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Final Analysis Results from the AGEHA Study: Emicizumab Prophylaxis for Acquired Hemophilia A with or without Immunosuppressive Therapy

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Abstract

Background Primary analysis of the phase III AGEHA study suggested a favorable benefit–risk profile for emicizumab prophylaxis in patients with acquired hemophilia A (PwAHA); however, only patients undergoing immunosuppressive therapy (IST; Cohort 1) were included.

Objectives To present final analysis results of AGEHA, including data on IST-ineligible patients (Cohort 2) and on long-term prophylaxis with emicizumab.

Methods For patients in both Cohorts 1 and 2, emicizumab was administered subcutaneously at 6 mg/kg on Day 1, 3 mg/kg on Day 2, and 1.5 mg/kg once weekly from Day 8 onward.

Results Twelve patients (Cohort 1) and two patients (Cohort 2) were enrolled. Duration of emicizumab treatment was 8 to 639 days (median: 44.5 days) in Cohort 1 and 64 and 450 days in Cohort 2. In both cohorts, no major bleeds were observed after initial emicizumab administration. Six patients started their first rehabilitation sessions during emicizumab treatment and no rehabilitation-related bleeds occurred. Twenty-three surgeries were performed under emicizumab prophylaxis and there were

Keywords
- Factor VIII deficiency, acquired
- long-term
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- rehabilitation
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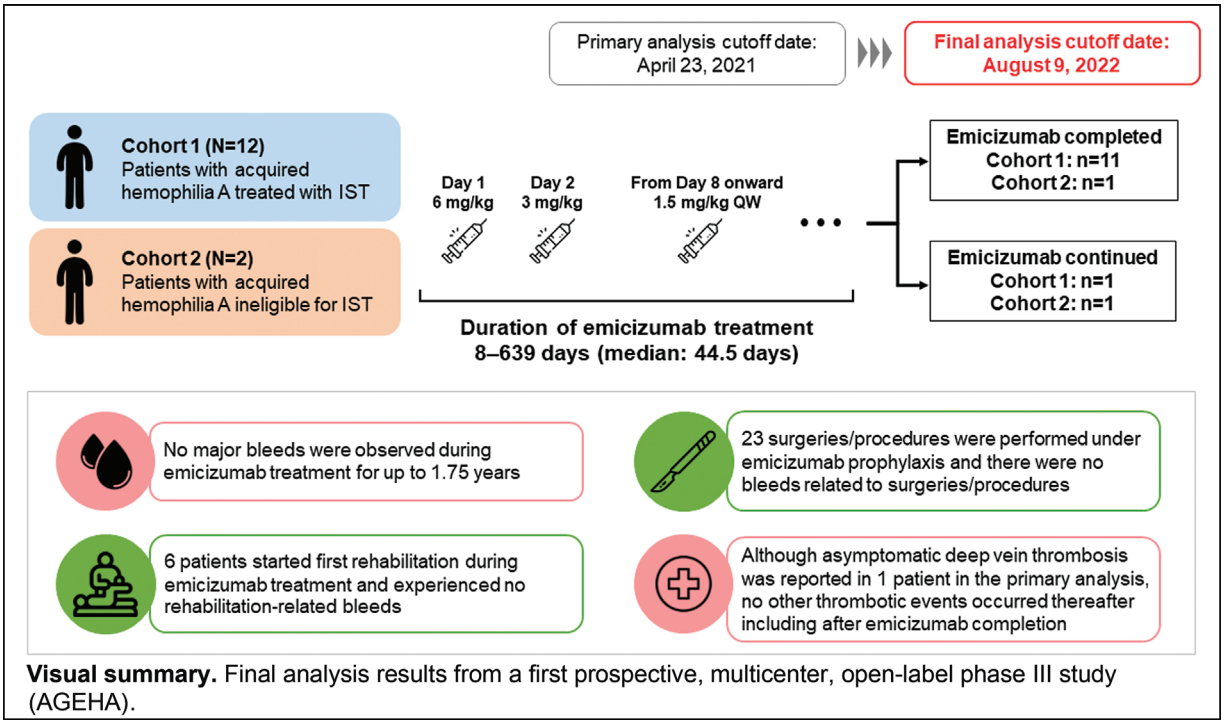

Visual summary. Final analysis results from a first prospective, multicenter, open-label phase III study (AGEHA).

no bleeds related to surgeries. Although asymptomatic deep vein thrombosis was reported in one patient in the primary analysis, no other thrombotic events occurred thereafter. Two patients developed anti-emicizumab antibodies, one of whom showed accelerated emicizumab clearance. Tailored IST approaches (delayed initiation, no use, or reduced dose) were successfully executed in three patients undergoing emicizumab prophylaxis.

Conclusion These results suggest that emicizumab prophylaxis has a favorable benefit–risk profile in PwAHA regardless of eligibility for IST.

Introduction

Acquired hemophilia A (AHA) is a disorder involving sudden onset of serious bleeding episodes caused by the development of autoantibodies (called "inhibitors") against coagulation factor VIII (FVIII). Patients with AHA (PwAHA) remain at a high risk of bleeding until remission of AHA is achieved.[1]

For hemostatic treatment, bypassing agents (e.g., recombinant activated factor VII [rFVIIa] or activated prothrombin complex concentrate [aPCC]) or recombinant porcine FVIII (rpFVIII) are used episodically.[2] However, although bypassing agents can be effective, there are cases where sufficient hemostatic effect cannot be achieved, necessitating multiple intravenous administrations at short intervals because of the short half-life of these agents. In addition, although rpFVIII can also be an effective treatment option if the patient's FVIII inhibitor does not cross-react with rpFVIII, de novo anti-rpFVIII antibodies are often induced, which can render rpFVIII treatment ineffective. Prophylactic treatment with bypassing agents has not been established as a standard of care for PwAHA,[2] but prophylactic treatment would be an optimal treatment option in some cases because serious bleeding often occurs even in the postacute phase, and patients at risk of such bleeding may require bed rest, with prolonged bed rest potentially increasing the risk of poor prognosis. Effective prophylaxis may also allow an earlier start to rehabilitation, improving the quality of life and prognosis of PwAHA.

For the treatment of AHA, it is recommended to initiate immunosuppressive therapy (IST) immediately after diagnosis to eliminate the FVIII inhibitors.[2] In general, as the standard of care for AHA, IST is started as prednisolone 1 mg/kg/day or as a combination of prednisolone plus cyclophosphamide. Although most patients achieve remission of AHA by IST, there are a certain number of patients who remain persistently refractory to IST. In addition, fatal or severe infections that occur due to IST are among the primary causes of death in PwAHA (4.2–16%).[3,4] Furthermore, patients at particularly high risk of infection (e.g., patients with autoimmune disease already receiving long-term IST, bedridden elderly patients, and diabetic patients) are not able to tolerate high doses of IST. Therefore, if bleeding risks

can be appropriately controlled by effective prophylactic treatment, then tailored IST approaches such as dose reduction, no use, or delayed initiation of IST based on each patient's specific condition could be considered.

Emicizumab is a recombinant, humanized, bispecific monoclonal antibody designed to bridge activated factor IX and factor X (FX), and exerts cofactor activity substituting for activated FVIII regardless of FVIII inhibitor status.[5] Phase III studies of emicizumab in patients with congenital hemophilia A (PwCHA) showed a clinically meaningful prophylactic effect of emicizumab irrespective of FVIII inhibitors,[6] and real-world experience with usage of emicizumab in PwCHA is accumulating.[7] Given that the pathogenesis of AHA is the emergence of FVIII inhibitors, evidence from nonclinical studies[8,9] suggested that emicizumab could be expected to become a treatment option for AHA.

To evaluate the benefit–risk profile of emicizumab prophylaxis with a new dosing regimen and completion criteria in PwAHA, we conducted a first prospective, multicenter, open-label phase III study (AGEHA). The previously reported primary analysis results from AGEHA suggested that emicizumab prophylaxis had a favorable benefit–risk profile in PwAHA; however, that analysis included only patients who had already started IST.[10] Results of a recent prospective clinical trial investigating the prophylactic effect of emicizumab without IST in 47 PwAHA regardless of their eligibility for IST suggested the efficacy of emicizumab prophylaxis for 12 weeks with delayed initiation of IST.[11] The final analysis of AGEHA reported here includes an additional two patients who were ineligible for IST to obtain data from a subpopulation for whom a tailored IST approach would be the most desired in clinical practice. In addition, at the primary analysis, most patients who had met the completion criteria had not completed the 24-week safety follow-up period during which emicizumab is remaining in plasma after partial remission of AHA (i.e., FVIII activity >50 IU/dL). We report herein pharmacokinetics, efficacy, and safety data of emicizumab prophylaxis from the fourteen patients in total from the entire study period including full data on the 24-week safety follow-up period as well as long-term emicizumab prophylaxis data exceeding 1 year. Furthermore, results of rehabilitation, performance status, and perioperative bleeding management are also reported.

Methods

Study Design and Patients

AGEHA was a prospective, multicenter, open-label, nonrandomized, phase III study investigating the safety, efficacy, and pharmacokinetics of emicizumab in PwAHA. AGEHA consisted of Cohort 1 (patients already undergoing or scheduled to immediately undergo IST) and Cohort 2 (patients for whom it was considered difficult to undergo IST; ►**Supplementary Fig. S1**, available in the online version). Patients are numbered consecutively from Cohort 1 into Cohort 2. The eligibility criteria, requirement for concomitant therapies, and study location are described in ►**Supplementary Method S1** (available in the online version).

This study was conducted from June 2020 (first patient first dose) to August 2022 (last patient last visit) in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice. The study protocol was approved by the institutional review board at each study site, and all patients and/or their legally authorized representatives provided written informed consent. This study is registered at https://jrct.niph.go.jp/ (JapicCTI-205151/jRCT2080225056).

Emicizumab was administered subcutaneously at 6 mg/kg on Day 1, 3 mg/kg on Day 2, and 1.5 mg/kg once weekly from Day 8 onward (AGEHA protocol), and the study protocol required weekly coagulation monitoring (FVIII activity and FVIII inhibitors). After the investigator confirmed that both of following criteria for completion of emicizumab administration had been met: (1) FVIII activity measured in the absence of interference of emicizumab and coagulation factor products had been confirmed to exceed 50 IU/dL and (2) more than 72 hours had passed since the last use of coagulation factor products for the last bleed requiring treatment, patients transitioned to a 24-week safety follow-up period.

Endpoints

In addition to the endpoints described in ►**Supplementary Method S2** (available in the online version), we also conducted an analysis of bleeding management on surgery (including procedures unless otherwise noted). Surgery data, perioperative use of coagulation factor products, and bleeding data were reported by the investigators. Surgery performed during the emicizumab treatment period and the safety follow-up period was included in our analysis. Surgery was classified as "major" or "minor" based on invasiveness: surgery that involved entering a body cavity, opening a fascial surface, or removing an organ was classified as major; other surgery was classified as minor.[12] Endoscopic procedures were classified according to the risk of bleeding referring to the guidelines for the management of antithrombotic agents for endoscopic procedures.[13] In the analysis of safety upon restoration of endogenous FVIII activity, the cutoff level defining FVIII activity overshoot was set as 150 IU/dL as previously reported.[14]

Statistical Analysis

AGEHA was ended when all patients completed the safety follow-up period, were withdrawn from the study, were lost to follow-up, or switched to a commercial emicizumab product (only for patients still on emicizumab), whichever was later. After the last visit of the last patient on August 9, 2022 (end of study), the final analysis was performed (►**Supplementary Fig. S1**, available in the online version).

Detailed definitions of the three evaluation periods (the pretreatment period [observation period before initial emicizumab administration], the on-treatment period [observation period during emicizumab treatment], and the safety follow-up period [follow-up period after completing emicizumab administration]) and derivation of calculated annualized bleeding rate (ABR) are described in ►**Supplementary Methods S3** and **S4** (available in the online version), respectively.

The start of a bleed was defined as the date/time of the initial appearance of the bleed regardless of bleed type. The end of a bleed was defined as the time of disappearance of symptoms or 72 hours after the last use of coagulation factor products for the bleeding event, whichever was later.

SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, United States) was used for the analyses.

Results

Patient Demographics

Fourteen patients were included in the final analysis: twelve patients in Cohort 1 and two patients in Cohort 2. No patient was excluded from any of the analyses. Patient demographics are provided in ►**Table 1**.

Patient Disposition and Emicizumab Treatment

At the time of the primary analysis, eleven of the twelve patients in Cohort 1 had met the emicizumab completion criteria, eight of the eleven were still under observation in the 24-week safety follow-up period. In this final analysis, seven of those eight patients had completed the safety follow-up period and the one remaining patient withdrew consent on Day 246 during the safety follow-up period. Among the two patients in Cohort 2, one had completed emicizumab administration and the safety follow-up period. Patient 04 in Cohort 1 and Patient 14 in Cohort 2 had not met the emicizumab completion criteria by the end of the study and continued on long-term emicizumab prophylaxis for the maximum duration of treatment in each cohort. Both patients were transitioned to a commercial emicizumab product after the end of the study (►**Supplementary Fig. S1**, available in the online version).

Overall, the duration of emicizumab treatment in the study ranged from 8 to 639 days (median: 44.5 days) in Cohort 1, and was 64 and 450 days in the two patients in Cohort 2. The patient disposition summary at the primary analysis and at the final analysis is shown in ►**Supplementary Table S1** (available in the online version).

Immunosuppressive Therapies

All twelve patients in Cohort 1 were receiving prednisolone at around 1 mg/kg or less on Day 1 (►**Table 2**). In addition, three received cyclophosphamide and one received cyclosporin during the study. In nine of the eleven patients in Cohort 1 who had met the emicizumab completion criteria, the intensity of IST was decreased from Day 1 until the end of the safety follow-up period or the date of study discontinuation. The dosage of prednisolone in Patient 04 in Cohort 1 who did not meet the emicizumab completion criteria was also tapered throughout the study to avoid serious side effects of IST.

Patient 13 in Cohort 2 started IST 4 days after initial emicizumab administration and finally met the emicizumab completion criteria. For this patient, it was deemed challenging to commence IST at enrollment owing to poor control of diabetes; however, once insulin treatment had improved glycemic control, it was subsequently determined that initiating IST was feasible after initiation of emicizumab treatment. Patient 14 in Cohort 2 has not received any ISTs for AHA throughout the study.

Pharmacokinetics

In an overall assessment through Cohorts 1 and 2, the mean plasma emicizumab concentration exceeded 30 µg/mL by 4 days after starting emicizumab treatment and was maintained at steady-state trough thereafter, ranging from 38.2 to 40.9 µg/mL during 1 to 4 weeks after starting emicizumab treatment ($n = 11$–14). There was no clear difference between Cohorts 1 and 2 in the time course of plasma emicizumab concentration. The mean (standard deviation) half-life after completing emicizumab administration was 34.2 (14.3) days ($n = 11$).

Table 1 Patient demographics

	Cohort 1	Cohort 2	
	$N = 12$	Patient 13	Patient 14
Age, y	76 (50–92)[a]	82	59
Sex	Male: $n = 6$ Female: $n = 6$	Female	Female
Body mass index, kg/m^2	21.08 (16.3–30.2)[a]	24.5	21.9
Duration from AHA diagnosis to enrollment, days	17.5 (2–2,167)[a]	6	1,009
FVIII activity at diagnosis, IU/dL	1.0 (<0.8 to 36.6)[a]	<1	<1
FVIII inhibitor titer at diagnosis, BU/mL	40.5 (1–149)[a]	58	33
Prior or current use of coagulation factor products or transfusion	Yes: $n = 8$ No: $n = 4$	Yes	Yes
Regimen of coagulation factor products	Episodic: $n = 8$ Prophylactic: $n = 0$	Episodic (rFVIIa and FFP)	Prophylactic and episodic (aPCC)

Abbreviations: AHA, acquired hemophilia A; aPCC, activated prothrombin complex concentrate; BU, Bethesda units; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; FFP, fresh frozen plasma; FVIII, factor VIII; IU, international units; rFVIIa, recombinant activated factor VII.
[a]The value is median (range).

Table 2 Emicizumab treatment period and status of immunosuppressive therapy

Patient ID	Emicizumab treatment period (days)	On Day1				At last observation			
		Medication[a]	Route	Dose/day (mg)	Body weight (kg)	Status	Medication[a]	Route	Dose/day (mg)
Cohort 1									
01	47	PSL	IV	30	52.1	Withdrawn from study	None	—	—
		CPA	Oral	50					
02	36	PSL	Oral	40	40.2	Completed	None	—	—
03	50	PSL	Oral	40	61.7	Completed	PSL	Oral	7
04	639	PSL	Oral	20	51.6	Ongoing emicizumab[b]	PSL	Oral	6
05	29	PSL	Oral	50	54.4	Completed	PSL	Oral	12
06	106	PSL	Oral	30	51.3	Withdrawn from study	PSL	Oral	9
07	29	PSL	Oral	60	85.2	Completed	PSL	Oral	12.5
							CPA	Oral	50
08	8	PSL	Oral	7.5	46.1	Completed	PSL	Oral	5
		CYA	Oral	100			CYA	Oral	100
09	42	PSL	Oral	40	38.4	Completed	PSL	Oral	15
10	64	PSL	IV	50	49.3	Completed	PSL	Oral	3
		CPA	Oral	50			CPA	Oral	50
11	57	PSL	Oral	60	56.5	Completed	None	–	–
12	15	PSL	Oral	5	50.2	Completed	PSL	Oral	5
Cohort 2									
13	64	None	–	–	52.2	Completed	PSL	Oral	2.5
							CPA	IV	500
14	450	None	–	–	54.2	Ongoing emicizumab[b]	None	–	–

Abbreviations: CPA, cyclophosphamide; CYA, cyclosporin; IV, intravenous; PSL, prednisolone.
[a]Immunosuppressive therapies indicated for acquired hemophilia A are included.
[b]Patients 04 and 14 did not meet the emicizumab completion criteria during the study and were transitioned to a commercial emicizumab product.

Prophylactic Effect for Bleeds

No major bleeds occurred in either cohort after starting emicizumab treatment. Nine of twelve patients (75%) in Cohort 1 and both patients (100%) in Cohort 2 had no treated bleeds during the on-treatment period, and no patient in either cohort had any treated bleeds during the safety follow-up period (►**Table 3**). For Cohort 1, only one patient experienced a treated bleed after the cutoff date of the primary analysis; it occurred on Day 587 (on-treatment period), and hemostasis was confirmed on Day 618. This was a traumatic bleed caused by a cat bite; it was treated by suturing and a single dose of rFVIIa but judged as nonmajor by the investigator. Among five of fourteen patients in the two cohorts who did not experience any major or treated bleeds during the pretreatment period, the number of all bleeds was zero or ABR of all bleeds decreased after starting emicizumab treatment.

Comparing the bleeding rates on a population level, the mean calculated ABRs of major bleeds, treated bleeds, and all bleeds for the on-treatment period were, respectively, 0.0, 3.2, and 5.3 in Cohort 1 and 0.0, 0.0, and 3.7 in Cohort 2, while those for the pretreatment period were 66.4, 35.6, and 77.0 in Cohort 1 and 15.9, 17.0, and 26.0 in Cohort 2 (►**Fig. 1**).

Rehabilitation

Of the fourteen patients in the two cohorts, six patients (42.9%) could start their first rehabilitation sessions 11 days (median) after starting emicizumab treatment, all of which were conducted during hospitalization and before the emicizumab completion criteria had been met (►**Table 4**). The rehabilitation sessions for five of these six patients comprised disuse syndrome rehabilitation, prevention of disuse syndrome, occupational therapy, physical therapy, or range of motion, all of which were not limited to rehabilitation to improve contractures at bleeding sites. The remaining patient conducted stretching and relaxation of left calf where bleeding had occurred. The median (range) FVIII activity on the day of first rehabilitation session or nearest sampling

Table 3 Bleeding events in each cohort

	Observation period, median (range), days	No. of patients with ≥1 treated bleeds (total no. of events), *n*	No. of patients with ≥1 major bleeds (total no. of events), *n*	No. of patients with ≥1 all bleeds (total no. of events), *n*
Pretreatment period: Cohort 1 (*N* = 12), Cohort 2 (*N* = 2)				
Cohort 1	68.0 (17–168)	6 (30)	7 (77)	11 (110)
Cohort 2	95.5 (23–168)	2 (3)	1 (2)	2 (5)
On-treatment period: Cohort 1 (*N* = 12), Cohort 2 (*N* = 2)				
Cohort 1	44.5 (8–639)	3 (6)	0 (0)	5 (34)
Cohort 2	257.0 (64–450)	0 (0)	0 (0)	2 (3)
Safety follow-up period: Cohort 1 (*N* = 11), Cohort 2 (*N* = 1)				
Cohort 1	168.0 (14–171)	0 (0)	0 (0)	7 (12)
Cohort 2	174 (174)	0 (0)	0 (0)	1 (1)

Note: A major bleed was reported by the investigator if any of the following conditions were met: (1) life-threatening, (2) symptomatic in an important region or major organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardiac bleeds, or muscle bleeds associated with compartment syndrome), or (3) associated with a decrease of ≥2 g/dL in hemoglobin or necessitating transfusion of ≥2 units of whole blood or packed red cells. A treated bleed was defined as a bleed directly followed by use of a coagulation factor product without an intervening bleed. Bleeds due to surgery/procedures were excluded.

point before it was 2.0 IU/dL (<1.0–11.9). In four out of the six patients, rehabilitation sessions were started after hemostasis of all active bleeds had been confirmed. There was no clear relationship between the timing of starting rehabilitation and restoration of endogenous FVIII activity levels. Regardless of the FVIII activity level when the rehabilitation sessions began, no rehabilitation-related bleeds occurred in any patient.

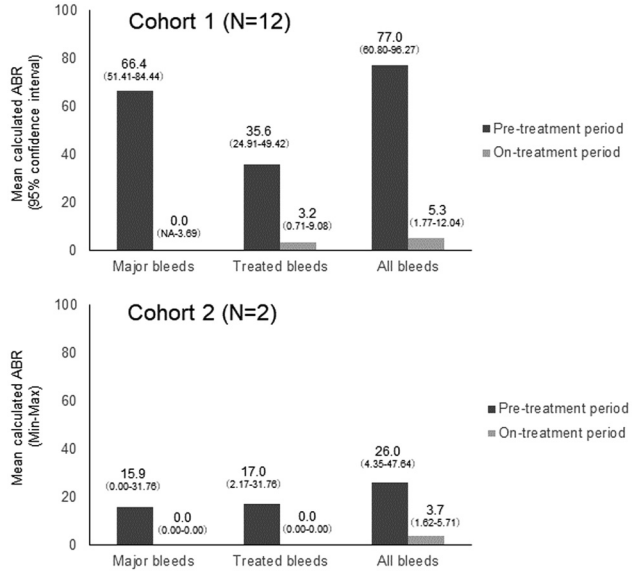

Fig. 1 Bleeding rate. Calculated ABRs were derived as 365.25 times the number of bleeding events that occurred in an evaluation period divided by the number of days in the corresponding evaluation period for each patient and each bleed definition. ABR, annualized bleeding rate.

Eastern Cooperative Oncology Group Performance Status

In Cohort 1, two patients had Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scores 0 (fully active) at baseline, at the date of emicizumab completion, and at the last observation (►**Table 5**). Among the other ten patients, ECOG-PS scores for four patients (40.0%) improved by 1 from baseline to the date of emicizumab completion and ECOG-PS scores for seven patients (70.0%) improved by 1 from baseline to the last observation. In Cohort 2, the ECOG-PS score for one patient improved by 2 from baseline to the date of emicizumab completion. For the remaining three patients in Cohort 1 (baseline scores: 1, 2, and 4) and one patient in Cohort 2 (baseline score: 1), ECOG-PS scores remained almost unchanged throughout the study.

In both cohorts, there was no clear association between improvement in ECOG-PS and duration from the diagnosis of AHA to the start of emicizumab. Among seven patients with high ECOG-PS (≥3) at baseline, emicizumab treatment was started within 1 week of diagnosis of AHA in three patients and within 1 month of diagnosis in the remaining four patients. All three patients who started emicizumab within 1 week of diagnosis showed ECOG-PS improvement at the date of emicizumab completion, but none of the patients with longer duration from diagnosis showed improvement or worsening at the date of emicizumab completion. Among five patients with low ECOG-PS (1 or 2) at baseline, emicizumab treatment was started more than 1 year after diagnosis of AHA in three patients and within 1 or 3 weeks of diagnosis in the remaining two patients. Although ECOG-PS improvement was observed in two of the five patients at the date of emicizumab completion, both patients had more than 1-week interval between AHA diagnosis and emicizumab initiation.

Table 4 Rehabilitation sessions started after initial emicizumab dose

	Patient ID	Type of rehabilitation session	Start day of first rehabilitation session (study day)	FVIII activity (IU/dL) (study day[a])
Cohort 1	03	Prevention of disuse syndrome	14	<1.0 (Day 8)
	04	Disuse syndrome rehabilitation	4	11.9 (Day 1)
	06	Prevention of disuse syndrome	15	2.4 (Day 15)
	09	Occupational therapy Physical therapy	8	1.5 (Day 8)
	11	Stretching and relaxation of left calf	17	8.7 (Day 16)
Cohort 2	13	Range of motion	6	<1.0 (Day 1)

Abbreviations: FVIII, factor VIII; IU, international units.
[a]Same day as the start day of first rehabilitation session or nearest sampling point before it.

Table 5 Duration from the date of AHA diagnosis to Day 1 (the date of starting emicizumab) and ECOG performance status at baseline, follow-up week 1 (the date of emicizumab completion), and last observation

	Patient ID	Duration from the date of AHA diagnosis to Day1 (days)	ECOG-PS		
			Baseline	Follow-up week 1	Last observation
Cohort 1	01	11	4	4	4
	02	6	2	2	2
	03	2	3	2	2
	04	419	2	1[a]	1[a]
	05	57	0	0	0
	06	14	3	3	2
	07	14	4	4	3
	08	2,167	1	1	1
	09	2	4	3	3
	10	29	4	4	3
	11	21	1	0	0
	12	36	0	0	0
Cohort 2	13	6	3	1	1
	14	1,009	1	1[a]	1[a]

Abbreviations: AHA, acquired hemophilia A; ECOG-PS, Eastern Cooperative Oncology Group Performance Status.
[a]For patients who did not meet the emicizumab completion criteria, the day of last observation was deemed the same day as follow-up week 1.

Hemostatic Management on Surgery and Procedure

From the start of emicizumab treatment, 32 surgeries/procedures were performed; 1 procedure (endoscopic papillotomy) was classified as major, and the others were classified as minor (13 endoscopic procedures, 7 dental treatments, 1 peripherally inserted central catheter, and 10 others). Twenty-three of the 32 surgeries/procedures, including 6 endoscopic procedures with high risk for bleeding (►**Supplementary Table S2**, available in the online version), were performed during the on-treatment period, and there were no bleeds related to surgeries/procedures.

At the time of the primary analysis, one patient had been administered a single prophylactic dose of rFVIIa (80 µg/kg) for endoscopic retrograde cholangiopancreatography, but no other perioperative prophylactic coagulation factor products were specifically provided throughout the study in either cohort. On the other hand, during on-treatment period, there were six minor surgeries where bypass agents (rFVIIa in all cases) were administered on the same day, but all were administered for existing bleeds unrelated to the surgeries.

Adverse Events

Adverse events are summarized in ►**Table 6**. At the time of the primary analysis, one thromboembolic event (deep vein thrombosis [DVT]) considered related to emicizumab and one death due to exacerbation of chronic kidney disease were reported in one patient each, but no other thromboembolic events or deaths were reported thereafter. No thrombotic microangiopathy or local injection-site reactions were reported throughout the study.

Table 6 Safety summary

	Both cohorts ($N = 14$)
Total number of AEs	120
Total number of patients with ≥1 AE, *n* (%)	
Any AE	14 (100)
Fatal AE	1 (7.1)[a]
Serious AE	6 (42.9)[b]
AE leading to treatment/study discontinuation	0
AE leading to dose modification/interruption	1 (7.1)[c]
Study treatment-related AE	5 (35.7)[d]
Study treatment-related AE with Grade ≥3 severity	2 (14.3)[e]
Study treatment-related serious AE	1 (7.1)[b]
Total number of patients with AEs of interest, *n* (%)	
Thromboembolic event	1 (7.1)[c]
Thrombotic microangiopathy	0
Systemic injection reaction	0
Local injection site reaction	0
Total number of patients with anti-emicizumab antibodies, *n* (%)	
Baseline prevalence	0
Post-baseline incidence	2 (14.3)

Abbreviation: AE, adverse event.
[a]One patient died owing to exacerbation of chronic kidney disease that was considered unrelated to emicizumab.
[b]Cholangitis acute and cholangitis chronic (1 patient), cholelithiasis and shock hemorrhagic (1 patient), pneumonia, chronic kidney disease, and orthostatic hypotension (1 patient each), all of which were considered unrelated to emicizumab. Basedow's disease (1 patient), considered related to emicizumab.
[c]Deep vein thrombosis necessitating interruption of emicizumab treatment (1 patient).
[d]Thrombocytopenia, prothrombin fragment 1.2 increased, deep vein thrombosis, Basedow's disease, and rash (1 patient each).
[e]Thrombocytopenia and Basedow's disease (1 patient each).

After the cutoff date of the primary analysis, two treatment-related adverse events (Basedow's disease and rash) were reported in one patient each in Cohort 2. Basedow's disease was a serious adverse event of Grade 4 severity which occurred during the on-treatment period. This patient originally had a complication of Hashimoto's disease, but a causal relationship between emicizumab and Basedow's disease was not completely ruled out by the investigator considering the temporal relationship with emicizumab initiation. The event was brought to remission by medication without modification or discontinuation of emicizumab treatment. Rash of Grade 2 severity occurred on Day 4 and resolved in 3 days by medication without modification or discontinuation of emicizumab treatment. The event was not classified as an injection-site reaction or systemic hypersensitivity by the investigator.

Safety of Concomitant Use of Coagulation Factor Products

Two patients, who had been using aPCC or plasma-derived factor VIIa and X mixture (pd-FVIIa/FX) until 3 days prior to the start of emicizumab treatment, each had a relatively high FX level at baseline (10.9 and 14.4 µg/mL, respectively; median [range] FX level of the other patients: 4.89 [2.89–6.57] µg/mL), but no laboratory findings indicating hypercoagulability were observed after starting emicizumab treatment.

Five patients used rFVIIa with doses ranging from 80 to 110 µg/kg, two used fresh frozen plasma, and one used coagulation factor XIII (FXIII) during the on-treatment period; one patient used fresh frozen plasma during the safety follow-up period. No thrombotic events were observed during or within 72 hours after the use of coagulation factor products. Of note, the patient who had DVT had had low FVIII activity and had been using FXIII from 11 to 9 days before diagnosis of the DVT.

Restoration of Endogenous FVIII Activity

Of the twelve patients who met the emicizumab completion criteria, seven patients (58.3%) experienced FVIII activity exceeding 150 IU/dL (range: 150.4–284.7 IU/dL) at least once after completing emicizumab administration. One of them had a peak FVIII activity of 284.7 IU/dL, which was the value at the date of death. For the other six patients, the range of FVIII activity exceeding 150 IU/dL was 150.4 to 200.0 IU/dL. No thrombotic events were observed after restoration of endogenous FVIII activity.

On the other hand, nine patients (75.0%) had FVIII activity decreasing to below 50 IU/dL (range: 1.1–45.7 IU/dL) at least

once after meeting the emicizumab completion criteria, but none had any treated bleeds during the safety follow-up period (►**Table 3**).

Immunogenicity

Two of the fourteen patients (14.3%) developed anti-emicizumab (drug) antibodies (ADAs; ►**Table 6**); 1 patient showed accelerated emicizumab clearance (half-life: 9.77 days) that was considered attributable to the ADAs. The ADAs were first detected at safety follow-up Week 13 or Week 25 after completing emicizumab administration, while not detected before completing emicizumab administration. The ADAs did not exhibit in vitro neutralizing activity.

Tailored IST Approaches

For two cases in Cohort 2 (Patients 13 and 14) and one case in Cohort 1 (Patient 04), tailored IST approaches were adopted comprising delayed IST, no IST, and low-dose IST, respectively. Details of these three cases are described in ►**Supplementary Result S1** (available in the online version).

Discussion

This final analysis included a total of fourteen patients judged eligible or ineligible for IST at enrollment, with results suggesting that emicizumab exerts a prophylactic effect in both types of patients. In addition, long-term emicizumab prophylaxis of up to 1.75 years showed sustained bleed prevention and a favorable safety profile. In the primary analysis, one patient experienced DVT, but no additional thrombotic events occurred thereafter throughout the study, including during concomitant use with coagulation factor products and after emicizumab completion following restoration of endogenous FVIII activity. Rehabilitation and minor surgeries were found to have been performed safely under emicizumab prophylaxis. Moreover, the clinical courses of three patients suggest that the introduction of emicizumab prophylaxis allows individualized IST approaches tailored to each patient's specific condition. Thus, emicizumab prophylaxis was suggested to be of consistent efficacy and safety, regardless of the patient's tolerance of IST. Furthermore, the results of this final analysis also suggest the usefulness of emicizumab prophylaxis during the course of AHA treatment involving concomitant use of coagulation factor products, AHA remission, rehabilitation, and surgery.

This final analysis indicated that the 1-week loading regimen adopted in this study achieved maximum prophylactic effect of emicizumab (plasma emicizumab concentration $>30\,\mu g/mL$) by 4 days after starting emicizumab treatment. Potentially owing to this rapid increase of emicizumab cofactor activity, the hemostatic effect of emicizumab, which was suggested in the primary analysis,[10] was reconfirmed in Patient 13 in whom two active major bleeds stopped within 3 days after initial emicizumab administration without influence of IST. There is accumulating evidence on the use of emicizumab to achieve hemostasis for acute bleeding and a subsequent sustained preventive effect.[15] Further accumulation of data on the 1-week loading regimen of emicizumab as a second-line hemostatic treatment for acute bleeding is needed.

In one retrospective study, overshoot of FVIII activity (i.e., $\geq$150 IU/dL) was observed in 64.7% of PwAHA after AHA remission.[14] Although it is unknown to what extent this supranormal elevation of FVIII activity actually contributes to the risk of thrombosis in PwAHA, FVIII is generally considered a major and dose-dependent risk factor for venous thrombosis.[16] In AGEHA, 58.3% of patients experienced FVIII activity exceeding 150 IU/dL at least once after completing emicizumab administration along with AHA remission; nonetheless, no thrombotic events related to restoration or supranormal level of endogenous FVIII activity occurred. These results support the appropriateness of the emicizumab completion criteria and the regular coagulation monitoring mandated in this study (►**Supplementary Table S3**, available in the online version).

To the best of our knowledge, there are few case reports evaluating the effectiveness of rehabilitation in PwAHA.[17,18] In the case reported by Goto et al,[17] rehabilitation during the period when FVIII inhibitors were detected was possible only immediately following prophylactic administration of rFVIIa, and was limited to low load rehabilitation for conditioning. Relatively stressful rehabilitation for muscle strengthening could not be started until after the FVIII inhibitor had disappeared. In AGEHA, the median FVIII activity at the time rehabilitation was started was 2 IU/dL (most rehabilitation was performed to prevent disuse syndrome aiming for early mobilization), and no hemorrhage associated with rehabilitation was reported, suggesting that rehabilitation can be started safely under emicizumab prophylaxis before restoration of FVIII activity. On the other hand, no firm conclusion on the impact of emicizumab prophylaxis on the timing of rehabilitation initiation can be reached from this study because the time from diagnosis of AHA to initiation of emicizumab varied widely from 2 to 2,167 days and because eight of the fourteen patients had either already started their first rehabilitation before starting emicizumab or did not engage in any rehabilitation throughout the study. In addition, there is a possibility that the implementation of rehabilitation itself may become unnecessary as a result of early emicizumab initiation, and this is also an important future research question.

Regarding performance status, improvements in ECOG-PS were observed in most patients after starting emicizumab. Because this study included patients with various ECOG-PS scores at baseline and some patients had been diagnosed with AHA more than 1 year previously, it could not be confirmed whether starting of emicizumab treatment soon after the diagnosis of AHA contributed to improvement in ECOG-PS. However, when analysis was limited to patients with high ECOG-PS ($\geq$3), all patients who had started emicizumab within 1 week of diagnosis of AHA achieved improvement in ECOG-PS at the time of emicizumab completion. This result suggests that an early start of emicizumab prophylaxis to prevent bleeding may provide improvements in performance status in PwAHA with poor performance status already before partial remission of AHA.

Even minor invasive procedures can cause severe bleeds in PwAHA, and therefore, it is currently recommended that any surgery or procedures be delayed until FVIII inhibitors have been eradicated if possible and that prophylactic use of bypassing agents or rpFVIII be considered both for minor and major surgeries.[2] In this study, a total of 23 surgeries or procedures were conducted during on-treatment period. Remarkably, none of these surgeries or procedures resulted in treated bleeds, although bypass agents were used on the day of surgery in 7 of the 23 events, either for short-term prophylaxis or for treatment of existing bleeds unrelated to the surgeries. These findings suggest that minor surgeries can be safely undertaken under emicizumab prophylaxis.

The incidence of ADAs in this study was 14.3% (two of fourteen patients), which is numerically higher than that reported in PwCHA (5.1%)[19] but was based on a small sample size. Although it is reported that autoimmune diseases may increase the likelihood of ADAs developing,[20] it remains unclear whether the incidence of ADAs substantially differs between PwAHA and PwCHA. ADAs affecting pharmacokinetics have been observed in PwCHA,[19] and such ADAs were observed in one patient in this study. Although the ADAs in this patient had an impact on pharmacokinetics, the ADAs did not exhibit in vitro neutralizing activity, suggesting that they might accelerate the clearance of emicizumab without directly inhibiting its cofactor activity. Of note, the ADAs in the two ADA-positive patients in this study were detected only in the safety follow-up period following completion of emicizumab administration. Further investigations are warranted to investigate whether there is any temporal association between the discontinuation of emicizumab treatment due to remission of AHA and the appearance of ADAs.

Controlling bleeds is especially challenging in PwAHA who cannot use IST due to high risk of infection or who are refractory to IST. A recent study has suggested that IST can be safely postponed while patients are receiving emicizumab prophylaxis, but patients were enrolled regardless of whether or not it was necessary to delay IST.[11] In AGEHA, we did not restrict the type or dosage of IST during the study, and we set up a sub-cohort for patients who were ineligible for IST. As a result, we have been able to present three cases highlighting different tailored IST approaches: not only delayed IST, but also no IST and low-dose IST. These results indicate that emicizumab prophylaxis may enable a variety of IST approaches tailored to the specific circumstances of individual patients.

AGEHA was the first prospective interventional clinical study of emicizumab prophylaxis with the new dosing regimen, predefined treatment completion criteria, and two cohorts according to the patients' tolerance to IST. This study was designed based on the standard treatment algorithm,[2] which is to start IST as early as possible after the diagnosis of AHA, and we prospectively collected data encountered in actual clinical practice such as concomitant use of coagulation factor products, remission of AHA, rehabilitation, and surgery. However, it had several limitations: it was a single-arm study, included only two patients in Cohort 2 (patients deemed ineligible for IST), and it was performed in a single country.

In conclusion, the final analysis results of AGEHA suggest that emicizumab prophylaxis has a favorable benefit–risk profile in PwAHA regardless of their IST eligibility. The data in this study have the potential to change the standard of care for AHA, including the establishment of hemostatic prophylaxis and more tailored IST approaches, and to contribute to increasing the available treatment options and improving the prognosis for PwAHA.

What is known about this topic?

- Severe bleeding and infections that occur due to immunosuppressive therapy (IST) are major causes of death in patients with acquired hemophilia A (PwAHA).
- The previously published primary analysis of this prospective phase III study of emicizumab prophylaxis (AGEHA) suggested its favorable benefit–risk profile in PwAHAs under IST.

What does this paper add?

- Tailored IST approaches (delayed initiation, no use, or reduced dose) were successfully executed in three patients under emicizumab prophylaxis.
- Long-term emicizumab prophylaxis for up to 1.75 years provided sustained bleed prevention.
- Rehabilitation and minor surgeries were safely conducted under emicizumab prophylaxis.

Data Availability Statement

Chugai's clinical trial data sharing policy is available at www.chugai-pharm.co.jp/english/profile/rd/ctds_request.html.

Authors' Contribution

M. Shima, R.K., and N.M. wrote and edited the manuscript. M. Shima, K.A., Y.O., R.K., R.O., K.Y., and K.N. designed the study. N.S., H.N., K.A., Y.O., E.S., M. Saito, T.O., T.I., N.H., S.H., and Y.S. acquired the data. K.Y. and R.O. analyzed the data. All authors interpreted the data, critically reviewed the manuscript, approved the final version, and supported the publication.

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Conflict of Interest

M. Shima has received research funding from Chugai Pharmaceutical Co., Ltd., CSL Behring, and Takeda; has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, Fujimoto Seiyaku, Sanofi, Novo Nordisk, Pfizer, and Takeda; holds patents with Chugai Pharmaceutical Co., Ltd.; and has participated on a data safety monitoring board or advisory board for Chugai Pharmaceutical Co., Ltd., Fujimoto Seiyaku, KYORIN Pharmaceutical Co., Ltd., Novo Nordisk, and Pfizer. N.S. has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, Japan Blood Products Organization, KM Biologics, Novo Nordisk, Pfizer, Sanofi, and Takeda. K.A. has received research funding from KM Biologics; has received consulting fees from Chugai Pharmaceutical Co., Ltd.; has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, Fujimoto Pharmaceutical Corporation, Japan Blood Products Organization, KM Biologics, Novo Nordisk, Pfizer, Sanofi, and Takeda; has participated on a data safety monitoring board or advisory board for Chugai Pharmaceutical Co., Ltd.; and is belong to endowed chair for CSL Behring. Y.O. has received consulting fees and honoraria from Chugai Pharmaceutical Co., Ltd. R.K. and R.O. are employees of Chugai Pharmaceutical Co., Ltd. K.Y. is an employee of Chugai Pharmaceutical Co., Ltd. and an inventor of patents related to anti-activated FIX/FX bispecific antibodies. N.M. is an employee of Chugai Pharmaceutical Co., Ltd. and has stocks of Chugai Pharmaceutical Co., Ltd. E.S. has received research funding from Eisai; has received honoraria from Janssen, Novartis, Pfizer, Sanofi, and Takeda, and has leadership or fiduciary role in other board, society, committee, or advocacy group (unpaid) for Japan Adult Leukemia Study Group and Japanese Society of Myeloma. S.H. has received research funding from Chugai Pharmaceutical Co., Ltd. and has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, Novo Nordisk, Sanofi, and Takeda. K.N. has received research funding from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, KM Biologics, Novo Nordisk, Sanofi, and Takeda; has received consulting fees from Chugai Pharmaceutical Co., Ltd.; and has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, KM Biologics, Novo Nordisk, Sanofi, and Takeda. The remaining authors have no conflicts of interest to declare.

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