Original article

Beneficial effect of prophylactic emicizumab on Thai hemophilia A with and without inhibitor: a case series report

Ampaiwan Chuansumrit[1], Monratta Panuwannakorn[2], Suphaneewan Jaovisidha[3], Tachit Jiravichitchai[2], Ketsuda Kempka[1], Werasak Sasanakul[1], Praguywan Kadegasem[1], Surapong Lertthammakiat[4], Pakawan Wongwerawattanakoon[5], and Nongnuch Sirachainan[1]

Department of [1]Pediatrics; [2]Rehabilitation Medicine; [3]Diagnostic and Therapeutic Radiology; [4]Chakri Naruebodindra Medical Institute; [5]Division of Pediatric Nursing, Nursing Department, Faculty of Medicine Ramathibodi Hospital, Mahidol University

Abstract:

Background: *Nonfactor replacement of emicizumab has shown an effectiveness in preventing bleeding episodes among patients with hemophilia with and without inhibitor.* ***Objective:*** *A retrospective evaluation of patients with severe hemophilia A with and without inhibitor receiving prophylactic emicizumab was conducted.* ***Subjects and methods:*** *Five patients with severe hemophilia A with and without inhibitor aged ≥ 12 years experiencing at least 5 bleeding episodes during the previous 6-month period, were enrolled. The standard loading dose of prophylactic emicizumab at 3 mg/kg weekly was given for 4 weeks, followed by the maintenance dose at 1.5 mg/kg weekly (n = 1) or 6 mg/kg every 4 weeks (n = 4). The occurrence of bleeding episode was monitored.* ***Results:*** *Five enrolled patients whose ages ranged from 13 to 28 years, were enrolled. Two patients had high inhibitor while the remaining three patients had no inhibitor. During a 3-year treatment, the zero annual bleeding rate was 12 of 15 (80%) accumulative patient-treatment years among 5 studied patients and additional 1 episode of annual bleeding rate was 3 of 15 (20%), which were markedly decreased compared with those of the pretreatment period. A total of 3 bleeding episodes included one each occurring at the iliopsoas muscle, lower gastro-intestine tract and knee hemarthrosis with multiple abrasion from motorcycle accident. All were responsive to the additional recombinant factor VIIa and factor VIII concentrate for patients with and without inhibitor accordingly. The musculoskeletal outcome was markedly improved in terms of pain, joint motion, muscle strength, functional status and physical fitness. Hemophilia Joint Health Score (HJHS) was also improved among 2 patients evaluated by this score.* ***Conclusion:*** *The standard dose of emicizumab has shown effectiveness in decreasing the annual bleeding rates among Thai patients with hemophilia A with and without inhibitor.*

Keywords : ● *Hemophilia* ● *Hemophilia with inhibitor* ● *Emicizuab* ● *Annual bleeding rate* ● *Prophylaxis*

J Hematol Transfus Med. 2022;32:235-44.

Received 25 January 2022 Corrected 27 April 2022 Accepted 5 July 2022

Correspondence should be addressed to Prof. Ampaiwan Chuansumrit, M.D., Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Rama VI Rd., Ratchathewi, Bangkok 10400 Email: ampaiwan.jua@mahidol.ac.th

นิพนธ์ต้นฉบับ

ผลดีของการให้ยาอีมิซิซูแมบเพื่อป้องกันอาการเลือดออกในผู้ป่วยไทยโรคฮีโมฟีเลีย เอ ที่มีและไม่มีสารต้าน: รายงานผู้ป่วย

อำไพวรรณ จวนสัมฤทธิ์[1] มลรัชฐา ภาณุวรรณากร[2] สุภานีวรรณ เชาว์วิศิษฐ์[3] เตชิต จิระวิชิตชัย[2] เกศสุดา แคมพ์กา[1] วีระศักดิ์ ศาสนกุล[1] ประกายวรรณ เกษเกษม[1] สุรพงศ์ เลิศธรรมเกียรติ[4] ผกาวรรณ วงศ์วีระวัฒนกูร[5] และ นงนุช สิระชัยนันท์[1]

[1]ภาควิชากุมารเวชศาสตร์ [2]ภาควิชาเวชศาสตร์ฟื้นฟู [3]ภาควิชารังสีวิทยา [4]สถาบันการแพทย์จักรีนฤบดินทร์ [5]งานการพยาบาลกุมารเวชศาสตร์ ภาควิชาพยาบาลศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล

บทคัดย่อ

ความเป็นมา *การรักษาทดแทนด้วยยาอีมิซิซูแมบที่ไม่ใช่แฟกเตอร์เข้มข้นมีประสิทธิภาพสูงในการป้องกันอาการเลือดออกในผู้ป่วยโรคฮีโมฟีเลีย เอ ที่มีและไม่มีสารต้าน* ***วัตถุประสงค์*** *ศึกษาย้อนหลังผลของการให้ยาอีมิซิซูแมบเพื่อป้องกันอาการเลือดออกในผู้ป่วยไทยโรคฮีโมฟีเลีย เอ ที่มีและไม่มีสารต้าน* ***ผู้ป่วยและวิธีการ*** *ศึกษาในผู้ป่วยโรคฮีโมฟีเลีย เอ ชนิดรุนแรงมากที่มีและไม่มีสารต้านจำนวน 5 ราย อายุ ≥ 12 ปีที่มีประวัติเลือดออกมากกว่าหรือเท่ากับ 5 ครั้งในระยะเวลา 6 เดือน ผู้ป่วยทุกรายได้รับยาอีมิซิซูแมบขนาดมาตรฐานเพื่อป้องกันอาการเลือดออก คือ 3 มก./กก. สัปดาห์ละครั้ง 4 ครั้ง ต่อด้วย 1.5 มก./กก. ทุกสัปดาห์ (n = 1) หรือ 6 มก./กก. ทุก 4 สัปดาห์ (n = 4) และติดตามอาการเลือดออกที่เกิดขึ้น* ***ผลการศึกษา*** *ผู้ป่วยโรคฮีโมฟีเลีย เอ ชนิดรุนแรงมากจำนวน 5 ราย อายุระหว่าง 13 ถึง 28 ปีร่วมในการศึกษา ผู้ป่วย 2 รายมีสารต้านระดับสูง อีก 3 รายไม่มีสารต้าน ในระยะเวลาการศึกษา 3 ปีที่ได้รับยาอีมิซิซูแมบ พบว่า ไม่มีอาการเลือดออกต่อปีเท่ากับ 12 จากระยะเวลาศึกษาสะสม 15 ปี (ร้อยละ 80) ในผู้ป่วย 5 รายและมีอาการเลือดออกเพียง 1 ครั้งต่อปี เท่ากับ 3 จาก 15 ปี (ร้อยละ 20) ซึ่งต่ำกว่าช่วงก่อนได้รับยาอีมิซิซูแมบอย่างชัดเจน อาการเลือดออก 3 ครั้งเกิดขึ้นที่กล้ามเนื้อ iliopsoas ทางเดินอาหาร และข้อเข่าร่วมกับแผลถลอกเนื่องจากอุบัติเหตุรถจักรยานยนต์ ซึ่งตอบสนองต่อการรักษาเพิ่มเติมด้วย recombinant factor VIIa และแฟกเตอร์ แปดเข้มข้นในผู้ป่วยที่มีและไม่มีสารต้าน การประเมินระบบกล้ามเนื้อและข้อต่อพบว่าดีขึ้นในแง่ของอาการปวด การเคลื่อนไหวข้อ กำลังกล้ามเนื้อ การใช้งาน และความสมบูรณ์โดยรวมของร่างกาย ผู้ป่วยสองรายที่ได้รับการประเมินด้วย Hemophilia Joint Health Score ก็มีคะแนนการประเมินดีขึ้นมาก* ***สรุป*** *การให้ยาอีมิซิซูแมบขนาดมาตรฐานช่วยลดอาการเลือดออกรายปีในผู้ป่วยไทยโรคฮีโมฟีเลีย เอ ที่มีและไม่มีสารต้านได้อย่างมีประสิทธิภาพ*

คำสำคัญ : ● *ฮีโมฟีเลีย* ● *ฮีโมฟีเลียที่มีสารต้าน* ● *อีมิซิซูแมบ* ● *อัตราเลือดออกรายปี* ● *การป้องกัน*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2565;32:235-44.

Introduction

Patients with hemophilia risk exhibiting frequent bleeding in their muscles and joints especially those with severe degree possessing the deficient factor of less than 1%. The effective management involves prophylactic treatment with frequent infusion of factor concentrate to achieve a trough level at least more than 1% upon the guidelines recommended by the World Federation of Hemophilia in the year 2013[1]. However, the recently published guidelines in 2020 recommend raising the deficient factor 3 to 5% or more to prevent damage to the joints[2]. Nevertheless, patients with severe hemophilia A are prone to developing inhibitor to the factor VIII clotting activity at 20 to 30%[3] that worsens the musculoskeletal system of these patients. They need eradicating the inhibitor by means of immune tolerance induction (ITI) within the first three years of inhibitor development[4]. The success rate of ITI is approaching 53 to 79%[5] depending on the protocol used and each patient's individualized response. Those without eligible ITI or unresponsive to ITI have to use bypassing agents of activated prothrombin complex concentrate (aPCC) or recombinant activated factor VII (rFVIIa)[6]. The cost of replacement therapy is much higher among patients with inhibitor than those without inhibitor.

Recently, the bispecific monoclonal antibody, namely, emicizumab binding to the factor IXa and factor X[7,8] has been found effective in decreasing the annual bleeding rate among patients with hemophilia A with and without inhibitor[8-12]. Here, we reported the beneficial effect of emicizumab on preventing and controlling bleeding episodes among Thai hemophiliacs with and without inhibitor.

Subjects and Methods

A retrospective analysis was conducted of five patients with severe hemophilia A with and without inhibitor, aged more than 12 years old, receiving the standard dose of emicizumab at the International Hemophilia Training Center-Bangkok, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. The study included patients exhibiting at least five bleeding episodes in the previous six months and excluded patients with acquired hemophilia. The study was approved by the Faculty Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University (MURA2017/862). Written informed consent was obtained from patients and parents.

The factor VIII clotting activity (FVIII:C) was determined using a one-stage assay based on partial thromboplastin time with factor VIII deficient plasma from the Instrumentation Laboratory, Bedford, MA, USA[13]. The factor VIII inhibitor was determined using the Nijmegen-Bethesda method[14]. After receiving emicizumab, the inhibitor was determined using chromogenic assay with bovine factor VIII deficient plasma as substrate[15].

DNA was extracted from the peripheral leucocyte using the salting out method, and inversion of intron 22 was initially performed[16]. Patients without inversion intron 22 had all exons of their factor VIII gene amplified and sequenced accordingly to search for the causative mutation.

Results

The demographic data of the studied patients are shown in Tables 1 and 2. Four of five patients had a family history of hemophilia while only one patient constituted a sporadic case. The identified factor VIII gene mutation was inversion of intron 22 (n = 2), nonsense mutation (n = 1) and missense mutation (n = 2). They started to receive episodic treatment with cryoprecipitate at ages ranging from 0.3 to 3.4 years and switched to early episodic treatment with heat-treated lyophilized cryoprecipitate and factor concentrate at ages ranging from 1.8 to 11.6 years. All parents were able to perform venipuncture properly after being trained except the youngest boy (No. 3) at 1.8 years of age who required infusion at a local hospital near his house. His mother was subsequently able to perform venipuncture when the patient was 8 years old.

Table 1 Demographic data of the studied patients

Patients No.	Family history	Age at diagnosis (year)	FVIII:C (%)	Mutation
1	Two uncles with hemophilia died	0.3	0.4	Inversion intron 22 distal type
2	One uncle with hemophilia died	0.7	0.1	c. 2767 ins T, p. I 923 F fsx11
3	No family history	1.0	0.5	c. 1681 G>A, p. D561 N
4	One elder brother with hemophilia (alive)	2.9	0.9	c. 830 T>C, p. I 277 T
5	One elder brother with hemophilia (alive)	3.4	0.2	Inversion intron 22 proximal type

FVIII:C, factor VIII clotting activity

Table 2 Previous factor replacement therapy among the studied patients

Patient No.	Birth	Episodic treatment with cryoppt		Early episodic treatment with lyophilized cryoppt & factor conc.			Episodic treatment with PCC, rFVIIa, aPCC				Prophylactic emicizumab	
		Age	Duration (y)	Age	Age self-infusion	Duration (y)	Age	Initial inhibitor	Highest inhibitor	Duration (y)	Age	Duration (y)
1	1989	0.3	11.3	11.6	12	2.2	13.8	1.9	104	14.7	28.5	3.2
2	1997	0.5	9.1	9.6	15	3.3	12.9	1.3	50.5	8.8	21.7	3.2
3	2000	1.0	0.7	1.8	13	16.1	-	-	-	-	17.9	3.0
4	2001	2.9	3.0	5.9	17	11.6	-	-	-	-	17.5	3.1
5	2005	3.4	3.8	7.2	10	6.2	-	-	-	-	13.4	3.0

aPCC, activated prothrombin complex concentrate; conc, concentrate; cryoppt, cryoprecipitate; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII

Two patients (Nos. 1 and 2) with intron 22 inversion and nonsense mutation were found to possess positive inhibitor of 1.9 and 1.3 Bethesda units (BU) on the routine 6-month screening at the age of 13.8 and 12.9 years, respectively. The inhibitor rose to the highest levels of 104 and 50.5 BU, respectively. They had to use prothrombin complex concentrates (PCC), aPCC and rFVIIa at the early bleeding episodes. The other two patients (Nos. 3 and 4) with missense mutation had no inhibitor while the last patient (No. 5) with intron 22 inversion also had no inhibitor. However, all the patients with and without inhibitor received inadequate replacement therapy resulting in chronic hemarthrosis. Three patients received radioactive synovectomy using intra-articular injections of Yttrium-90 to lessen the frequency of bleeding episode. Patient No. 1 received yttrium injection in his right shoulder and right elbow at the age of 24 and 25 years, respectively. Patient No. 3 received yttrium injection in his left knee at 3 years of age while patient No. 4 received yttrium injection in bilateral elbows at 15 years of age. All patients had negative test results for anti-human immunodeficiency virus (HIV), anti-hepatitis C virus (HCV) and hepatitis B surface antigen (HBsAg), anti-hepatitis B surface antibody (anti-HBs) and anti-hepatitis core antibody (anti-HBc) except three patients exhibiting transient positive protective anti-HBs of more than 10 million IU.

All patients received the subcutaneous standard loading dose of emicizumab at 3 mg/kg weekly for four weeks followed by maintenance of 1.5 mg/kg weekly in patient No. 5 while the remaining patients received 6 mg/kg every four weeks. At initiating emicizumab, patients Nos. 1 and 2 had their current inhibitor of 88 and 1.3 BU, respectively.

The results revealed zero annual bleeding rate at 12 of 15 (80%) accumulative patient-treatment years among the 3-year treatment in five patients and one episode of annual bleeding rate at 3 of 15 (20%), which were markedly decreased compared with those before emicizumab treatment (Table 3). Essentially, the musculoskeletal outcome was markedly improved in terms of pain, joint motion, muscle strength and function. Overall fitness was also improved. The patients could also participate in recreation activities and in fitness club training implying better quality of life They had more motivation and self-confidence in home exercise with more awareness of bleeding. Hemophilia Joint Health Score (HJHS) in two evaluated patients was markedly improved (Table 4). Patient No. 4 could also reduce the extra weight.

Table 3 Annual bleeding rate and the factor replacement therapy used

Patient No.	Factor replacement		Annual bleeding rate			
	BW (kg)	Factor concentrate	Before emicizumab	After emicizumab		
				Year 1	Year 2	Year 3
1	72	rFVIIa 26 mg	15	1	0	0
2	60	-	12	0	0	0
3	60	-	24	0	0	0
4	72	Factor VIII 21,500 units	24	1	0	0
5	63	Factor VIII 11,000 units	12	0	0	1

BW, body weight; rFVIIa, recombinant activated factor VII

Table 4 Improvement of the musculoskeletal system from emicizumab treatment

Patient No.	Before emicizumab treatment	After emicizumab treatment
1	● Hemarthrosis and pain at right elbow & right shoulder every 2 -3 months (status post radiosynovectomy) ● Could not titrate exercise due to pain ● Imaging showed effusion and soft tissue swelling	● Significantly decreased frequency of hemarthrosis and pain at right shoulder and no bleeding at right elbow ● Ability to maintain aerobic exercise and weight bearing ● Imaging showed hemophilic arthropathy without inflammation
2	● Right elbow stiffness ● Need unilateral axillary crutch on ambulation ● Only isometric exercise of right quadriceps could be performed ● HJHS of 34 (0/11/2/11/4/2+4)	● Improvement of ROM of right knee and elbow ● Ambulation without gait aids ● Ability to maintain aerobic and progressive resistive exercise ● HJHS of 22 (0/6/0/8/3/3+2)
3	● Hemarthrosis at left ankle every 2 months ● Pain at left ankle on ambulation ● Could not titrate aerobic exercise	● No history of joint & muscle bleeding and pain ● Mild improvement of ROM of left ankle ● Ability to maintain aerobic exercise and weight training
4	● Hemarthrosis of both elbows and left knee every 3 months (status post radiosynovectomy) ● Could not titrate aerobic exercise except resistive exercise of left quadriceps	● No history of joint & muscle bleeding and pain ● Ability to maintain aerobic exercise and weight training ● Significant weight reduction
5	● Hemarthrosis of left ankle every 2 months ● HJHS of 28 (0/1/8/5/7/3+4)	● No history of joint & muscle bleeding and pain except right knee hemarthrosis and abrasion wound from motorcycle accident ● Improvement of ROM of both ankles ● Ability to generate progressive resistive exercise both ankles ● HJHS of 9 (1/0/1/1/1/3+2)

HJHS, Hemophilic joint health score at left and right elbow, knee, ankle and global gait; ROM, range of motion

Regarding the bleeding control during the emicizumab administration, three major bleeding episodes were found in the current study. First, patient No. 1 experienced iliopsoas muscle bleeding at the first loading dose of emicizumab (D0). Additional daily intravenous rFVIIa at the dose of 90 μg/kg for four days combined with cold compression and completely absolute bed rest showed effectiveness in bleeding control by lessening the clinical symptom starting from D1 to D2 after management. The ultrasonography demonstrated no change in size of hematoma but a clot was formed on D7 when the second loading of emicuzumab was given, followed by decreasing the size on the D28 receiving the first four-weekly maintenance dose of emicuzumab at 6 mg/kg as shown in Table 5 and Figure 1. The patient fully recovered and had not experienced recurrent bleeding episode up to 3-year treatment shown by the complete resolution of hematoma by the ultrasonography study.

Second, the lower gastrointestinal bleeding in patient No.4 occurred on the 21st day of the four-weekly maintenance dose of emicizumab at 6 mg/kg. The patient did not inform the local physician taking care of him at a provincial hospital that he has had emicizumab administration. The local physician found that he had normalized activated partial thromboplastin time (APTT) which might have been due to factor VIII concentrate administered by himself. Therefore, only tranexamic acid and packed red cells were prescribed. Upon the call from his mother, we suggested the local physician give him 4,000 units of factor VIII concentrate before transferring him to our hospital in Bangkok. A total of 21,500 units of factor VIII concentrate was given for seven days and the subsequent esophago-gastro-duodenoscopy and colonoscopy revealed acute colitis which was treated accordingly.

Lastly, the motorcycle of patient No. 5 hit a car on the day receiving weekly maintenance emicizumab at 1.5 mg/kg. He was transferred to our hospital within five hours of the accident. The patient had right knee hemarthrosis and multiple abrasions on the trunk and extremities. A total of 11,000 units of factor VIII concentrate was given for five days. A face-to-face conference among the medical personnel, patient and parents was conducted to ascertain the avoidance of bleeding risk before continuing the treatment.

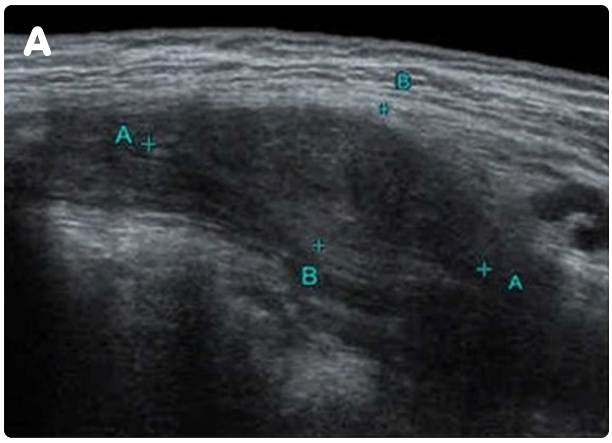
Discussion

Four of five enrolled patients had a family history of bleeding disorders. Mothers of patients No. 1 and 2 had maternal uncles who passed away several years before conceiving the enrolled patients. Without intensive history taking at the antenatal clinic, they were not recognized as possible carrier of hemophilia requiring laboratory testing of carrier state and prenatal diagnosis

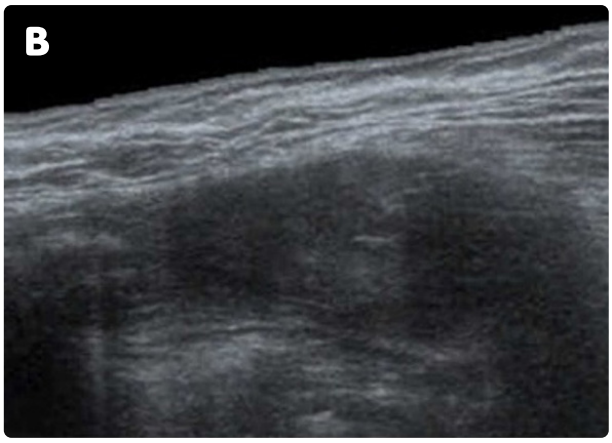
Table 5 Management for the iliopsoas muscle bleeding in patient No. 1

Day of treatment	Emicizumab	rFVIIa	Ultrasonography
D0	1st loading dose 3 mg/kg	6,500 μg (90 μg/kg)	
D1	-	6,500 μg (90 μg/kg)	Multistage hematoma
D2	-	6,500 μg (90 μg/kg)	-
D3	-	6,500 μg (90 μg/kg)	-
D4	-	-	No change in size
D7	2nd loading dose 3 mg/kg	-	No change in size but clot was formed
D14	3rd loading dose 3 mg/kg	-	-
D21	4th loading dose 3 mg/kg	-	-
D28	1st maintenance dose 6 mg/kg	-	Further decreased size

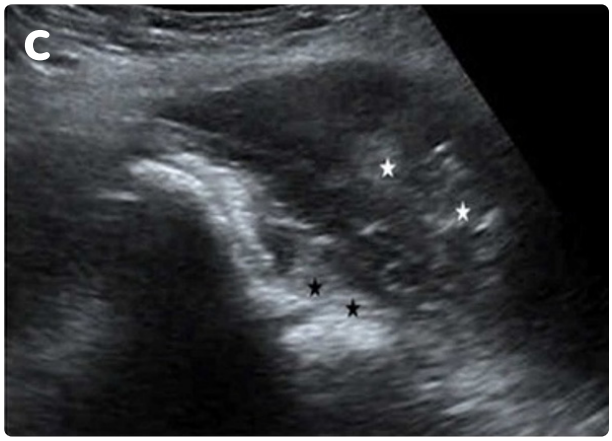
rFVIIa, recombinant activated factor VII



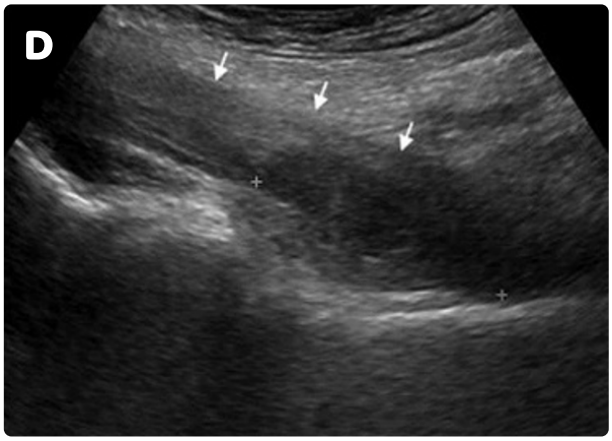
The first ultrasound study (day 1) reveals multistage hematoma distending the distal left iliopsoas muscle



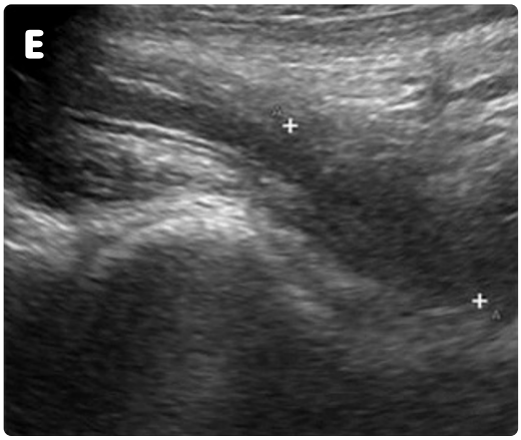
The second ultrasound study (day 4) reveals no significant change in size of the pre-existing hematoma



The third ultrasound study (day 7) reveals no significant change in size of the pre-existing hematoma. The centrally increased echogenicity (white stars) suggests clot formation reflecting more chronic stage of blood. Hyperechogenicity in the left hip joint (black stars) could be blood clot or synovial hypertrophy.



The fourth ultrasound study (day 28) reveals that the left iliopsoas muscle returned to its normal contour (arrows). The size of hematoma (between cursors) further decreased so that it can be contained within normal-sized muscle.



Follow-up ultrasound study three years later reveals decreased size and inhomogenously increased echogenicity of the hematoma bed. This could be resolution of hematoma and leaving some architectural distortion. No evidence of new bleeding is detected by ultrasound and by clinical profile.

Figure 1 Ultrasonography of the iliopsoas muscle of patient No. 1

of hemophilia in their male offspring. However, the facility of the prenatal diagnosis had not been established in the previous three decades. In addition, mothers of patients Nos. 4 and 5 already had had one son with hemophilia. They should be counseled concerning the possibility to be carriers of hemophilia possessing 50% chance of having sons with hemophilia. Therefore, four of five patients with hemophilia in the current study reflected inadequate carrier detection among females at risk that should be strengthened in the future services[17,18]. Moreover, the mutation is related to the risk of inhibitor development. Patients with nonsense mutation and intron 22 mutation risk developing inhibitor at 52.2 and 47.2%, respectively[19].

Although all five patients received cryoprecipitate to treat their episodic bleeding initially and subsequently switched to early treatment with heat-treated lyophilized cryoprecipitate and factor concentrate, they all presented negative results for the annual monitoring of anti-HIV, anti-HCV and HBsAg. Apart from additional donor self-exclusion starting in 1992, the National Blood Centre, Thai Red Cross Society and hospital blood banks have successively performed infectious marker screening in every blood donor as follows: serology for syphilis in 1952, serology for anti-HIV and HBsAg in 1987, anti-HCV and HIV-p24 Ag in 1991, minipool nucleic acid test of six samples for HIV, HCV and HBsAg in 2000 and switched to be individual nucleic acid test in 2007 and nationwide in 2015. Comprehensive donor screening is helpful in protecting receipts from transfusion-transmitted diseases[20].

All patients' mothers were able to perform proper venipuncture to infuse the lyophilized cryoprecipitate and factor concentrate at home except patient No. 3 whose mother was able to perform venipuncture when he was 8 years old. The ability to perform venipuncture is the key issue for successful home treatment. The blood product and factor concentrate were infused to stop the bleeding promptly[21]. Interestingly, they all were able to perform self-venipuncture at ages ranging from 10 to 17 years.

The standard loading dose of emicizumab at 3 mg/kg weekly for four weeks followed by maintenance dose of either 1.5 mg/kg weekly, 3 mg/kg every two weeks or 6 mg/kg every four weeks showed effectiveness in decreasing the annual bleeding rates. Also, emicizumab acted as an adjunctive therapy with additional rFVIIa or factor VIII concentrate in controlling serious bleeding episodes efficiently. The favorable results in decreasing annual bleeding rates among hemophiliacs with and without inhibitor in several studies and the current study urge medical personnel to apply for budget support from health authorities. Patients face long term suffering from frequent bleeding episodes with inadequate treatment especially those with inhibitor. The real world evidence of mean (SD) annual medical cost for treating severe bleeding episode among hemophiliacs with inhibitor was 983,744 (2,602,304) THB[22]. This was ineffectively-spent because morbidity and mortality rates among these patients were still high.

One pitfall shown in the current study was the normalized APTT among patients receiving emicizumab[8]. It was wrongly interpreted as having normalized FVIII:C among patients with hemophilia A. This pitfall has been warned to patients and family members that they should inform the medical team regarding their emicizumab treatment. This up-to-date knowledge has been emphasized in the continued education for hematologists. The plasma trough level of emicizumab among patients receiving the standard dose of emicizumab is approximately 45 μg/mL which is equivalent to the levels of factor VIII at 15% (0.3% factor VIII per μg/mL of emicizumab)[8]. This level is sufficient to prevent spontaneous bleeding episodes but insufficient for trauma-related or other serious bleeding episodes. The additional replacement therapy of bypassing agents or factor VIII concentrate should be prescribed accordingly for patients with and without inhibitor. Also, medical personnel should emphasize to patients and parents that traffic accidents are one of the common leading causes of death among adolescents and adults with hemophilia in Thailand[23]. The mortality and morbidity

rates are higher than those of the general population. Patient No. 5 was lucky to survive, and to not have succumbed at the scene.

The current study was limited by the retrospective design. The data were retrieved from medical records, and data such as subclinical bleeding in the joints were missing and irrelevant to the study. In addition, the quality of life was not included in the study. Further, a small sample size of five cases is insufficient to conclude the effectiveness of this nonfactor replacement therapy. A larger number of enrolled patients is warranted but the constraint would be funding to support this high cost medication.

As a result, the standard dose of emicizumab has shown effectiveness in decreasing the annual bleeding rates among Thai patients with hemophilia A with and without inhibitor. The musculoskeletal system was impressively improved for all enrolled patients. It would be challenging for health authorities to consider the possibility in providing proper treatment for patients with hemophilia and high-titer inhibitor. They face the life-long suffering from inadequate replacement and dream for effective treatment.

References

1. *Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19:e1-47.*
2. *Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26(Suppl 6):1-158.*
3. *van den Berg HM, Fischer K, Carcao M, Chambost H, Kenet G, Kurnik K, et al. Timing of inhibitor development in more than 1,000 previously untreated patients with severe hemophilia A. Blood. 2019;134:317-20.*
4. *Ljung RCR. How I manage patients with inherited haemophilia A and B and factor inhibitors. Br J Haematol. 2018;180:501-10.*
5. *Mariani G, Siragusa S, Kroner BL. Immune tolerance induction in hemophilia A: a review. Semin Thromb Hemost. 2003;29:69-76.*
6. *Collins PW, Chalmers E, Hart DP, Liesner R, Rangarajan S, Talks K, et al. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition). UK Haemophilia Centre Doctors Organization. Br J Haematol. 2013;160:153-70.*
7. *Kitazawa T, Igawa T, Sampei Z, Muto A, Kojima T, Soeda T, et al. A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model. Nat Med. 2012;18:1570-4.*
8. *Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, et al. Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. N Engl J Med. 2016;374:2044-53.*
9. *Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377:809-18.*
10. *Young G, Liesner R, Chang T, Sidonio R, Oldenburg J, Jiménez-Yuste V, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood. 2019;134:2127-38.*
11. *Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med. 2018;379:811-22.*
12. *Pipe SW, Shima M, Lehle M, Shapiro A, Chebon S, Fukutake K, 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:e295-305.*
13. *Hardisty RM, Macpherson JC. A one-stage factor VIII (antihaemophilic globulin) assay and its use on venous and capillary plasma. Thromb Diath Haemorrh. 1962;7:215-28.*
14. *Duncan E, Collecutt M, Street A. Nijmegen-Bethesda assay to measure factor VIII inhibitors. Methods Mol Biol. 2013;992:321-33.*
15. *Nogami K, Soeda T, Matsumoto T, Kawabe Y, Kitazawa T, Shima M. Routine measurements of factor VIII activity and inhibitor titer in the presence of emicizumab utilizing anti-idiotype monoclonal antibodies. J Thromb Haemost. 2018;16:1383-90.*
16. *Lakich D, Kazazian HH Jr, Antonarakis SE, Gitschier J. Inversions disrupting the factor VIII gene are a common cause of severe haemophilia A. Nat Genet. 1993;5:236-41.*
17. *Sasanakul W, Chuansumrit A, Ajjimakorn S, Krasaesub S, Sirachainan N, Chotsupakarn S, et al. Cost-effectiveness in establishing hemophilia carrier detection and prenatal diagnosis services in a developing country with limited health resources. Southeast Asian J Trop Med Public Health. 2003;34:891-8.*
18. *Chuansumrit A, Sasanakul W, Promsonthi P, Sirachainan N, Panburana P, Kadegasem P, et al. Prenatal diagnosis for haemophilia: the Thai experience. Haemophilia. 2016;22:880-5.*
19. *Chuansumrit A, Sasanakul W, Sirachainan N, Kadegasem P, Wongwerawattanakoon P, Mahaklan L, et al. Association of factor VIII and factor IX mutations, HLA class II, tumor necrosis factor α and interleukin-10 on inhibitor development among Thai haemophilia A and B patients. Haemophilia 2017:23:e518-23.*
20. *Nuchprayoon C. The development of transfusion medicine, National Blood Centre, Thai Red Cross Society. J Hematol Trans-Fus Med. 2020;30:3-5.*

21. *Chuansumrit A, Isarangkura P, Chantanakajornfung A, Panthangkool W, Hathirat P. Home treatment for patients with congenital bleeding disorders in a developing country. J Med Assoc Thai. 1999;82(Suppl 1):S57-62.*
22. *Chuansumrit A, Sirachainan N, Natesirinilkul R, Srikala K, Masaya-Anon N, Haemophilia Inhibitor Study Group. Real-world evidence on health resource use among patients with haemophilia and inhibitor exhibiting severe bleeding episodes. Haemophilia. 2021;27:69-80.*
23. *Chuansumrit A, Krasaesub S, Angchaisuksiri P, Hathirat P, Isarangkura P. Survival analysis of patients with haemophilia at the International Haemophilia Training Centre, Bangkok, Thailand. Haemophilia. 2004;10:542-9.*