Perioperative management of total hip arthroplasty in hemophilia A following gene therapy

Hemophilia A (HA) is an X-linked recessive bleeding disorder caused by pathologic genetic variants in the *F8* gene, leading to deficient production of coagulation factor VIII (FVIII).[1] Patients with severe HA (defined as FVIII activity level <1 IU/dL) typically experience recurrent spontaneous bleeding into soft tissues and joints, culminating in progressive hemophilic arthropathy characterized by chronic pain and irreversible joint mobility impairment.[2,3] Adeno-associated virus (AAV)-mediated gene therapy has emerged as a promising treatment modality for severe HA, by enabling sustained therapeutic FVIII expression and effective control of hemorrhagic episodes.[4,5] However, the therapeutic strategy demonstrates limited efficacy in reversing established hemophilic arthropathy, thereby ultimately requiring orthopedic interventions to restore optimal joint function in affected patients. This scenario also poses new challenges in maintaining hemostatic balance of these patients, which involves reconciling elevated hemostatic demands with potential anticoagulant needs.[6-8] Here, we report the clinical course and treatment of a HA patient who had undergone total hip arthroplasty (THA) after receiving gene therapy.

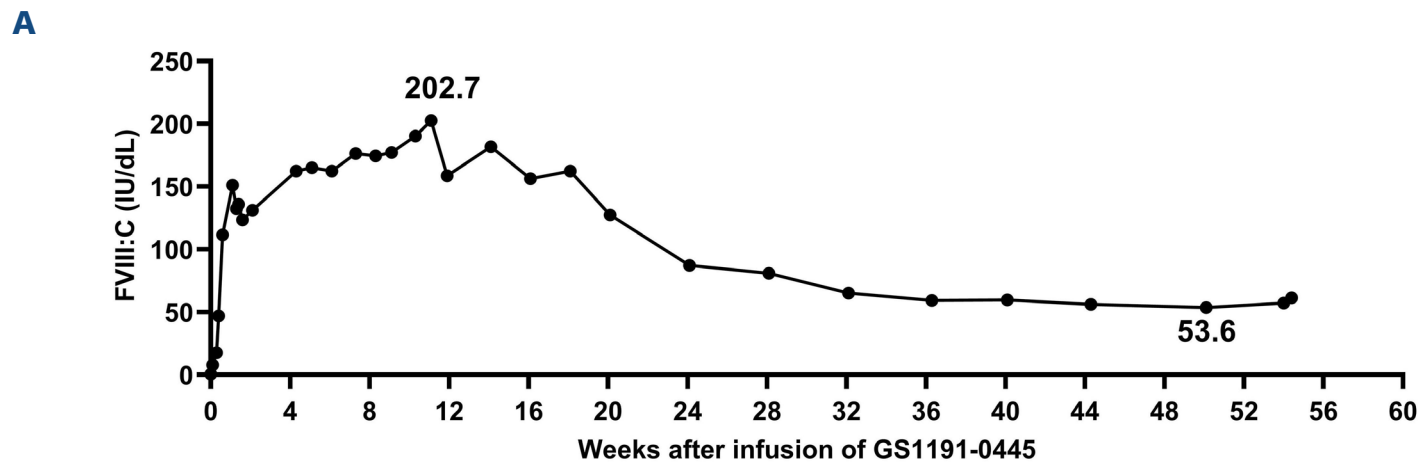
A 27-year-old man with severe HA was enrolled in a gene therapy clinical trial (*clinicaltrials gov. Identifier: NCT04728841*).[9] The gene therapy product GS1191-0445, developed using an AAV8 vector platform integrated with a liver-specific expression cassette encoding B-domain-deleted FVIII, has been granted Breakthrough Therapy Designation (BTD) by China's National Medical Products Administration (NMPA) Center for Drug Evaluation (CDE). This therapeutic candidate has successfully advanced into phase III clinical trial (*clinicaltrials gov. Identifier: NCT06833983*) following promising clinical outcomes. Clinical data from earlier stages demonstrated sustained therapeutic efficacy in subjects receiving the target dose of 3×10^{12} vg/kg or higher, with endogenous FVIII activity levels (FVIII:C) consistently maintained above the threshold for effective bleeding control (≥5 IU/dL) throughout the 12-month monitoring period. Compared to baseline, GS1191-0445 achieved a 99% reduction in annualized bleeding rate (*unpublished data*). After treatment with AAV-delivered FVIII, the expression level, as measured by one-stage clotting assay (OSA) using Dade Actin FSL activated partial thromboplastin time (APTT) reagent (Siemens), gradually declined from peak level of 202.7 IU/dL, to ~60 IU/dL by week 56 (Figure 1A). At this time point, THA was scheduled due to end-stage hemophilic arthropathy of the hip. While antithrombotic prophylaxis (minimum 10-14 days starting ≥12 hours post-operatively) is a standard protocol for general THA patients,[10,11] this recommendation presents a clinical dilemma in hemophilic populations. The inherent thrombotic risk in arthroplasty patients must be carefully weighed against the amplified bleeding hazards associated with anticoagulant use in individuals with HA. Previously, Xue *et al.*[12] have reported a case of successful unilateral total knee arthroplasty (TKA) without perioperative FIX supplementation following FIX-Padua gene transfer. In this case, given the dual clinical challenges of higher intraoperative blood loss and elevated postoperative venous thromboembolism (VTE) risks associated with THA compared to TKA,[6,13] the optimal balance between intraoperative hemostatic management and postoperative antithrombotic prophylaxis remains clinically unsolved.

This study was approved by the Ethics Committee of Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine. The patient gave his informed consent to participate. Without supplement of FVIII prior to the surgical procedure, the patient experienced moderate intra-operative blood loss, estimated at 300 mL. Thromboelastography (TEG) parameters measured pre-operatively and intra-operatively demonstrated normal coagulation in the patient (Table 1), but continuous post-operative wound oozing prompted transfusion of 200 mL fresh frozen plasma (FFP) and 2 U leukocyte-reduced red blood cells (RBC). On day 1 and 2 after

Table 1. Thromboelastography during the perioperative period of total hip arthroplasty.

	Citrated Kaolin				Citrated rapid TEG			
	R, min	Angle, degree	K, min	MA, mm	R, min	Angle, degree	K, min	MA, mm
Ref. range	5-10	53-72	1-3	51-69	0-1	64-80	1-2	52-71
Pre-op	7.8	58.3	2.2	57.2	0.8	75.2	1.2	70.5
Intra-op 1 h	ND	ND	ND	ND	0.8	75.4	1.1	67.9
POD3	5.8	68.0	1.7	68.9	1.0	77.4	1.0	72.9

TEG: thromboelastography; min: minutes; Ref.; reference; h: hour; R: reaction time; Angle: kinetics of clot development; K: kinetics time; MA: maximum amplitude; ND: not done; Pre-op: pre-operative day; Intra-op: intra-operative day; POD: post-operative day.



D **Summary of FVIII:C in the Perioperative Period**

FVIII:C (IU/dL)	Pre-op	Intra-op 1h	POD1	POD1 15 min post FVIII transfusion	POD2	POD3	POD5	POD7	POD14	POD41
OSA	61.4	40.6	39.6	121.5	83.1	106.9	98.5	84.7	75.4	68.6
CSA	50.1	35.1	32.1	109.6	87.3	92.8	79.3	66.8	46.0	58.4
CSA /OSA	0.8	0.9	0.8	0.9	1.1	0.9	0.8	0.8	0.6	0.9

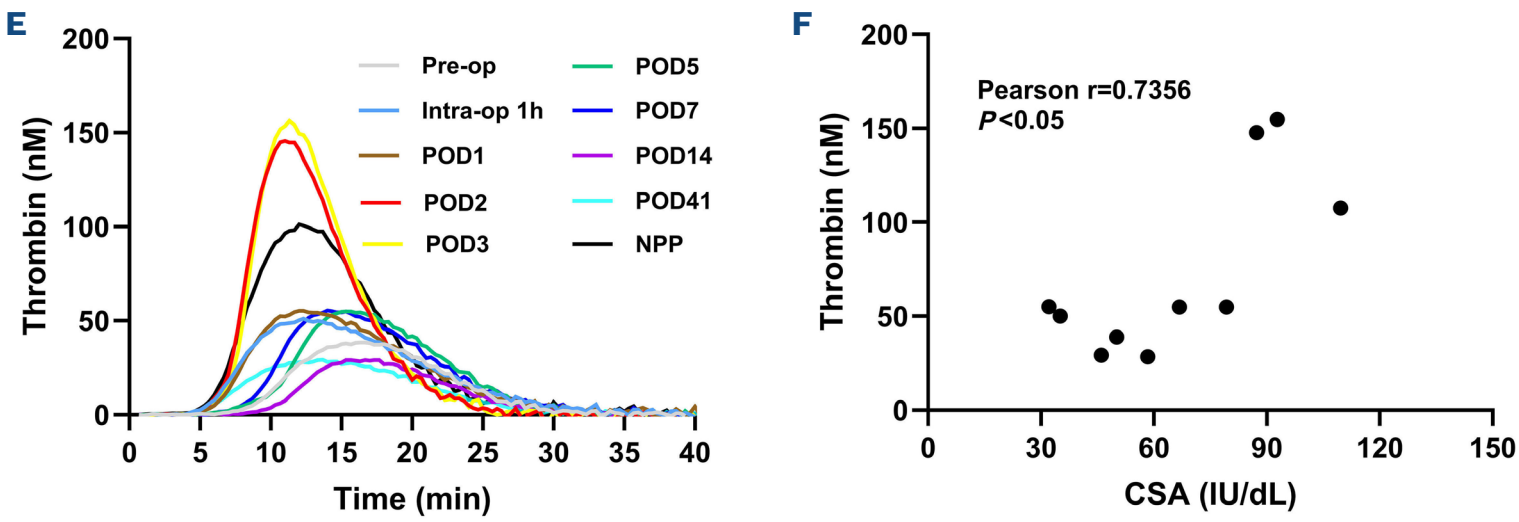


Figure1. Patient with hemophilia A who underwent total hip arthroplasty after gene therapy. (A) The coagulation factor VIII (FVIII) level after the infusion of GS1191-0445, a FVIII gene product, determined by one-stage clotting assay using Dade Actin FSL activated partial thromboplastin time (APTT) reagent (Siemens). (B) Perioperative management and FVIII activity (FVIII:C) monitoring of the patient. (C) Observed and model-predicted FVIII levels plotted against time. The zero point on the X-axis represented the peak level 15 minutes after the initial FVIII infusion. (D) Summary of FVIII:C in the perioperative period measured by one-stage clotting assays with Dade Actin FSL APTT reagent (Siemens), and the chromogenic substrate assay (Hyphen Biomed). (E) Results of the retrospective thrombin generation assay (TGA) in the perioperative period. NPP: normal pooled plasma; (F) Correlation between thrombin peaks in TGA and FVIII:C in the chromogenic assay. FFP: fresh frozen plasma; RBC: leukocyte-reduced red blood cells; OSA: one-stage clotting assay; CSA: chromogenic substrate assay; Pre-op: pre-operative day; intra-op: intraoperative day; POD: postoperative day.

operation, two doses of recombinant FVIII concentrates (1,000 IU/dose) were administered due to decline in FVIII:C and progressive decrease of hemoglobin level. FVIII:C was elevated to 106.9 IU/dL by day 3 and maintained through day 5 (98.5 IU/dL for 60 hours post-infusion). Upon sustained restoration of FVIII activity, thrombosis prophylaxis was then initiated with 4,000 IU low-molecular-weight heparin (LMWH) and continued for 3 consecutive days, before switching to rivaroxaban 10 mg daily for a further 10 days on the day of discharge. No significant discomfort or signs of bleeding was reported by the patient (Figure 1B).

On post-operative day 2 (POD2) and 3 (POD3), the measured FVIII:C levels were 83.1 IU/dL and 106.9 IU/dL, respectively. These values, resulting from the combined activity of transgene-produced FVIII and infused recombinant FVIII, exceeded the pharmacokinetic (PK) modeling projections (73.6 IU/dL and 80.8 IU/dL) by 12.9% and 32.3%.[14] Notably, on POD5, when PK analysis indicated near-complete clearance of exogenous FVIII (60 hours after the second infusion), the FVIII:C level remained steady at 98.5 IU/dL, which was 60.4% higher compared to pre-operative levels. Although declining gradually thereafter, FVIII:C remained above pre-operative levels through POD41 (FVIII:C 68.6 IU/dL) (Figure 1C, D). Interestingly, the enhanced transgenic coagulation factor expression boosted by surgical procedures was also described in a hemophilia B patient undergoing unilateral TKA following AAV-mediated FIX-Padua gene transfer.[12] Whether post-operative enhancement of transgenic expression occurs in other hemophilia patients receiving gene therapy, and the mechanism underlying this unexpected phenomenon deserve further investigation.

FVIII levels were comprehensively monitored perioperatively via a chromogenic substrate assay (CSA, Hyphen Biomed). Consistent with prior reports,[1,15] the FVIII:C quantified with the CSA revealed a 0.9±0.1-fold reduction *versus* measurements obtained with the OSA Dade Actin FSL APTT reagent (Figure 1D). Retrospective thrombin generation assay (TGA) revealed that despite near-normal FVIII:C, the patient overall exhibited a hypocoagulable state, supporting the requirement for post-operative replacement therapy (Figure 1E). Thrombin peaks in TGA exhibited moderate correlations with FVIII:C levels in the CSA (r=0.7356; P<0.05) but not in OSA (Figure 1F). In this case, we suggest that CSA correlates better with the hemostatic potential and bleeding phenotype of the patient.

Liver dysfunction screening was conducted peri-operatively, and elevation in the alanine amino-transferase level (ALT, above the upper limit of normal; laboratory reference range, 9-50 IU/L) was observed starting from POD5. The patient received on-demand glucocorticoids due to ALT levels above 1.5-times baseline on POD9, which quickly turned to normal on POD14 (Figure 2).

Overall, this case indicates that in clinical monitoring of FVIII:C after gene transfer, CSA showed superior correlation with hemostatic efficacy compared to OSA, as validated by TGA results. *In vivo* FVIII:C in these patients may be insufficient to maintain hemostasis during major hemostatic challenges, though upregulation of transgenic FVIII may reduce exogenous FVIII requirements. Following FVIII replacement for postoperative hemostasis, whether thromboprophylaxis should be systematically initiated warrants further clinical investigation.

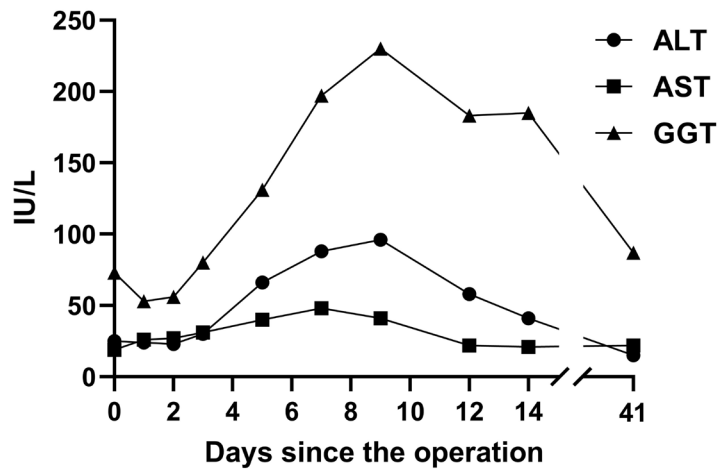


Figure.2 Liver dysfunction screening in the perioperative period. Laboratory reference range: alanine amino-transferase (ALT), 9-50 IU/L; aspartate amino-transferase (AST), 15-40 IU/L; γ-glutamyl transferase, 10-60 IU/L.

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Disclosures

No conflicts of interest to disclose.

Contributions

YS performed research, analyzed data and wrote the manuscript. CW and CH performed orthopedic surgery on the patient. WL and LZ oversaw the enrollment, trial design, and data collection in the hemophilia A gene therapy clinical trial. YL performed research. QD and WW analyzed data and reviewed the manuscript. XW supervised the study conducted in Ruijin Hospital. JD collected clinical history, analyzed data, and critically reviewed the manuscript.

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Data-sharing statement

Data are available from the corresponding author and the first author upon request. For original data, please contact dj40572@rjh.com.cn or roger3212@126.com.

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