annualized spontaneous bleeding rate) fell to zero across all participants in groups on 7-,

10-, and 14-day prophylactic regimens [1], with no noted outliers. At our Center, 25 patients have been switched to rFIX-FP since its licensure, and the vast majority have done well, with ABRs <2, at similar dosing to our three reported cases, 65 U/kg every 2 weeks. Despite the apparent success in the majority of our patients, the experiences of our three cases are notable for their remarkable departure from previous experiences on standard half-life drugs.

It is unclear what accounts for the poor therapeutic response in this subset of patients. One possibility may be related to the relatively low volume of distribution (V_D) of rFIX-FP. Although a study looking at the distribution of radiolabeled rFIX-FP in rats showed the tissue distribution of rFIX-FP and rFIX was comparable, both penetrating predominantly into bone and well-perfused tissues [6], studies in humans suggest otherwise. Indeed, from pharmacokinetic studies in HB patients, the reported V_D for rFIX and rFIX-Fc are 216 (+/- 66) [2–3] and 227 (+/- 57) mL/kg [4], respectively, while that of rFIX-FP is much lower at 92 (+/- 15) mL/kg [5]. This suggests that the albumin fusion molecule has limited access to the extravascular space in humans. The fusion of albumin to the FIX molecule increases the molecular mass of FIX from 55 kDa to 125 kDa; larger molecules tend to have reduced access to the extravascular space. Additionally, albumin fusion allows FIX to engage the Fc receptor and avoid lysosomal degradation, thus delaying clearance and conferring prolonged plasma half-life [7], though it remains unclear to what extent this affects the molecule's ability to participate in hemostasis.

Recent studies have highlighted the importance of FIX adherence to collagen IV in the extravascular space in securing hemostasis [8]. This has been well demonstrated in mouse models of HB, where treatment with both wild-type FIX (Benefix™) and rFIX-Fc (Alprolix™) maintained adequate hemostasis for 7 days, despite undetectable plasma FIX activity [9]. The authors speculated that bleed protection was maintained in the setting of low plasma levels because of the presence of extravascular FIX. In this case series, we observed the opposite scenario, namely impaired hemostasis in the presence of seemingly adequate FIX plasma levels in patients on the albumin fusion protein product. One possibility is that these individuals fail to adequately saturate their extravascular compartment with hemostatically-active FIX at the usual prescribed prophylactic doses of 65 U/kg every 14 days. Infused FIX can distribute into the extravascular space and even displace wild-type FIX that may be present [9]. This has potential implications for patients with HB who have mutations in F9 that allow endogenous FIX to take up binding sites on collagen IV but not participate in clot formation. Whether this might account for poor hemostatic control in patients such as the ones we described here requires further research.

Why only a small minority of patients on rFIX-FP prophylaxis experience inadequate bleed control remains unexplained. It is clear, however, that this is a clinical phenomenon that warrants further investigation. A recent abstract reports the results of a survey of providers at four centers in the United States, in which a total of 13 out of 24 patients with severe HB on rFIX-FP experienced “unexpected bleeding or poorly controlled bleeding events” [10].

In conclusion, the trend that we observed in these patients with an unexpectedly high frequency of breakthrough bleeds while on prophylactic rFIX-FP raises concern that a proportion of treated patients fail to achieve adequate hemostatic control, even in the setting

of apparently adequate plasma activity levels. It is clear from these cases that prolongation of the plasma half-life of FIX in bioengineered molecules may not always equate to effective hemostasis. Clinicians who care for patients with hemophilia B on rFIX-FP prophylaxis should be alert to unexpected breakthrough bleeding and consider an adjustment in pharmacotherapy. More research is needed to determine the factors that contribute to breakthrough bleeds on fusion protein extended half-life products, and who is at risk for this phenomenon.

Acknowledgements

B Kleiboer was supported by NIH grant T32 HL007149

Declarations of Interest

Dr. Kleiboer reports personal fees from Novo Nordisk, personal fees from Grifols, personal fees from Takeda, outside the submitted work.

Ms. Nielsen has no conflicts of interest to disclose.

Dr. Ma reports personal fees from Novo Nordisk, personal fees and other from Shire/Takeda, personal fees from CSL Behring, outside the submitted work.

Dr. Abajas reports personal fees from CSL Behring, personal fees from Bayer, personal fees from National Hemophilia Foundation, personal fees from Octapharma, personal fees from Genentech, outside the submitted work.

Dr. Monroe has no conflicts of interest to disclose.

Dr. Key reports personal fees from Uniqure, grants from Shire, grants from Pfizer, grants from Grifols, outside the submitted work.

References

1. Santagostino E, Martinowitz U, Lissitchkov T, et al. Long-acting recombinant coagulation factor IX albumin fusion protein (rFIX-FP) in hemophilia B: results of a phase 3 trial. *Blood*. 2016; 127(14): 1761–9. [PubMed: 26755710]
2. Korth-Bradley JM, Rendo P, Smith L, et al. Altisent C Pharmacokinetics, efficacy, and safety of Nonacog Alfa in previously treated patients with moderately severe to severe hemophilia B. *Clin Ther*. 2016; 38(4):936–944. [PubMed: 26969334]
3. Björkman S Population pharmacokinetics of recombinant factor IX: implications for dose tailoring. *Haemophilia*. 2013; 19(5):753–757. [PubMed: 23731351]
4. Diao L, Li S, Ludden T, Gobburu J, Nestorov I, Jiang H. Population pharmacokinetic modelling of recombinant factor IX Fc fusion protein (rFIXFc) in patients with haemophilia B. *Clin Pharmacokinet*. 2014; 53(5): 467–477. [PubMed: 24452809]
5. Santagostino E, Negrier C, Klamroth R, et al. Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rFIX-FP) in hemophilia B patients. *Blood*. 2012; 120(12): 2405–2411. [PubMed: 22859609]
6. Herzog E, Harris S, Henson C, et al. Biodistribution of the recombinant fusion protein linking coagulation factor IX with albumin (rFIX-FP) in rats. *Thromb Res*. 2014; 133(5): 900–907. [PubMed: 24680550]
7. Chia J, Loubser J, Glauser I, et al. Half-life– extended recombinant coagulation factor IX– albumin fusion protein is recycled via the FcRn-mediated pathway. *J Biol Chem*. 2018; 293(17):6363–6373. [PubMed: 29523681]
8. Feng D, Stafford KA, Broze GJ, Stafford DW. Evidence of clinically significant extravascular stores of Factor IX. *J Thromb Haemost*. 2013 12; 11(12): 2176–2178. [PubMed: 24112220]

9. Stern DM, Drillings M, Nossel HL, Hurlet-Jensen A, LaGamma KS, Owen J. Binding of factors IX and IXa to cultured vascular endothelial cells. *Proc Natl Acad Sci USA*. 1983; 80(13):4119–23. [PubMed: 6602986]
10. Malec LM, Croteau SE, Callaghan M, Sidonio R. Spontaneous bleeding and poor bleeding response with extended half-life factor IX products: a survey of select US hemophilia treatment centers. *Res Pract Thromb Haemost*. 2019;3(Suppl. 1):45

Table 1.

Demographic and Clinical Characteristics of Patients

	Age (years)	Race	Endogenous Baseline Factor IX Activity	History of FIX Inhibitor	<i>F9</i> Pathogenic Variant
Case 1	71	Caucasian	<1%	No	<i>F9</i> c.967G>T; p.Glu323*
Case 2	32	African-American	<1%	No	<i>F9</i> c.1230T>G; p.Asp410Glu
Case 3	56	Caucasian	<1%	No	<i>F9</i> c.689G>A; p.Gly230Glu