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D Quon; J Wang; M Wang; D Pepperell; Johnny Mahlangu ...

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Outcomes and management of invasive procedures in participants with hemophilia A post gene therapy: a post hoc analysis of the GENEr8-1 phase III trial

Ther Adv Hematol

2024, Vol. 15: 1–10

DOI: 10.1177/20406207241304645

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Doris V. Quon, Jiaan-Der Wang, Michael Wang, Dominic Pepperell, Young-Shil Park, Gili Kenet, Johnny Mahlangu, Teh-Liane Khoo, Tara M. Robinson, Konstantia-Maria Chavele and Steven W. Pipe

Correspondence to:
Doris V. Quon
Orthopaedic Hemophilia Treatment Center, 403 West Adams Blvd., Los Angeles, CA 90007, USA
DQuon@mednet.ucla.edu

Jiaan-Der Wang
Center for Rare Disease and Hemophilia, Taichung Veterans General Hospital, Taichung, Taiwan

Michael Wang
Hemophilia and Thrombosis Center, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Dominic Pepperell
Department of Haematology, Fiona Stanley Hospital, Murdoch, WA, Australia

Young-Shil Park
Kyung Hee University Hospital at Gangdong, Seoul, South Korea

Gili Kenet
The National Hemophilia Center and Amalia Biron Research Institute of Thrombosis and Hemostasis, Sheba Medical Center, Tel Hashomer, Tel Aviv University, Tel Aviv, Israel

Johnny Mahlangu
Hemophilia Comprehensive Care Center, Charlotte Maxeke Johannesburg Academic Hospital, University of the Witwatersrand and NHLS, Johannesburg, South Africa

Teh-Liane Khoo
Haematology Department, Haemophilia Treatment Center, The Royal Prince Alfred Hospital, Sydney, NSW, Australia

Tara M. Robinson
Konstantia-Maria Chavele
BioMarin Pharmaceutical Inc., Novato, CA, USA

Steven W. Pipe
Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, MI, USA

Abstract

Background: Hemophilia A is caused by coagulation factor VIII (FVIII) deficiency and increases bleeding risk during invasive procedures.

Objectives: To investigate FVIII concentrate use and bleeding outcomes for invasive procedures after valoctocogene roxaparvovec gene transfer.

Design: This manuscript presents post hoc analysis of the phase III GENEr8-1 trial.

Methods: A post hoc analysis was performed for GENEr8-1, a global, single-arm, open-label, phase III trial that enrolled 134 adults with severe hemophilia A. FVIII activity and bleeding were evaluated after 2 years of follow-up. Invasive procedures were reviewed and categorized as major or minor. FVIII activity was measured with a chromogenic assay. Bleeding was self-reported by participants. Principal investigators completed questionnaires about perioperative management.

Results: In total, 111 invasive procedures were performed in 65 participants during GENEr8-1 as of the data cut. Procedures performed with FVIII treatment included 33 minor and 11 major procedures. The remaining 67 invasive procedures were minor and performed without FVIII treatment. When considering these 67 minor procedures, 43/46 investigators completing the questionnaires reported that the gene-therapy-derived FVIII activity was sufficient for the type of procedure. Minor procedures performed without FVIII treatment were associated with participants' higher mean endogenous FVIII activity (50.5 IU/dL) compared with major procedures (14.2 IU/dL) or minor procedures (16.4 IU/dL) performed with concomitant FVIII. Fourteen participants experienced 18 procedure-related bleeds (13 co-occurring with FVIII use). Participants who received FVIII treatment for procedure-related bleeds had numerically lower mean endogenous FVIII activity than those who did not receive FVIII treatment.

Conclusion: Invasive procedures were safely performed in participants following treatment with valoctocogene roxaparvovec. The questionnaire responses from investigators generally suggest they used endogenous FVIII activity derived from valoctocogene roxaparvovec to inform clinical decisions in a manner comparable to exogenously administered FVIII, and more commonly prescribed supplementary FVIII concentrate in the peri-procedural period for participants with lower FVIII activity levels.

Keywords: bleeding risk, gene therapy, hemophilia A, invasive procedures, valoctocogene roxaparvovec

Received: 10 May 2024; revised manuscript accepted: 15 November 2024.

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Introduction

Hemophilia A is an X-linked recessive bleeding disorder caused by coagulation factor VIII (FVIII) deficiency.[1] Severe hemophilia A, defined as FVIII levels <1 IU/dL, affects approximately 9.5 out of 100,000 males globally and is associated with an increased risk of spontaneous bleeding.[2] Currently, the standard of care for people with severe hemophilia A is prophylactic treatment with FVIII concentrate or bispecific antibodies that mimic activated FVIII function.[1] Despite the use of prophylaxis, on-demand treatment is still necessary for breakthrough and trauma-related bleeds or in advance of high-risk bleeding activities such as contact sports and some surgical procedures.[1] The need for frequent intravenous infusions can be burdensome and can have a negative impact on quality of life, and FVIII concentrate use is complicated by the risk of inhibitor formation.[1,3,4]

Valoctocogene roxaparvovec is an approved gene therapy for severe hemophilia A in the United States and Europe[5,6] that employs an adeno-associated virus serotype 5 vector to transfer a B-domain-deleted FVIII gene cassette under the regulatory control of a liver-selective promoter.[7] Valoctocogene roxaparvovec was evaluated in phase I/II (NCT02576795)[8–12] and phase III (GENEr8-1; NCT03370913)[13–15] clinical trials. The GENEr8-1 trial was a single-arm, open-label study of 134 participants with severe hemophilia A designed to evaluate the safety and efficacy of valoctocogene roxaparvovec. Collectively, results at 1, 2, and 3 years post gene therapy demonstrated that a single infusion of valoctocogene roxaparvovec supported endogenous FVIII production and reduced bleeding and FVIII use compared with FVIII prophylaxis.[13,14]

As life expectancy has increased among people with hemophilia A, treatment for age-related complications—both related and unrelated to hemophilia—have become more frequent, increasing the need for invasive procedures.[16,17] FVIII levels are an important consideration when individuals with hemophilia A need to undergo invasive procedures.[1] The World Federation of Hemophilia (WFH) has set generalized lower-limit guidelines for peak plasma FVIII levels according to procedure category. Recommendations for major procedures include preoperative FVIII levels of 60–80 IU/dL and postoperative FVIII levels of 30–40 IU/dL for 1–3 days with tapering of FVIII thereafter for up to 2 weeks. For minor procedures, WFH recommends preoperative FVIII levels of 40–80 IU/dL and subsequent FVIII levels of 20–50 IU/dL to maintain perioperative hemostatic support for an additional 1–5 days.[1] However, lower FVIII levels may be sufficient to enable hemostasis for certain procedures, and these guidelines may be conservative estimates that do not sufficiently acknowledge challenges with the availability of hemophilia A medication in some parts of the world.[18]

Generally, the risk of bleeding for individuals with hemophilia A is inversely correlated with circulating FVIII activity.[1] Whether valoctocogene roxaparvovec may provide hemostatic control during and after invasive medical procedures is therefore of key interest to clinicians and people with hemophilia A. To address this need, we performed a post hoc analysis of the 134 participants from the GENEr8-1 trial to characterize invasive procedures that were performed after participants received gene therapy, including whether exogenous FVIII was used and if bleeding occurred.

Methods

GENEr8-1

Briefly, male participants ⩾18 years of age were eligible to enroll in GENEr8-1 if they had severe congenital hemophilia A (residual FVIII activity level ⩽1 IU/dL), had been on a prophylactic FVIII concentrate regimen ⩾1 year prior to enrollment, and were negative for FVIII inhibitors. Participants were given a single infusion of 6×10^{13} vg/kg of valoctocogene roxaparvovec via peripheral vein and continued their prophylactic regimen of FVIII for at least 4 weeks following infusion. After discontinuing prophylaxis, FVIII concentrate was used as needed. Endogenous FVIII activity was measured with a chromogenic substrate assay (CSA) throughout the study. The CSA lower limit of quantitation changed from 3.0 to 1.5 IU/dL between years 1 and 2. The study protocol was approved by the independent ethics committees or institutional review boards of all study sites, and all participants provided written informed consent prior to enrollment. The reporting of this study conforms to the TREND statement,[19] and further details about GENEr8-1 have been published previously.[13,14]

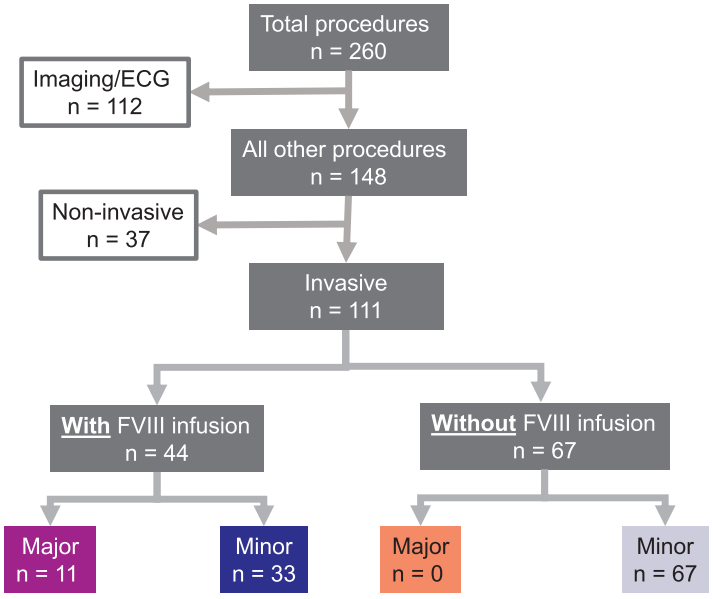

Figure 1. Procedure categorization and concomitant FVIII concentrate use. There were 77 participants who underwent a total of 260 procedures prior to the 2-year data cut. From these, 111 invasive procedures were performed in 65 participants.
ECG, electrocardiogram; FVIII, factor VIII.

Post hoc analysis

Throughout the GENEr8-1 trial, principal investigators documented all medical procedures for the trial participants after valoctocogene roxaparvovec infusion. For this post hoc analysis, the medical procedures as reported by the principal investigators were then categorized as either noninvasive (e.g., dental cleaning or tattooing) or invasive by the study authors. Invasive procedures were further subcategorized as major (e.g., joint debridement) or minor (e.g., dental extraction, depending on the number and type of teeth) according to previously published criteria.[16] Briefly, major procedures included general invasive surgical procedures, orthopedic surgical procedures except for chemical- or radio-arthroscopic synovectomies, and dental procedures involving ⩾3 teeth. Study participants self-reported all bleeding episodes by submitting bleed logs, in which they additionally noted if the episode was related to a medical procedure. The endogenous FVIII activity measurement most proximal to the medical procedure or bleeding event was used for this analysis. Decisions regarding the management of invasive procedures with exogenous FVIII were made at the discretion of the principal investigator, and no criteria were defined or included as part of this study. In addition to the information that was captured in the electronic database, principal investigators were then sent a questionnaire to obtain further information on clinical decision-making regarding the use of exogenous FVIII in these cases. For some types of minor procedures in which there was minimal risk of bleeding, such as phlebotomy or SARS-CoV-2 antibody tests, principal investigators were not sent questionnaires regarding decisions on FVIII use. All results are described as mean ± standard deviation unless otherwise noted; no hypothesis testing was performed.

Results

Study population and procedures

There were 134 participants in the GENEr8-1 intent-to-treat population, defined as those who received a single dose of 6×10^{13} vg/kg valoctocogene roxaparvovec.[14] Of these, 77 participants underwent a total of 260 procedures prior to the 2-year data cut. Imaging procedures and electrocardiograms, which carry minimal bleeding risk, were excluded from the analysis, and of the remaining 148 procedures, 37 were categorized as noninvasive procedures (Figure 1). The presented analysis focused on the remaining 111

Table 1. Demographics of participants who underwent procedures after gene therapy with valoctocogene roxaparvovec.

Baseline characteristic	Major procedure with FVIII treatment (*n* = 7)	Minor procedure with FVIII treatment (*n* = 21)	Minor procedure without FVIII treatment (*n* = 37)
Age at enrollment, years, mean ± SD	41.3 ± 14.3	35.8 ± 12.8	34.4 ± 11.1
Race			
White	4 (57.1)	13 (61.9)	27 (73.0)
Asian	3 (42.9)	4 (19.0)	7 (18.9)
Black or African American	0	3 (14.3)	2 (5.4)
Native Hawaiian or other Pacific Islander	0	0	1 (2.7)
Not provided	0	1 (4.8)	0
Ethnicity			
Not Hispanic or Latino	7 (100)	21 (100)	34 (91.9)
Hispanic or Latino	0	0	3 (8.1)
BMI, kg/m^2, mean ± SD	25.02 ± 3.42	25.23 ± 5.09	25.72 ± 4.62
Medical history			
History of exposure to HBV	2 (28.6)	4 (19.0)	4 (10.8)
History of exposure to HCV	5 (71.4)	8 (38.1)	16 (43.2)
History of HIV	1 (14.3)	1 (4.8)	1 (2.7)
Number of target joints			
0	5 (71.4)	18 (85.7)	23 (62.2)
1	0	1 (4.8)	5 (13.5)
2	0	1 (4.8)	5 (13.5)
3	2 (28.6)	0	2 (5.4)
>3	0	1 (4.8)	2 (5.4)

Data are presented as *n* (%) unless otherwise specified.
BMI, body mass index; FVIII, factor VIII; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation.

invasive procedures that were performed in 65 participants (Table 1). Concomitant FVIII treatment took place for 44/111 (39.6%) invasive procedures, 11 of which were categorized as major procedures and 33 as minor procedures. The 11 major procedures were performed for 7 participants (Table 2). The remaining 67/111 procedures were performed without concomitant FVIII treatment, and all were categorized as minor. The types of minor procedures performed with (Supplemental Table 1) or without (Supplemental Table 2) FVIII infusion are

Table 2. FVIII activity, reported bleeds, and concomitant medications associated with major procedures.

Procedure type	Preoperative* FVIII activity (CSA), IU/dL	Days post gene therapy	Reported bleeds	Concomitant medication dosing
Radial head excision, synovectomy, and debridement, including excision of the tip of the olecranon	22.6	372	No	No
Subtalar joint arthrodesis	<3.0	854	No	No
Bone allograft	<3.0	854	No	No
Right revision total elbow replacement	18	483	No	Dexamethasone, 6600 µg, once, IV
Left-ankle fusion	11.2	332	No	No
Right-ankle arthroscopy/ debridement	11.5	1087	No	Dexamethasone, 4 mg, once, IV
Left subtalar joint arthrodesis surgery	<1.5	1022	Yes	No
Excision arthroplasty	52.1	973	No	Dexamethasone, 6.6 mg, once, IV; tranexamic acid, 1 g, once, IV; tranexamic acid, 1000 mg, once, IV; tranexamic acid, 1000 mg, once, IV; tranexamic acid, 1000 mg, once, IV
CABG 4 vessels (ascending aorta-RSVG1-OM2-PLB-PDA, ascending aorta-RSVG2-LAD)	24.8	518	Yes	Tranexamic acid, 2 g, once, IV, premedication; red blood cells, 2 units, once, IV; plasma, 6 units, once, IV; hydrocortisone sodium succinate, 200 mg, once, IV
Fundoplication surgery	8.9	745	No	Tranexamic acid, 1 g, tid, PO
Wisdom tooth extraction	7.1	603	No	No

*The FVIII activity reported is the closest assessment recorded prior to the indicated procedure. The LLOQ for the CSA used to assess FVIII activity was 3.0 or 1.5 IU/dL.
CABG, coronary artery bypass graft; CSA, chromogenic substrate assay; FVIII, factor VIII; IV, intravenously; LAD, left anterior descending; LLOQ, lower limit of quantitation; OM2, obtuse marginal 2; PDA, posterior descending artery; PLB, posterior lateral branch; PO, orally; RSVG, reversed saphenous vein graft; tid, three times a day.

reported in the supplement. Minor dental surgeries, endoscopic procedures, and intra-articular joint injections were among those minor procedures performed both with and without FVIII treatment.

FVIII activity levels prior to medical procedures

For procedures that were managed with FVIII treatment, the participants' mean endogenous FVIII activity level prior to the procedures was 14.2 IU/dL (range, <3.0–52.1 IU/dL) for major procedures and 16.4 IU/dL (range, <3.0–93.2 IU/dL) for minor procedures (Table 3). For procedures that were managed without FVIII treatment, the participants' mean endogenous FVIII activity level prior to the procedures was 50.5 IU/dL (range, <3.0–255.7 IU/dL).

Procedure-associated FVIII administration

As expected, the mean total dose of FVIII concentrate administered for major procedures (255.4 IU/kg; range, 102.8–538.2 IU/kg; Table 3)

Table 3. Perioperative FVIII management for invasive procedures.

Procedure-associated FVIII administration	Minor invasive procedures	Major invasive procedures
Number of procedures, *n*	33	11
Mean endogenous FVIII* activity, IU/dL (range)	16.4 (<3.0–93.2)	14.2 (<3.0–52.1)
Mean FVIII dose, IU/kg (min–max)	67.2 (14–324)	255.4 (103–538)
Mean number of FVIII infusions, *n* (min–max)	2.2 (1–13)	8.8 (3–21)
Mean days of postoperative FVIII treatment, *n* (min–max)	1.8 (1–7)	6.9 (2–14)

FVIII, factor VIII; max, maximum; min, minimum.

was numerically higher compared with minor procedures (67.2 IU/kg; range, 13.7–324.3 IU/kg). Furthermore, major procedures were associated with a mean of 8.8 FVIII concentrate infusions (range, 3–21 infusions) over a mean of 6.9 days (range, 2–14 days). Minor procedures were associated with a mean of 2.2 FVIII infusions (range, 1–13 infusions) over a mean of 1.8 days (range, 1–7 days). Of the 33 minor procedures managed with FVIII treatment, 25 (75.8%) were managed with a single dose. Adjuvant therapies such as antifibrinolytic agents (tranexamic acid and aminocaproic acid) were also used during 10 procedures, including 2 minor procedures without FVIII administration, 5 minor procedures with FVIII administration, and 3 major invasive procedures with FVIII administration.

Bleeding episodes and associated FVIII activity

There were 18 acute procedure-related bleeding episodes (16 from minor procedures and 2 from major procedures) reported by 14 participants. From these, 13 were managed with FVIII treatment, and 5 were untreated (Figure 2). Participants reported that most bleeding episodes (14/18) occurred within 48 h of the procedure, whereas 2/18 were delayed, and there were insufficient data to determine the timing of the remaining two bleeding episodes. The maximum number of bleeds associated with any single procedure was three bleeds that occurred for a minor procedure performed with FVIII treatment. The mean endogenous FVIII activity for participants who did not receive treatment for a bleeding episode was 60.4 IU/dL (range, 14.1–117.9 IU/dL; $N=5$ bleeding episodes). The mean endogenous FVIII activity for participants who did receive treatment for a bleeding episode was 10.4 IU/dL (range, <3.0–45.2 IU/dL; $N=13$ bleeding episodes). In these cases of procedures managed with exogenous FVIII, the FVIII activity levels reported refer to FVIII activity derived from only the gene therapy, measured by the CSA, most proximal to the bleeding episode and do not include any contribution of FVIII activity derived from the exogenous FVIII administration.

Investigator rationales for treatment decisions

Study investigators were given questionnaires to determine the reasons underlying their decision to supplement individuals undergoing minor or major invasive procedures with FVIII. While there were a total of 67 invasive procedures performed without FVIII treatment, questionnaires were not sent for some procedures that carried minimal bleeding risk. Study investigators completed 46/52 questionnaires that were sent for minor procedures with bleeding risk that were performed without FVIII treatment. In 43/46 questionnaires, the clinician deemed endogenous FVIII activity derived from valoctocogene roxaparvovec treatment to be sufficient for the given procedure type. In the 11 major procedures, 6 questionnaires were completed, with 5/6 investigators indicating that the participant's FVIII levels achieved by the gene therapy were considered when making decisions about exogenous FVIII treatment and 1/6 suggesting that they were not considered.

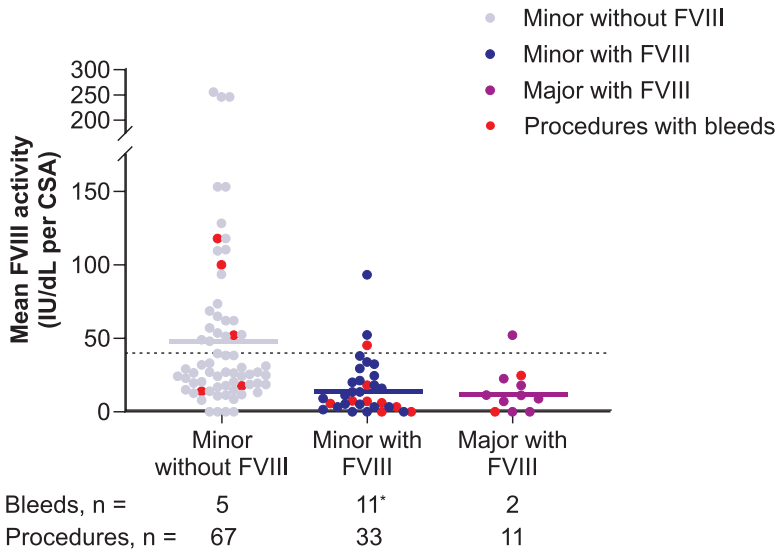

Figure 2. Mean FVIII activity and procedure-related bleeds by procedure category and concomitant FVIII concentrate use.
*For a minor procedure performed with FVIII, there were three associated bleeds. In the figure, these bleeding events are represented by a single FVIII value. The mean endogenous FVIII activity for each group is depicted by the horizontal bars. The *Y*-axis represents the closest mean FVIII activity recorded for each participant prior to the time of a procedure. FVIII activity was assessed by the CSA.
CSA, chromogenic substrate assay; FVIII, factor VIII.

We sought to examine these findings in the context of WFH guidelines for procedures performed in people with severe hemophilia A. The WFH recommends for minor procedures a minimum peak plasma FVIII level of 40 IU/dL preoperatively and 20 IU/dL postoperatively. During the GENEr8-1 trial, the participants' FVIII activity level met WFH preoperative guidelines for 24/67 (35.8%) minor procedures, and they met postoperative guidelines for 42/67 (62.7%) minor procedures.[1] Notably, 22/67 minor procedures were performed for participants with a FVIII activity level below 20 IU/dL (range, 0–19.7 IU/dL), and from these, only one participant reported a bleeding episode with an associated FVIII level of 14.1 IU/dL. The 13 investigators who completed questionnaires related to these procedures indicated that the participant's endogenous FVIII expression was sufficient for the procedure. For the remaining procedures, there were no completed questionnaires available.

Discussion

Individuals with severe hemophilia A have a high risk of bleeding when undergoing invasive procedures. While valoctocogene roxaparvovec supports endogenous FVIII production to prevent bleeding and reduce FVIII concentrate use in people with severe hemophilia A, it was unknown how these parameters affect invasive procedure-related outcomes. We used data from the GENEr8-1 trial population to investigate these relationships and present them in the context of current standard-of-care guidelines.

Decisions on whether to manage invasive procedures with FVIII treatment were left to the discretion of the principal investigators managing the participants. Most of the minor invasive procedures performed in participants of GENEr8-1 were managed without supplementary FVIII concentrate use, and similar types of procedures, such as dental, endoscopic, and joint-related procedures, were performed both with and without FVIII treatment. For the minor procedures that were managed with FVIII treatment, the respective participants generally had lower endogenous FVIII levels derived from the gene therapy. However, regardless of the participant's gene-therapy-derived FVIII level, all major procedures were managed with FVIII treatment. Importantly, there were only 18 procedure-related bleeding episodes reported by the participants for all procedure types. Overall, the results suggest that after valoctocogene roxaparvovec infusion,

invasive procedures can be safely performed with appropriate use of concomitant FVIII treatment as needed.

These findings on procedure-related bleeding outcomes in participants of GENEr8-1 contribute to the field by leveraging the continuous FVIII monitoring included as part of the GENEr8-1 study design to provide insight on real-world management decisions in relation to FVIII status. There were 43 minor procedures performed for participants with FVIII activity levels below 40 IU/dL. However, the majority of investigators still indicated that they felt the participant's endogenous FVIII levels were sufficient for the respective minor procedure. Furthermore, of the 22 minor procedures performed for participants with FVIII activity levels below 20 IU/dL, only 1 experienced a procedure-related bleed. Of note, the FVIII levels reported in this manuscript were measured using the CSA; these values would be higher (approximately 1.5-fold) if measured with the one-stage assay.[13] Collectively, these outcomes reinforce that individualized decisions should take into account the participant's health, medical history, FVIII level, procedure type, and bleeding risk.

Limitations

Whereas self-reported bleeding logs facilitated the large dataset analyzed here, the lack of clinician-reported bleeds introduces the possibility that some procedure-related bleeds were unreported or, conversely, that some nonrelated bleeds were misattributed to a procedure. The bleed logs also did not collect data on the type of bleed or the severity of the bleed. By extension, even though a bleed may have been related to a procedure, we cannot definitively attribute the cause to FVIII deficiency without clinician input. For example, some bleeds may have been expected based on the procedure type, such as the coronary artery bypass graft, even for individuals without hemophilia A. Finally, as the timing of FVIII infusions (pre- vs postoperative) was not included as part of our dataset, we are only able to report whether FVIII concentrate use occurred on the day of a procedure.

Conclusion

Invasive procedures can be safely performed with and without concomitant FVIII use in people with severe hemophilia A after treatment with valoctocogene roxaparvovec. Although most participants in the GENEr8-1 trial had sufficient endogenous FVIII activity to avoid additional FVIII supplementation for minor procedures, FVIII concentrate was used if necessary. Thus, valoctocogene roxaparvovec-induced endogenous FVIII production facilitates personalized healthcare. In most instances, the confluence of individual FVIII levels, participant-investigator discussions, and procedure type determined the use of FVIII concentrate for an invasive procedure.

Declarations

Ethics approval and consent to participate

This manuscript presents a post hoc analysis of a previously conducted study and does not include the addition of new studies with human participants or human tissue. The GENEr8-1 protocol was previously reported and approved by the institutional review boards or independent ethics committees of all participating sites. All GENEr8-1 participants provided written informed consent. The trial was performed in accordance with the ethical principles set forth by the Declaration of Helsinki.

Consent for publication

Not applicable.

Author contributions

Doris V. Quon: Investigation; Writing – review & editing.

Jiaan-Der Wang: Investigation; Writing – review & editing.

Michael Wang: Investigation; Writing – review & editing.

Dominic Pepperell: Investigation; Writing – review & editing.

Young-Shil Park: Investigation; Writing – review & editing.

Gili Kenet: Investigation; Writing – review & editing.

Johnny Mahlangu: Investigation; Writing – review & editing.

Teh-Liane Khoo: Investigation; Writing – review & editing.

Tara M. Robinson: Conceptualization; Project administration; Writing – review & editing.

Konstantia-Maria Chavele: Formal analysis; Writing – review & editing.

Steven W. Pipe: Investigation; Writing – review & editing.

Acknowledgements

We thank all study participants and their families, trial principal investigators, and study site personnel. We also thank members of all valoctocogene roxaparvovec development teams at BioMarin Pharmaceutical Inc. Medical writing support was provided by Tony Sallese, PhD, and M. Amin Ghane, PhD, of AlphaBioCom, a Red Nucleus company, and funded by BioMarin Pharmaceutical Inc. Jonathan Morton, PhD, of BioMarin Pharmaceutical Inc. provided project management support.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by funding from BioMarin Pharmaceutical Inc.

Competing interests

D.V.Q. has received payments from Bayer, BioMarin Pharmaceutical Inc., Novo Nordisk, Octapharma, Roche/Genentech, and Sanofi; served as a principal investigator for BioMarin Pharmaceutical Inc., Bioverativ/Sanofi, Roche/Genentech, Shire/Takeda, and uniQure; and received honoraria from BioMarin Pharmaceutical Inc., CSL Behring, Novo Nordisk, Roche/Genentech, Sanofi, and Takeda. D.P. has received fees from BioMarin Pharmaceutical Inc. and Sanofi. Y.S.P. has received research support from or participated as a principal investigator for BioMarin Pharmaceutical Inc., Chugai, CSL Behring, Novo Nordisk, Pfizer, Sanofi, and Takeda. G.K. has received grants and payments from Alnylam, Bayer, BioMarin Pharmaceutical Inc., Bio Products Laboratory, CSL, Novo Nordisk, OPKO Biologics, Pfizer, Roche, Sanofi, Takeda, and uniQure. J.M. has received payment and funding from BioMarin Pharmaceutical Inc., Catalyst Biosciences, Chugai, CSL Behring, Novo Nordisk, LFB, Roche, Shire, Spark, and Sobi. J.W. has served as a principal investigator for BioMarin Pharmaceutical Inc., Chugai, Novo Nordisk, Pfizer, and Sanofi; and received honoraria from Bayer, Chugai, Novo Nordisk, Pfizer, Sanofi, and Takeda. M.W. has received honoraria from BioMarin Pharmaceutical Inc., Bioverativ/Sanofi, CSL Behring, Genentech/Roche, HEMA Biologics, Novo Nordisk, and Takeda. S.W.P. has received payment from ApcinteX, ASC Therapeutics, Bayer, BioMarin Pharmaceutical Inc., CSL Behring, Freeline, HEMA Biologics, LFB, Novo Nordisk, Pfizer, Roche/Genentech, Sanofi, Spark Therapeutics, Takeda, and uniQure; and served as a clinical trial investigator for BioMarin Pharmaceutical Inc., Freeline, Genentech/Roche, Sanofi, and uniQure. T.K. has received honoraria from Roche/Genentech, Novo Nordisk, Sanofi, and BioMarin Pharmaceutical Inc. T.M.R. is a former employee and potential shareholder of BioMarin Pharmaceutical Inc. K.C. is an employee and shareholder of BioMarin Pharmaceutical Inc.

Availability of data and materials

The deidentified individual participant data that underlie the results reported in this article (including text, tables, figures, and online appendices) will be made available, together with the research protocol and data dictionaries, for noncommercial, academic purposes. Additional supporting documents may be available upon request. Investigators will be able to request access to these data and supporting documents via a data sharing portal beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of the relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria available at www.BioMarin.com/patients/publication-data-request/ to determine if access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

ORCID iD

Doris V. Quon https://orcid.org/0000-0002-9148-3268

Supplemental material

Supplemental material for this article is available online.

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