


Clinical Utility of Subcutaneous Factor VIII Replacement Therapies in Hemophilia A: A Review of the Evidence

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Abstract: Hemophilia therapies have tremendously improved over the last decades with the development of prolonged half-life factor VIII (FVIII) and FIX concentrates, non-factor therapies, such as emicizumab, anti-TFPI antibodies or siRNA antithrombin and gene therapy. All of these new molecules significantly reduced the burden of the disease and improved the quality of life of patients with severe hemophilia. Emicizumab, a non-factor therapy, is currently the only subcutaneous molecule available for prophylactic treatment of severe hemophilia A. Because of the subcutaneous route of delivery and similar efficacy to FVIII replacement therapy, emicizumab has been rapidly adopted by patients and their families. This clinical observation emphasizes the relevance and need for the development of subcutaneous FVIII concentrates. Here, we report evidence-based advantages and interest in the subcutaneous route of administration for the treatment of hemophilia A and review the stages of development of the different subcutaneous FVIII molecules.

Keywords: hemophilia A, factor VIII, recombinant von Willebrand factor fragment, prophylaxis, subcutaneous injection

Therapeutic Progress in Hemophilia A

Hemophilia A (HA) is an X-linked inherited bleeding disorder resulting from the partial or total deficiency of coagulation factor VIII (FVIII). Severe HA, characterized by a complete plasma FVIII deficiency, is a rare disease with a prevalence of 6 per 100,000 males.¹ Patients with severe HA have a lifelong spontaneous bleeding tendency with frequent joint bleeds, muscle hematomas, intracranial hemorrhages, and hematuria occurring even in the absence of any noticeable trauma. Repeated joint bleeds lead to chronic arthropathy responsible for limitation of movements, pain, disability and decrease in patients' quality of life.

Early prophylaxis is currently the standard of care for severe HA because it significantly reduces the risk of life-threatening bleeding, hemarthroses and joint damage, compared to on-demand therapy, which consists of treating bleeding episodes.^{2,3} The need for frequent intravenous injections, due to the short half-life of FVIII molecule, ie 10–14 hours, has been one of the major barriers to the widespread use of prophylaxis, associated with difficult vein access and affordability. Thus, in the last decades extended half-life (EHL) coagulation factors have been developed to reduce the number of intravenous injections. Conjugation with

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polyethylene glycol (PEG) and fusion with albumin or Fc fragment of IgG1 have been used to generate several EHL products.⁴ Pharmacokinetic (PK) improvements obtained with EHL-FVIII products were 1.3 to 1.8 fold-increased terminal half-life, mean trough FVIII levels between 1 and 3 IU/dL with infusions every 3–5 days and 30% reduction in the number of intravenous injections.⁵ These characteristics improved patient adherence to prophylaxis, quality of life of patients and their families and opened new perspectives for more personalized prophylaxis regimens.⁶ Despite the advantages of EHL-FVIII, it is to be noted that the improvements of PK for EHL-FVIII were modest compared to EHL-factor IX products produced with similar technologies and having 3 to 5 times-prolonged half-life. This difference is explained by the fact that EHL-FVIII molecules can still interact with endogenous von Willebrand factor (VWF), which has a relatively short half-life (~15 hours) and are cleared as part of the FVIII-VWF complex.⁷ The experience with the first EHL molecules allowed a better understanding of the mechanisms responsible for the prolonged half-life and led to the development of new molecules. Thus, a novel recombinant FVIII molecule BIVV001 was recently bioengineered to overcome this limited half-life extension issue imposed by VWF.⁸ BIVV001 is an EHL-FVIII fused to Fc fragment coupled with the FVIII binding D'D3 domain of VWF and two XTEN linkers aiming to reduce degradation and clearance.⁹ A recent Phase 1–2a open-label clinical trial reported a significantly prolonged half-life of BIVV01 that was up to four times the half-life associated with standard recombinant FVIII (rFVIII), allowing an FVIII prophylaxis with a weekly treatment interval.¹⁰

Despite the improvements achieved, the exclusive intravenous route of administration of EHL-FVIII products remains a substantial source of burden for patients and caregivers. To date, only one non-factor therapy, emicizumab, has been administered subcutaneously. Emicizumab is a bispecific humanized monoclonal antibody mimicking activated FVIII activity into the tenase complex.¹¹ The molecule, designed for prophylaxis with once a week to once a month regimens and delivered subcutaneously, showed similar effectiveness to reference molecules in patients with and without inhibitors.¹² The transition from factor concentrates administered intravenously to a subcutaneous route of administration with emicizumab has been a strong argument in favor of the new drug for patients and their families.

Novel Routes for the Administration of Coagulation Factors

For a medication to be effective it must be administered appropriately. The route of administration of a drug affects its bioavailability, which determines both the onset and the duration of the pharmacological effect. The vast majority of treatments available for hemophilia are usually delivered intravenously. However, some subcutaneous drugs are used in certain situations, and research is very active for the development of new molecules with more convenient routes of administration.

The hemostatic drug desmopressin (DDAVP) is commonly and effectively used in most cases of mild or moderate bleedings of patients with mild HA. DDAVP can be administered intravenously, subcutaneously and as a nasal spray.¹³ The nasal spray and subcutaneous DDAVP are very convenient for home treatment. Knowledge accumulated through research on EHL-factors and their interaction with neonatal Fc receptor (FcRn) might open new perspectives for nasal delivery of coagulation factors to treat hemophilia. It is known that the prolonged half-life of these molecules is related to the FcRn-mediated recycling of the modified FVIII/FIX molecules. FcRn is expressed in the nasal airway and the olfactory epithelium, and we may speculate that FcRn may play a role in Fc-mediated transport of IgG or albumin fused to FVIII/FIX across the nasal epithelium and might have significant potential for intranasal delivery.

Recently, Nichols et al¹⁴ reported the first experience of orally delivered FVIII in a HA dog model. The authors evaluated safety and efficacy of delivering FVIII via orally ingestible robotic pills. Results were compared to a similar dose of FVIII 150 IU/kg administered intravenously or intraperitoneally. This early preclinical study showed that orally delivered FVIII restored hemostasis in HA dog. While waiting for the maturation of this work clinically, the progress achieved in adopting the subcutaneous route remains appealing.

Subcutaneous Coagulation Factors for the Treatment of Hemophilia A with or without Inhibitors

Subcutaneous deliveries of biotherapeutics for hemophilia, such as emicizumab or fitusiran (small interfering RNA that knocks down the synthesis of antithrombin), are convenient alternatives to intravenously delivered factor VIII. The first subcutaneous monoclonal antibodies were

developed and labeled in oncology. These drugs became rapidly preferred by patients as they reduced the burden of intravenous administrations. Subcutaneously delivered drugs have been proven effective, safe and are associated with lower healthcare costs,¹⁵ even though they have different pharmacokinetic profiles compared to their peers administered intravenously. Maximum serum concentrations (C_{max}) of these molecules are usually delayed because of a slow absorption rate from the subcutaneous tissue. In addition, a linear relationship was reported between molecular weight (MW) of biotherapeutics and the rate of lymphatic absorption. Molecules with MW greater than 16,000 Da are first absorbed by lymphatic vessels and pass through the thoracic duct, whilst smaller molecules cross directly through the capillary wall into the blood stream.¹⁶ Human FVIII is a large molecule with an MW of 330,000 Da; B-domain deleted rFVIII is a metal ion linked 80,000- and 90,000- Da heterodimer.¹⁷

The first attempt of subcutaneous FVIII administration was reported in the late 1990s by Spira et al.¹⁸ However, subcutaneous delivery of standard FVIII resulted in limited bioavailability: 5% to 10% in several animal models. In a mice model, Shi et al¹⁹ confirmed this observation. The authors investigated whether subcutaneously administered FVIII could be transferred from extra-vascular space into the vascular space. They did not detect FVIII in the plasma following subcutaneous injection.

Fatouros et al studied the mechanisms underlying the low bioavailability of subcutaneous FVIII.²⁰ They concluded that subcutaneous rFVIII was inactivated in the subcutaneous tissue by proteolytic degradation, after binding to phospholipids. Von Willebrand (VWF) factor and FVIII circulate in blood as a non-covalently linked complex. VWF protects FVIII from proteolytic degradation by phospholipid-binding proteases like activated protein C.²¹ This protection is due to the binding of D3 domain of the VWF molecule to the C1 domain of FVIII.

In the light of this knowledge, small recombinant VWF fragments were bioengineered to protect FVIII from phospholipid binding. Among the bioengineered VWF fragments, the best bioavailability results were obtained with vWF-12 construct. In a recent preclinical study, FVIII was co-administered with this “protector” recombinant VWF fragment to mini-pigs²² and to factor VIII knock-out mice.²³ Solecka-Witulska et al²² expressed the vWF-12 fragment as a dimer of the VWF-D'D3 region containing amino acids 1 to 1268 of the VWF sequence fused to a highly O-glycosylated 31 amino acids sequence repeated

twice at the C terminus. This VWF fragment has binding capacity to FVIII with high affinity (in the nM range) and inhibits the interaction between FVIII and phospholipids, which supports subcutaneous uptake of FVIII. Aachener mini-pigs received 100 IU/kg rFVIII co-delivered with VWF-12 fragment. Blood was taken prior, and 11 blood samples were taken at different time points up to 120 h after drug administration, and FVIII antigen concentrations were measured in each sample. The authors showed that the bioavailability of rFVIII alone was 2% whilst the co-administration of rFVIII with VWF-12 fragment increased the bioavailability of rFVIII to 41%.

Recently, Vollack-Hesse et al²³ compared pharmacokinetic (PK) profiles after a single dose of rFVIII administered intravenously (200 IU/kg) or subcutaneously (1000 IU/kg) in the presence or absence of the VWF-12 construct in a HA mice model. They confirmed enhanced bioavailability (up to 18.5%) of subcutaneous rFVIII co-administered with VWF-12. As expected, PK profiles of intravenous and subcutaneous rFVIII were very different. Subcutaneous FVIII had a slow absorption leading to a plasma C_{max} 6 hours after drug administration and had 2.5-fold longer half-life compared to intravenous rFVIII. Pharmacodynamics of the co-administered rFVIII with vWF-12 fragment was evaluated with tail-clip assay that showed an efficient protection against bleeding during 24 hours after a single subcutaneous injection. These promising results, obtained using VWF-12 fragment as a chaperone to FVIII for subcutaneous administration, open new perspectives for the development of novel subcutaneous rFVIII molecules and an opportunity for patients with severe HA who may have replacement therapy with a subcutaneous rFVIII.

Subcutaneous delivery of coagulation factors was always feared for concerns about immunogenicity, particularly for FVIII. The mice data reports that the formation of anti-FVIII IgG antibodies did not increase after subcutaneous administration compared to intravenous route, which plays in favor of this approach.

Preclinical studies with glycopegylated rFVIII N8-GP in HA mice and cynomolgus monkeys showed improved bioavailability of the molecule compared to standard half-life FVIII.²⁴ Using this EHL-rFVIII molecule, Klamroth et al²⁵ reported the results of the first human subcutaneous rFVIII trial. This phase 1, double-blinded, multicenter trial had two parts: in the first part, patients received a single subcutaneous (SQ) dose (12.5–25–50 or 100 IU/kg) of turoctocog alfa pegol (N8-GP). The second part was

a multiple dose study and patients received 2000 or 4000 IU SQ N8-GP daily during 3 months. Administered dose was dependent on the patient's body weight (below or ≥ 60 kg respectively). The authors studied pharmacokinetics, safety and preliminary efficacy of SQ N8-GP in previously treated patients with severe HA. The multiple dose study reported FVIII activity levels of 11.9% (9.0 to 15.6) at week 1 and 9.6% (7.3 to 12.7) at week 13 of the study. Five of the 26 patients (19.2%) developed non-neutralizing anti-N8-GP binding antibodies and 1 patient developed inhibitors to FVIII.

In parallel, a bioengineered subcutaneous factor VIIa has also been developed (activated marzeptacog alfa).²⁶ Activated recombinant factor VII (rFVIIa), administered intravenously, is commonly used for the treatment of hemophilia with inhibitors. The molecule has a very short half-life of 2.3 hours (range 1.7–2.7). Activated marzeptacog alfa (MarzAA) is a variant of rFVIIa with 4 amino acids substitutions. Two of the substitutions (Q286R and M298Q in the heavy chain) increase the catalytic activity of the molecule for factor X activation and two others (T128N and P129A, in the light chain) provide extended duration of biological activity. Recently, the results of a Phase 2 study investigating the prophylactic efficacy of subcutaneous MarzAA in hemophiliacs with inhibitors were published.²⁷ All patients had a baseline annualized bleeding rate (ABR) ≥ 12 events/year, as determined during the 6-months pre-treatment period. MarzAA was administered subcutaneously at a daily dose of 30 $\mu\text{g}/\text{kg}$ for 50 days. The volume of subcutaneous injection was low (0.6 mL). Subcutaneous MarzAA prophylaxis reduced mean ABR from 19.8 (range 12.2–26.7) to 1.6 ($p = 0.009$).

Strengths and Weaknesses of Subcutaneous FVIII Molecules

The rationale behind the design of subcutaneous FVIII molecules is to overcome the difficulties of intravenous delivery. While peripheral venipuncture is the first choice for venous access, central venous access devices are frequently used to facilitate repeated administration of clotting factor concentrates, particularly in very young children and adults with poor IV access. Subcutaneous route can also reduce the need for central venous access devices and their common complications, such as infection and thrombosis.²⁸ The development of subcutaneous FVIII concentrates may improve prophylaxis feasibility and patient's adherence.

Each intravenous injection of prophylaxis that cannot be performed increases the risk of breakthrough bleeds.

In addition, there are several advantages of subcutaneous FVIII concentrates over non-factor therapies that are delivered subcutaneously. These benefits include:

- The possibility of laboratory monitoring with usual, widely available, easy to perform and cheap routine FVIII assays. The utility of laboratory monitoring is obvious in certain situations such as surgical settings and to individualize therapy and tailor it to patient's needs and lifestyle.

- No need to administer other procoagulant molecules in case of acute bleeding or surgery. This need persists with nonfactor therapy in some circumstances. Adding to the complexity of this scenario, where monitoring poses a major problem and concerns about interference between the two drugs persist, patients used to subcutaneous injections may lose with time the expertise and autonomy of intravascular administration. Subcutaneous FVIII molecules may help to overcome this issue.

- Non-factor therapies do not cover any potential non-hemostatic role of FVIII, and the long-term impact of nonfactor replacement therapy in patients with no inhibitors is still unclear. In addition to the concerns about the maintenance of immunological tolerability, the effect of such therapies on joint health remains the focus of ongoing research. Indeed, several clinical studies have described osteopenia in patients with HA. Twenty-seven per cent of patients with severe HA experience osteoporosis, responsible for a significant risk of fracture. It has been demonstrated that FVIII replacement partly prevents the loss of bone mineral density in patients with severe HA. Some authors suggest that the effect of FVIII on bone might be associated with the regulation of RANKL–OPG, which can influence the synthesis of osteoclasts and therefore bone resorption.²⁹ Thus, if these preliminary data are confirmed in well-designed clinical studies, FVIII replacement therapy may have a relevant advantage over non-factor therapies.

In addition, the main advantages of subcutaneous FVIII concentrates over intravenous FVIII concentrates are:

- better quality of life and comfort for patients and their families
- no need for central venous access devices, allowing to start conveniently prophylaxis at very early age
- better adherence of patients to treatment and reduced breakthrough bleeds

- highest autonomy of patients with their treatment and lower costs
- potential lower immunogenicity as suggested by pre-clinical studies: decreased immunogenicity observed in animal models with co-delivery of rFVIII and VWF-12 fragment is promising. Some previous studies reported that VWF protects FVIII against endocytosis by dendritic cells, and reduces the presentation of FVIII to immune cells. Co-administration of FVIII with a particular VWF fragment may potentially reduce the recognition of FVIII by the immune system. If confirmed in clinical trials, this will allow to study whether SQ FVIII with VWF can be optimal to establish immune tolerance to FVIII in previously untreated patients, especially those at high risk of inhibitor development.

However, subcutaneous route of administration may also have some disadvantages. Large volumes of injection may be an issue in young children and may require multiple SQ injections, which is a clear source of discomfort for patients.

Conclusion

In conclusion, the development of subcutaneous FVIII molecules is of great clinical interest, reducing tremendously the burden of prophylaxis in severe HA patients, and therefore improving treatment adherence with subsequent reduction in breakthrough bleeds and better joint protection. However, even though a subcutaneous injection is easier to perform than an intravenous injection, it remains a painful procedure. Other administration routes that are less painful in nature and more practical for a busy school or professional schedule, such as the oral or intranasal route, may in the future expand the recent improvements offered by the subcutaneous route.

Disclosure

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References

1. Iorio A, Stonebracker 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;171:540–546. doi:10.7326/M19-1208
2. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med.* 2007;357:535–544. doi:10.1056/NEJMoa067659
3. Gringeri A, Lundin B, von Mackensen S, Mantovani L, Mannucci PM; ESPRIT Study Group. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). *J Thromb Haemost.* 2011;9:700–710. doi:10.1111/j.1538-7836.2011.04214.x
4. Mannucci PM. Hemophilia therapy: the future has begun. *Haematologica.* 2020;105:545–553. doi:10.3324/haematol.2019.232132
5. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. *Lancet.* 2021;397:630–640. doi:10.1016/S0140-6736(20)32722-7
6. Oldenburg J, Hay CRM, Jiménez-Yuste V, et al. Design of a prospective observational study on the effectiveness and real-world usage of recombinant factor VIII Fc (rFVIII-Fc) compared with conventional products in haemophilia A: the A-SURE study. *BMJ Open.* 2019;9(5):e028012. doi:10.1136/bmjopen-2018-028012
7. Pipe SW, Montgomery RR, Pratt KP, Lenting PJ, Lillicrap D. Life in the shadow of a dominant partner: the FVIII-VWF association and its clinical implications for hemophilia A. *Blood.* 2016;128(16):2007–2016. doi:10.1182/blood-2016-04-713289
8. Chhabra ES, Liu T, Kulman J, et al. BIVV001, a new class of factor VIII replacement for hemophilia A that is independent of von Willebrand factor in primates and mice. *Blood.* 2020;135:1484–1496. doi:10.1182/blood.2019001292
9. Fuller JR, Knockenhauer KE, Leksa NC, Peters RT, Batchelor JD. Molecular determinants of the factor VIII/von Willebrand factor complex revealed by BIVV001 cryo-electron microscopy. *Blood.* 2021;137:2970–2980. doi:10.1182/blood.2020009197
10. Konkle B, Shapiro AD, Quon DV, et al. BIVV001 fusion protein as factor VIII replacement therapy for hemophilia A. *N Engl J Med.* 2020;383:1018–1027. doi:10.1056/NEJMoa2002699
11. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med.* 2017;377:809–818. doi:10.1056/NEJMoa1703068
12. Rodriguez-Merchan EC, Valentino AL. Emicizumab: review of the literature and critical appraisal. *Haemophilia.* 2019;25:11–20. doi:10.1111/hae.13641
13. Noye J, Rowell JA, Zeissink B, Connolly A, Mason JA. A fixed ‘single vial’ dose of subcutaneous desmopressin (DDAVP) produces adequate biologic responses for persons with mild haemophilia A. *Haemophilia.* 2021;27(4):e540–e542. doi:10.1111/hae.14287
14. Hashim MA, Yamaguchi A, Vo AT, et al. Orally delivered factor VIII restores hemostasis in a hemophilia A dog. ISTH 2021 Congress. Abstract number: OC 48.4.
15. Bittner B, Richter W, Schmidt J. Subcutaneous administration of biotherapeutics: an overview of current challenges and opportunities. *BioDrugs.* 2018;32:425–440. doi:10.1007/s40259-018-0295-0
16. Supersaxo A, Steffen WRH, Steffen H. Effect of molecular weight on the lymphatic absorption of water-soluble compounds following subcutaneous administration. *Pharm Res.* 1990;7:167–169. doi:10.1023/A:1015880819328
17. Lind P, Larsson K, Spira J, et al. Novel forms of B-domain deleted recombinant factor VIII molecules. Construction and biochemical characterization. *Eur J Biochem.* 1995;232:19–27. doi:10.1111/j.1432-1033.1995.tb20776.x

18. Spira J, Widlund L, Österberg T, et al. Pharmaceutical formulation for subcutaneous, intramuscular or intradermal administration of factor VIII of factor IX. International patent application: US patent US5925739A, European patent EP0772452. International filing. 1995 March 30.
19. Shi Q, Kuetner EL, Schroeder JA, Fahs SA, Montgomery RR. Intravascular recovery of VWF and FVIII following intraperitoneal injection and differences from intravenous and subcutaneous injection in mice. *Haemophilia*. 2012;18:639–646. doi:10.1111/j.1365-2516.2011.02735.x
20. Fatouros A, Liden Y, Sjostrom B. Recombinant factor VIII SQ-stability of FVIII:C in homogenates from porcine, monkey and human subcutaneous tissue. *J Pharm Pharmacol*. 2000;52:797–805. doi:10.1211/0022357001774651
21. Sadler JE. New concepts in von Willebrand disease. *Annu Rev Med*. 2005;56:173–191. doi:10.1146/annurev.med.56.082103.104713
22. Solecka-Wituska BA, Wuschko S, Kannicht C. Pharmacokinetics of subcutaneously administered simoctocog alfa with von Willebrand factor fragment candidates in a minipig model. *Blood*. 2017;130(9):1073. doi:10.1182/blood-2017-07-793356
23. Vollack-Hesse N, Olshko O, Werwitzke S, Solecka-Witulska B, Kannicht C, Tiede A. Recombinant VWF fragments improve bioavailability of subcutaneous factor VIII in hemophilia A mice. *Blood*. 2021;137:1072–1081. doi:10.1182/blood.202006468
24. Rode F, Almholt K, Petersen M, et al. Preclinical pharmacokinetics and biodistribution of subcutaneously administered glycoPEGylated recombinant factor VIII (N8-GP) and development of a human pharmacokinetic prediction model. *J Thromb Haemost*. 2018;16:1141–1152. doi:10.1111/jth.14013
25. Klamroth R, Feistritz C, Friedrich U, et al. Immunogenicity, safety, pharmacokinetics and preliminary efficacy results from the first human subcutaneous factor VIII trial (subcutaneous turoctocog alfa pegol, SC N8-GP) in previously treated patients with hemophilia A (Alleviate 1). *J Thromb Haemost*. 2020;18:341–351. doi:10.1111/jth.14660
26. Pittman D, Weston S, Shields K, et al. A novel FVIIa variant with increased potency and duration of effect compared to wildtype FVIIa. A study in a dog model of hemophilia A. *Blood*. 2011;118:2252. doi:10.1182/blood.V118.21.2252.2252
27. Mahlangu J, Levy H, Kosinova MV, et al. Subcutaneous engineered factor VIIa marzeptacog alfa (activated) in hemophilia with inhibitors: phase 2 trial of pharmacokinetics, pharmacodynamics, efficacy, and safety. *Res Pract Thromb Haemost*. 2021;5:e12576. doi:10.1002/rth2.12576
28. Titapiwatanakun R, Moir C, Pruthi RK, Stavlo PL, Schmidt KA, Rodriguez V. Central venous access devices for paediatric patients with haemophilia: a single-institution experience. *Haemophilia*. 2009;15:168–174. doi:10.1111/j.1365-2516.2008.01906.x
29. Cadé M, Muñoz-García J, Babuty A, et al. FVIII at the crossroad of coagulation, bone and immune biology: emerging evidence of biological activities beyond hemostasis. *Drug Discov Today*. 2021. doi:10.1016/j.drudis.2021.07.015

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