Annals of Case Reports
Chuansumrit A, et al. Ann Case Rep: 9: 101872
www.doi.org/10.29011/2574-7754.101872
www.gavinpublishers.com

OPEN ACCESS

Research Article

GAVIN PUBLISHERS

Effectiveness of Monthly Low Dose Emicizumab, and Sequential Monthly Low Dose Emicizumab and Factor VIII Concentrate Prophylaxis among Patients with Hemophilia A: A Case Series Report of 3-Year Follow-Up

Ampaiwan Chuansumrit[1*], Suphaneewan Jaovisidha[2], Nongnuch Sirachainan[1], Tachit Jiravichitchai[3], Praguywan Kadegasem[1], Ketsuda Kempka[1], Monratta Pitakcharoen[3], Wannaphorn Rotchanpanya[4]

[1]Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[2]Department of Diagnostic and Therapeutic Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[3]Department of Rehabilitation Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[4]Department of Medicine, Chiang Rai Regional Hospital, Chiang Rai, Thailand

***Corresponding author**: Ampaiwan Chuansumrit, Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400 Thailand

Citation: Chuansumrit A, Jaovisidha S, Sirachainan N, Jiravichitchai T, Kadegasem P, et al (2024) Effectiveness of Monthly Low Dose Emicizumab, and Sequential Monthly Low Dose Emicizumab and Factor VIII Concentrate Prophylaxis among Patients with Hemophilia A: A Case Series Report of 3-Year Follow-Up. Ann Case Report. 9: 1872. DOI:10.29011/2574-7754.101872

Received: 01 July 2024, **Accepted:** 04 July 2024, **Published:** 08 July 2024

Abstract

Aim: The effectiveness of low dose monthly emicizumab, and sequential monthly low dose emicizumab and factor VIII concentrate prophylaxis among patients with hemophilia A, were evaluated. **Methods:** Four patients with hemophilia A (severe 2, moderate 2) without inhibitor received monthly low dose emicizumab prophylaxis at the median dose (IQR) of 1.23 (1.05, 1.31) mg/kg without 4-week loading doses for 2 years, and sequential monthly low dose emicizumab of 1.57 (1.36-1.66) mg/kg in the first week and factor VIII concentrate 15 units/kg twice weekly in the 4th week for the third year. Patients were closely monitored for bleeding episodes, quality of life, hemophilia joint health score (HJHS), HEAD-US and ultrasonography study of bilateral elbows, knees and ankles before and after prophylaxis on the yearly basis. **Results:** The mean (SD) age of patients at enrolment was 29.4 (13.4) years. The median (IQR) trough level of plasma emicizumab concentration was maintained at 10.7 (6.1, 13.4) mg/mL. Their median (IQR) annual bleeding rate (ABR) decreased from baseline of 33.0 (12.0, 36.7) to 4.5 (2.5, 6.5) in the first year, 1.5 (0.2, 5.7) in the second year and 0.5 (0, 3.2) in the third years of prophylaxis with p-values of 0.068. Zero to 1 ABR was found in 3 of 4 patients during the second and third years of prophylaxis. Their quality of life, HJHS and ultrasonography study were also improved. **Conclusion:** Both monthly low dose emicizumab, and sequential monthly low dose emicizumab and factor VIII concentrate prophylaxis showed effectiveness among patients with hemophilia A.

Keywords: Hemophilia; Prophylaxis; Low Dose; Emicizumab; Nonfactor Therapy

Introduction

Nonfactor therapy of emicizumab, a humanized, bispecific and monoclonal antibody, has proven to be a highly effective prophylaxis among patients with hemophilia A with and without inhibitor [1-6]. However, emicizumab is costly and unaffordable for patients from low and lower-middle income countries. The low dose emicizumab prophylaxis at 0.3 mg/kg/week significantly decreased the annual bleeding rate (ABR) from 32 to 4 and higher doses of 1-3 mg/kg/week resulted in zero ABR first reported among a total of 18 Japanese hemophiliacs by Shima M, et al. in 2016 [7]. Moreover, the effectiveness of low dose emicizumab at maintenance among 3 Malaysian hemophiliacs previously receiving compassionate conventional 4-week loading doses was reported in 2021 [8]. Essentially, the low dose emicizumab prophylaxis of 1.2 to 2.4 mg/kg every 1 to 3 weeks with 4-week reduced loading doses was reported among 11 patients with hemophilia with previous thrombotic complications or a high thrombotic risk was reported from Finland in 2022 [9]. Furthermore, the effectiveness of monthly low dose emicizumab at 1.05 to 1.66 mg/kg without 4-week loading doses was reported from Thailand in 2023 [10]. Reproducible results were also reported among 8 Indian hemophiliacs in 2023 [11]. These studies introduced the major cost savings without compromising the treatment efficacy. The modified low dose emicizumab offers an affordable price for patients with hemophilia from low and lower-middle income countries.

This study aimed to evaluate the effectiveness of monthly low dose emicizumab without 4-week loading doses, and the successive sequential monthly low dose emicizumab and factor VIII concentrate prophylaxis with a total of 3-year follow-up among patients with hemophilia A.

Patients and Methods

A single-arm, exploratory prospective study was conducted among patients with hemophilia A without inhibitor at the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok and Chiang Rai Regional Hospital, Chiang Rai, Thailand from March 2021 to February 2024. The sample size was based on feasibility and clinical concerns rather than statistical considerations. A whole vial of emicizumab to achieve a minimal dose of more than 1 mg/kg was administered subcutaneous monthly without 4-week loading doses for 2 years, followed by sequential monthly low dose emicizumab in the first week and factor VIII concentrate 15 units/kg twice weekly in the 4th week for the third year.

The medical personnel of the International Hemophilia Treatment Center-Bangkok closely monitored the occurrence of bleeding episodes using regular telephone calls every 4 weeks and the patients called back in cases of bleeding episode for the appropriate treatment of early bleeding episodes. The pre-emicizumab observation of bleeding episodes of 1 year was compared with those during 3-year emicizumab prophylaxis.

The quality of life was evaluated before and after emicizumab prophylaxis on the yearly basis for 3 successive years using the Haemo-Qol-Kids [12] and Haemo-Qol-A questionnaire [13,14]. Also, the Hemophilia Joint Health Score (HJHS) [15,16], Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) and ultrasonography study of bilateral elbows, knees and ankles [17] were also evaluated before and after emicizumab prophylaxis on the yearly basis for 3 successive years.

Laboratory Investigation

Coagulogram and factor VIII clotting activity (FVIII:C) were assayed within 4 hours or in the plasma stored at -20°C for less than 3 months before testing. The FVIII:C was assayed based on one-stage, activated partial thromboplastin time (APTT) using the ACL 200 Coagulometer with commercial factor VIII deficient plasma purchased from Instrumentation Laboratories, Lexington, MA, USA. The inhibitor to FVIII:C at baseline was determined using the Nijmegen-Bethesda assay [18]. After receiving emicizumab, FVIII:C was measured by a chromogenic assay using bovine factor VIII deficient plasma as substrate and the result was applied to measure inhibitor to FVIII:C [19]. The plasma emicizumab concentration was determined by a modified one stage factor VIII assay using an emicizumab calibrator [20].

Statistical analysis

Descriptive data were presented as mean (standard deviation, SD). Comparison of continuous variables were performed by Mann-Whitney U or Wilcoxon Signed rank test. A p-value less than 0.05 was considered statistical significance.

Results

Four male patients with hemophilia A (severe 2, moderate 2) without inhibitor were enrolled in the study at the mean (SD) age of 29.4 (13.4) years as shown in Table 1. They encompassed low bleeding risk circumstances including avoidance of contact sports and high velocity activities. The studied patients initially received episodic treatment, early bleeding treatment and low dose prophylaxis of standard half-life factor VIII concentrate at 15-20 units/kg twice weekly but breakthrough bleeding episodes frequently occurred. Therefore, all patients were switched to receive the whole vial of emicizumab at the median (IQR) monthly low dose of 1.23 (1.07, 1.40) mg/kg and 1.19 (1.05, 1.31) mg/kg without 4-week loading doses for the first and second years, respectively and sequential monthly low dose emicizumab of 1.57 (1.36, 1.66) mg/kg in the first week and factor VIII concentrate 15 units/kg twice weekly in

the 4th week in the third year as shown in Table 2.

The median (IQR) peak emicizumab concentration at 7 days after emicizumab administration during the first year of 13.2 (11.6, 17.5) μg/mL did not differ from that of the second year of 16.1 (13.4, 16.5) μg/mL (p=0.866) and both concentrations were slightly lower than that of the third year of 16.5 (15.2, 17.8) μg/mL but without statistically significant difference (p=0.499 and 0.237). Furthermore, the median (IQR) trough level of plasma emicizumab concentration during the 3-year prophylaxis was maintained at 10.7 (6.1, 13.4) μg/mL as shown in Figure 1. The level of plasma emicizumab concentration in the first year of 8.7 (4.9,12.0) μg/mL did not differ from that of the second year of 9.45 (6.7, 13.0) μg/mL (p=0.273), but the level of the first year trended to be lower than that of the third year of 12.9 (7.4, 14.8) μg/mL with a p-value of 0.068. However, the level of the second year did not significantly differ from that of the third year (p=0.109).

Their median (IQR) annual bleeding rates (ABR) decreased from baseline of 33.0 (12.0, 36.7) to 4.5 (2.5, 6.5) in the first year, 1.5 (0.2, 5.7) in the second year and 0.5 (0, 3.2) in the third year representing a difference of 81.9, 95.3 and 98.3%, respectively (p=0.068). The ABR of the third year trended to be lower than that of the first year with a p-value of 0.066 as shown in Table 2. Importantly, zero to 1 ABR was found in 3 of 4 patients from the second (n=2) and third years (n=1) of prophylaxis. The causes of bleeding occurrence during the first and second year of monthly low dose emicizumab prophylaxis were both spontaneous and trauma-related while only a few trauma-related bleeding episodes occurred during the third year of sequential monthly low dose emicizumab and factor VIII concentrate prophylaxis. Interestingly, most of the spontaneous bleeding occurred during the 4th week after receiving emicizumab. A total of 33 episodes of bleeding occurred in the first year (n=18), second year (n=10) and third year (n=5) of prophylaxis. They involved 24 episodes of hemarthrosis from spontaneous bleeding (target 19, non-target 2) and trauma-related bleeding (target 1, nontarget 2); and 9 other sites of spontaneous bleeding (n=5) including ecchymosis, iliopsoas muscle bleeding, external hemorrhoid bleeding, hematoma at axilla and waist; and trauma-related bleeding (n=4) at buccal mucosa, tongue, dorsum of foot and abrasion at forehead. All bleeding episodes were responsive to one administration of factor VIII concentrate 10-30 units/kg except iliopsoas muscle bleeding.

Three responsive patients (Nos. 1,3 and 4) also had their target joints at knee and elbow resolved according to the criteria of <3 bleeding episodes over a 52-week period starting from the first year among 2 patients (Nos. 1 and 3) with an addition of patient No. 4 in the second year of prophylaxis. All these 3 patients selected to have daily non-vigorous exercise of walk for 30 minutes or thread-mill walk of 5 km. They slowly gained muscle mass and strength. Even though patient No. 2 tried to walk 30 minutes at least 3 times weekly, sometimes he had more vigorous exercise of long distance walk of 14 km and aggressive swimming. He ended up with exercise inducing hemarthrosis requiring additional episodic treatment of factor VIII concentrate.

For the structural and functional musculoskeletal system evaluated by HJHS, 2 patients (Nos. 1 & 3) had their baseline HJHS <20 while the other patients (Nos. 2 & 4) had their baseline HJHS approaching 40. After receiving effective prophylaxis with zero ABR, those with HJHS <20 (Nos. 1 & 3) had decreased their HJHS approaching 10 which was less than the maximum HJHS of 12-15 among healthy adults aged 18-50 years [16]. However, both patients Nos. 2 and 4, who had markedly decreased their ABR from 36 to 4-7 and from 30 to 1-5, respectively, had their HJHS ranging from 31 to 38 which was higher than those of moderate and severe hemophilia (27.5-31.0) aged 30-40 years receiving both episodic and prophylactic treatment [16].

The comparison of HEAD-US and ultrasonography of bilateral knees, ankles and elbows at baseline and successive 3-year prophylaxis among studied patients was conducted. Patient No. 1 had lower synovium thickness at his target joint of left knee while the remaining joints were unchanged. Patient No. 2 had unchanged bilateral knees but increased thickening of synovium at some parts of his target joints of right ankle and left elbow, along with the right elbow, reflecting additional bleeding while the left ankle showed lesser synovium thickening. Patient No. 3 had slightly lower synovium thickness in his target joint of right elbow, but the echogenicity of synovium was rather stable in terms of chronicity. The other joints were unchanged. Patient No. 4 presented lower thickening synovium at all studied joints except dynamic change concerning both increased and decreased synovium thickening at posterior part of his target joint of right elbow. The imaging study was in concordance with the musculoskeletal evaluation of HJHS.

The quality of life of 1 boy and 3 adults was evaluated using the Haemo-QoL-Kids and Haemo-QoL-A questionnaire, respectively. One boy (patient No. 1) had a lower median total score during 3-year prophylaxis of 25.0, 25.0 and 18.7 representing better quality of life related to physical health, feeling, attitude, family members, friends, other individuals, sport, coping and treatment compared with baseline of 27.1 but no statistically significant difference was found (p=0.067 to 0.766). On the contrary, 3 adults presented a slightly lower median total score during the first year of prophylaxis of 71.2 compared with baseline of 72.7 representing no improvement of quality of life. However, the median total score in the second and third years increased to 81.0 and 76.1 representing a better quality of life related to physical function, role function, worry, consequence of bleeding, emotional impact and treatment concern compared with baseline of 72.7 but no statistically significant difference was found (p=0.109 to 0.285). Interestingly,

patient No. 2 exhibited a statistically significant difference from baseline total scores of 52.7 to 76.6, 86.3 and 78.5 during 3-year prophylaxis with p-values of 0.017, 0.018 and 0.018, respectively.

The median (IQR) APTT of all patients during the first year of prophylaxis of 27.2 sec (25.9, 28.5) and the third year of prophylaxis of 25.9 sec (25.3, 31.6) were significantly shortened compared with baseline of 57.1 sec (54.7, 96.1) (p=0.043) confirming the presence of emicizumab and the likely absence of anti-emicizumab antibodies. Also, no inhibitor to factor VIII clotting activity was detected among all patients after emicizumab prophylaxis.

Discussion

The whole vials of emicizumab at 30 and 60 mg were used among the studied patients according to the patients' weight. The calculated dose of emicizumab (mg/kg) was gradually increased resulting in the slightly higher trough level of plasma emicizumab concentration in the third year compared with those in the first two years. Even though factor VIII concentrate was administered in the 4th week during the third year, the trough plasma emicizumab concentrations were determined when patients abstained from factor VIII administration for at least 72 hours.

The reason of adding factor VIII concentrate during the 4th week after administering emicizumab was due to the breakthrough bleeding during the first and second years of prophylaxis often occurred during the 4th week. The trough plasma concentration of emicizumab at the 4th week was lower than that of the peak level during the first week of emicizumab prophylaxis. Therefore, the administration of factor VIII concentrate was helpful in preventing bleeding during the 4th week. Moreover, factor VIII concentrate provide other biological activities beyond hemostasis related to bone remodelling, dysregulated macrophage polarization and inflammatory processes among patients with hemophilia [21]. Also, the continuous exposure to factor VIII may partly induce tolerance to factor VIII coagulation protein.

The ABR among the studied patients was markedly decreased to achieve zero to 1 among 3 of 4 studied patients starting from the second year of prophylaxis as well as the resolution of target joints in responsive patients. Spontaneous bleeding episodes were gradually decreased to accomplish zero spontaneous ABR while the remaining bleeding episodes were trauma-related. However, the sequential low dose monthly emicizumab and factor VIII prophylaxis for 1 year in the current study could not certainly demonstrate the superior over the low dose monthly emicizumab because the baseline clinical data before applying these 2 regimens differed and a long term period of more than 2 years emicizumab prophylaxis yielded more patients with zero ABR [22]. Ultimately, both regimens of prophylaxis were effective in preventing bleeding episodes.

The daily regular exercise was essentially required to gain muscle mass as well as strength. Vigorous exercise should be prohibited to prevent additional bleeding episodes. Moreover, 2 patients had decreased HJHS representing the improvement of structural and functional musculoskeletal system while the other 2 patients had slightly changed HJHS representing the irreversible pre-existing joint arthropathy [23].

The limitation encountered in the current study is the heterogeneously small number of patients with boys and adults with moderate and severe hemophilia A without inhibitor. However, the strength of long term, 3-year follow-up demonstrated the bimonthly trough levels of plasma emicizumab concentration, clinical manifestations of bleeding episodes from both spontaneous and trauma-related causes at target and non-target joints as well as complete evaluation of HJHS, HEAD-US and ultrasonography study. MRI was not included because of the unaffordable cost.

No.	Age (years)	Age at diagnosis	FVIII:C (%)	Mutation	Age of replacement therapy		
					Episodic	Early bleeding	Low-dose prophylaxis
1	12.3	3 months	0.2	Inversion intron 22	7 months using factor conc.	2 years using factor conc.	11 years using factor conc.
2	25.5	7 days	0.3	c.2003 T>C p. Leu 668 Pro	7 days using frozen cryoppt prepared from paternal plasmapheresis	1.2 years using factor conc.	21 years using factor conc.
3	41.3	5 years	2.2	Duplication exon 1-6	5 years using frozen cryoppt	10 years using lyophilized form of FFP	27 years using factor conc.
4	38.7	2 years	1.6	Duplication exon 1-6	2 years using frozen cryoppt	7 years using lyophilized form of FFP	24 years using factor conc.

conc, concentrate; cryoppt, cryoprecipitate; FFP, fresh frozen plasma

Table 1: Demographic data among 4 studied patients.

Patients	Study year	Weight (Kg)	Emicizumab		Bleeding site 1 year before and after emicizumab for 3 years				Annual rate bleeding	HJHS	Target joint	Used factor during prophylaxis	
			Monthly dose		Joint (target/ non target)		Other sites					Episodic (unit)	Prophylaxis (unit)
			mg	mg/kg	Spontaneous	Trauma	Spontaneous	Trauma					
1	Before	40.0	-	-	20/0	8./0	3	6	37	18	Lt knee	18,500	48,000
	Y1	41	60	1.46	2/0	0/0	0	2	4	11	No	1,500	0
	Y2	45	60	1.33	0/0	0/0	1	0	1	11	No	0	0
	Y3	55	90	1.64	0/0	0/0	0	0	0	11	No	0	12,000
2	Before	57	-	-	24/0	0/6	6	0	36	36	Rt ankle, Lt elbow	18,000	72,000
	Y1	59	60	1.02	6/0	0/0	1	0	7	31	Rt ankle, Lt elbow	14,000	0
	Y2	59	60	1.02	1/1	1/2	2*	0	7	31	Rt ankle, Lt elbow	59,000	0
	Y3	60	90	1.50	0/0	4/0	0	0	4	38	Rt ankle, Lt elbow	7,000	24,000
3**	Before	60	-	-	3/0	0/0	3	0	6	16	Rt elbow	6,000	48,000
	Y1	60	75	1.25	0/0	0/0	0	2	2	14	No	3,000	0
	Y2	60	75	1.25	0/0	0/0	0	0	0	14	No	0	0
	Y3	68	90	1.32	0/0	0/0	0	0	0	9	No	0	24,000
4**	Before	92	-	-	18/0	6/0	3	3	30	40	Rt elbow	30,000	48,000
	Y1	86	105	1.22	4/0	0/0	1	0	5	32	Rt elbow	4,750	0
	Y2	92	105	1.14	2/0	0/0	0	0	2	33	No	0	0
	Y3	90	150	1.67	0/0	0/1	0	0	1	34	No	750	24,000

Y1, Y2, Y3, the first, second and third years of emicizumab prophylaxis, respectively; HJHS, hemophilia joint health score; *one episode of iliopsoas muscle bleeding; ** the second vial of emicizumab 30 mg was shared among siblings to achieve 75 and 105 mg, respectively

Table 2: Annual bleeding rate, bleeding sites, HJHS, target joint and the used standard half-life factor VIII concentrate while receiving monthly low dose emicizumab in Years 1 and 2, followed by sequential monthly low dose emicizumab and factor VIII concentrate in Year 3 compared with low dose prophylaxis 1 year before emicizumab prophylaxis.

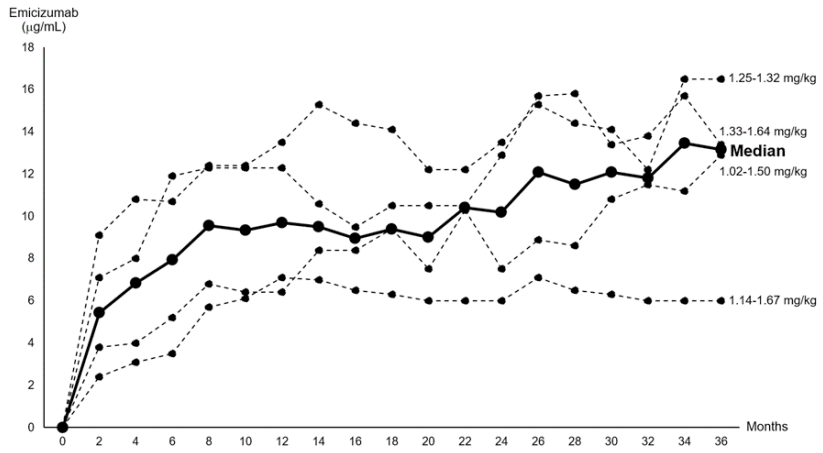

Figure 1: Individual and median of bi-monthly trough plasma emicizumab concentration among 4 studied patients receiving the median emicizumab dose of 1.29 mg/kg (range 1.02-1.67).

Conclusion

Both monthly low dose emicizumab without 4-week loading doses, and sequential monthly low dose emicizumab and factor VIII concentrate prophylaxis showed effectiveness among patients with hemophilia A. The musculoskeletal system and quality of life were also improved.

Disclosure: The authors state that they have no interest which might be perceived as posing a conflict or bias.

Author Contributions: A.C.; designed and conducted the study using data analysis, wrote the manuscript. S.J.; performed imaging studies and took care of patients. N.S.; took care of patients and data analysis. T.J.; provided rehabilitation advice, performed HJHS and data analysis. P.K.; performed laboratory investigations of hemophilia and emicizumab. K.K.; took care of patients and analyzed the quality of life. M.P.; provided rehabilitation advice, performed HJHS and data analysis. W.R.; took care of patients and monitored compliance. All authors approved the manuscript.

ORCID

Ampaiwan Chuansumrit: https://orcid.org/0000-0003-1230-1591

Suphaneewan Jaovisidha: https://orcid.org/0000-0002-4838-3245

Nongnuch Sirachainan: https://orcid.org/0000-0001-8039-5476

Tachit Jiravichitchai: https://orcid.org/0000-0003-4144-0072

Praguywan Kadegasem: https://orcid.org/0000-0003-0216-1660

Ketsuda Kempka: https://orcid.org/0009-0003-6591-5244

Noppawan Tungbubpha: https://orcid.org/0000-0001-9639-9447

Wannaphorn Rotchanpanya: https://orcid.org/0000-0003-4679-8647

Funding: This research received no external funding.

Institutional Review Board Statement: The study was approved by the Faculty Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University (COA.MURA 2021/257 and 2023/428) and registered to the Thai Clinical Trial Registry (20210725001 and 20230705005). The study was conducted following the Declaration of Helsinki and written informed consent was obtained from patients and parents.

Data Availability Statement: The data from the findings of the study are available from the corresponding author upon reasonable request.

Acknowledgments: The authors would like to thank the patients and families participating in the study.

Conflicts of Interest: None.

References

1. Kitazawa T, Igawa T, Sampei Z, Muto A, Kojima T, et al. (2012) A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model. Nat Med. 18: 1570-1574.
2. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, et al (2017) Emicizumab prophylaxis in hemophilia A with Inhibitors. N Engl J Med. 377: 809-818.
3. Young G, Liesner R, Chang T, Sidonio R, Oldenburg J, et al. (2019) A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood. 134:2127-38.
4. Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, et al. (2018) Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med. 379:811-22.

5. Pipe SW, Shima M, Lehle M, Shapiro A, Chebon S, et al. (2019) 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. 6:e295-305.

6. Yang R, Wang S, Wang X, Sun J, Chuansumrit A, Zhou J, et al. (2022) Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: A randomized study (HAVEN 5). Res Pract Thromb Haemost. 6:e12670.

7. Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, et al. (2016) Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. N Engl J Med. 374:2044-53.

8. Tang ASO, Leong TS, Ko CT, Chew LP. (2021) Efficacy of reduced-dose emicizumab in haemophilia A with inhibitors: real world experience in east Malaysia [abstract]. Res Pract Thromb Haemost. 5. PB0567.

9. Lehtinen AE, Lassila R. (2022) Do we need all that emicizumab? Haemophilia. 28:e53-55.

10. Chuansumrit A, Sirachainan N, Jaovisidha S, Jiravichitchai T, Kadegasem P, et al. (2023) Effectiveness of monthly low dose emicizumab prophylaxis without 4-week loading doses among patients with haemophilia A with and without inhibitors: A case series report. Haemophilia. 29: 382-385.

11. Bansal S, Donners AAMT, Fischer K, Kshirsagar S, Rangarajan S, et al (2023) Low dose emicizumab prophylaxis in haemophilia A patients: A pilot study from India. Haemophilia. 29: 931-934.

12. von Mackensen S, Bullinger M; Haemo-QoL Group (2004) Development and testing of an instrument to assess the quality of life of children with haemophilia in Europe (Haemo-QoL). Haemophilia. 10: 17-25.

13. Rentz A, Flood E, Altisent C, Bullinger M, Klamroth R, et al (2008) Cross-cultural development and psychometric evaluation of a patient-reported health-related quality of life questionnaire for adults with haemophilia. Haemophilia. 14: 1023-1034.

14. Chinthammitr Y, Pengchata P, Suwanawiboon B, Pongtannakul B, Nakkinkun Y, et al (2015) Quality of life among haemophilia in Thailand [abstract]. J Thromb Hemost. 13:849. PO268-WED.

15. Feldman BM, Funk SM, Bergstrom BM, Zourikian N, Hilliard P, et al (2011) Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: validity of the hemophilia joint health score. Arthritis Care Res (Hoboken). 63: 223-230.

16. St-Louis J, Abad A, Funk S, Tilak M, Classey S, Zourikian N, et al (2022) The Hemophilia Joint Health Score version 2.1 validation in adult patients study: a multicenter international study. Res Pract Thromb Haemost. 6: e12690.

17. Martinoli C, Della Casa Alberighi O, Di Minno G, Graziano E, et al (2013) Development and definition of a simplified scanning procedure and scoring method for Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US). Thromb Haemost. 109: 1170-1179.

18. Duncan E, Collecutt M, Street A (2013) Nijmegen-Bethesda assay to measure factor VIII inhibitors. Methods Mol Biol. 992: 321-333.

19. Adamkewicz JI, Kiialainen A, Paz-Priel I (2020) Effects and interferences of emicizumab, a humanized bispecific antibody mimicking activated factor VIII cofactor function, on lupus anticoagulant assays. Int J Lab Hematol. 42: e71-e75.

20. Kershaw G, Dix C, Chen VM, Cai N, Khoo TL (2022) Emicizumab assay evaluations and results from an Australian field study of emicizumab measurement. Pathology. 54: 755-762.

21. Wang H, Bai X (2021) Mechanisms of bone remodeling disorder in hemophilia. Semin Thromb Hemost. 47: 43-52.

22. Callaghan MU, Negrier C, Paz-Priel I, Chang T, Chebon S, et al (2021) Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. Blood. 137: 2231-2242.

23. Manco-Johnson MJ, Lundin B, Funk S, Peterfy C, Raunig D, et al (2017) Effect of late prophylaxis in hemophilia on joint status: a randomized trial. J Thromb Haemost. 15: 2115-2124.