A Phase III clinical trial of a mixture of plasma-derived factor VIIa and factor X (MC710) in hemophilia patients with inhibitors: hemostatic efficacy and safety

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Introduction

MC710, a 1:10 protein weight ratio mixture of plasma-derived activated factor VII (FVIIa) and factor X (FX) is a novel bypassing agent for hemostasis in hemophilia patients with inhibitors. MC710 administers FVIIa and its substrate FX concomitantly for greater potency than FVIIa alone, and is long acting due to the long half-life of FX [1]. We have already clarified dose-dependency of the pharmacokinetic (PK) / pharmacodynamic (PD) parameters of MC710 [2, 3], and demonstrated hemostatic efficacy in a small number of joint bleedings in hemophilia patients with inhibitors [4]. Moreover, we confirmed the safety of MC710 up to 120 μg/kg per dose (as FVIIa dose) [2, 4]. We evaluated the hemostatic efficacy and safety of one to two administrations of MC710 in joint, muscle, and subcutaneous bleeding episodes in Japanese male hemophilia patients with inhibitors.

Study design and Methods

This trial was a multi-center, open-label, non-randomized clinical study. All subjects provided written informed consent. Subjects were intravenously administered between one and two doses of 60 or 120 μg/kg MC710 (to a maximum of 180 μg/kg) (**Fig. 1**). The hemostatic efficacy of MC710 was determined for each episode by investigator's evaluation using changes in the visual analogue scale (VAS) for pain relief, and/or knee joint or muscle circumference for swelling reduction, and range of motion (ROM) for improvement of joint mobility (**Table 1**).

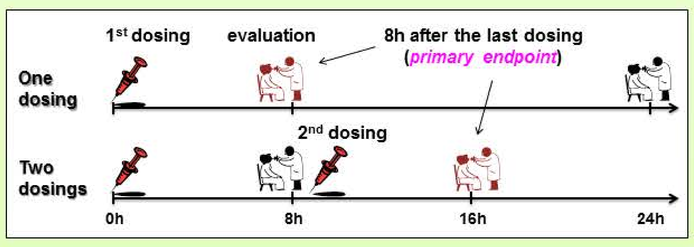

Fig. 1. Study flow

Table 1. Definition of hemostatic efficacy

excellent	complete pain relief and clear improvement in bleeding signs (swelling and/or joint mobility)
effective (either of 1 to 3)	1) complete pain relief and no changes in bleeding signs 2) definite pain relief and slight improvement in bleeding signs 3) slight pain relief and improvement in bleeding signs
partially effective	slight pain relief and slight improvement in bleeding signs
ineffective	no improvement or worsening of symptoms

Results and Discussion

1. Subjects and treatment

MC710 was administered for 21 bleeding episodes in 14 subjects (8 HA and 6 HB patients). Two subjects were treated for multiple episodes. There were 16 joint, 3 intramuscular, and 2 subcutaneous bleedings, 7 of which were mild, 13 moderate, and 1 severe. A single 60 μg/kg dose was applied for 3 episodes, a single 120 μg/kg dose for 7 episodes, double 60 μg/kg doses for 1 episode, and a single 120 μg/kg dose followed by a 60 μg/kg dose for 10 episodes (**Table 2**).

2. Efficacy

The efficacy rate, defined as the proportion of episodes which were rated "excellent" or "effective" at 8 h after the last dosing of MC710, was 90.5% (*primary endpoint*) (**Table 3**). The efficacy rate was 85.7% 8 h after the first dosing, and 90.5% 24 h after the first dosing or 8 h after the second dosing, demonstrating a strong and long-lasting hemostatic effect (**Table 3**). The efficacy rate was 80.0% or greater regardless of the various dosing of MC710 in subpopulation analysis by treatment regimen (**Table 4a**), over 85.7% except for FIX inhibitor titer ≥5 BU/mL in subpopulation analysis by subject background (**Table 4b**), and was at least 87.5% in all groups except for one episode of severe bleeding in subpopulation analysis by bleeding episode characteristics (**Table 4c**). The VAS significantly decreased over time and the ROM significantly improved over time after treatment (**Fig. 2**). Of two "ineffective" episodes, one (No. 9-1) was severe knee joint bleeding. The subject showed clear improvement of swelling (a 1.5 cm reduction in the knee joint circumference) 8 h after the first MC710 dosing (**Fig. 2**), and efficacy was rated as "partially effective". This shows that MC710 has potential for hemostatic efficacy even in severe hemorrhage.

3. Safety

One mild adverse reaction, decreased blood potassium, and two serious adverse events, both knee joint bleeding, were observed within one week after the first administration, with no significant effect on safety. In the subjects administered two doses of MC710, D-dimer increased approximately two-fold 24 h after first administration compared to pre-treatment. However, disseminated intravascular coagulation (DIC) induction was unlikely, because the platelet count and fibrinogen levels did not decrease in association with D-dimer (**Fig. 3**). Subjects did not develop new viral antigens or produce new antibodies following MC710 administration.

Table 2. Subject, bleeding episode, treatment, and hemostatic efficacy

Subject No.	Hemophilia type*	Age (years old)	Body weight (kg)	Inhibitor titer** (BU/mL)	Episode No.	Bleeding site (L, left; R, right)		Bleeding severity	Time from bleeding to 1st dosing (h)	MC710 1st dosing (μg/kg)	MC710 2nd dosing (μg/kg)	Hemostatic efficacy: 8 h after 1st dosing	24 h after 1st dosing or 8 h after 2nd dosing	8 h after the last dosing (*primary endpoint*)
1	HA	41	62.0	3.2	1-1	muscle	L. forearm	mild	3.82	120	60	effective	effective	effective
2	HB	32	59.7	< 0.5	2-1	joint	R. knee	moderate	4.97	60	60	effective	effective	effective
3	HB	19	71.5	31.2	3-1	joint	R. elbow	moderate	1.75	120	-	excellent	excellent	excellent
4	HB	14	52.0	119	4-1	subcutaneous	R. inguinal	mild	4.38	120	-	effective	excellent	effective
5	HA	17	80.4	281	5-1	joint	R. elbow	moderate	4.62	120	60	ineffective	ineffective	ineffective
6	HA	29	75.0	106	6-1	joint	L. elbow	moderate	4.13	120	-	excellent	excellent	excellent
7	HA	31	74.4	10.5	7-1	joint	L. ankle	mild	2.33	120	-	effective	effective	effective
8	HA	26	82.4	46.0	8-1	muscle	R. thigh	moderate	4.88	120	60	effective	effective	effective
9	HB	20	49.0	25.7	9-1	joint	R. knee	severe	2.83	120	60	partially effective	ineffective	ineffective
10	HA	14	41.2	3.1	10-1	subcutaneous	L. hip	mild	2.43	120	-	effective	excellent	effective
11	HA	29	60.0	4.3	11-1	joint	L. elbow	moderate	3.53	120	60	partially effective	effective	effective
12	HB	21	56.8	3.0	12-1	muscle	R. thigh	mild	3.38	120	-	effective	effective	effective
13	HA	12	35.3	169	13-1	joint	L. knee	mild	4.65	60	-	effective	excellent	effective
					13-2	joint	L. knee	moderate	3.75	60	-	effective	effective	effective
					13-3	joint	L. knee	moderate	4.70	60	-	effective	effective	effective
					13-4	joint	R. knee	moderate	4.25	120	-	effective	effective	effective
14	HB	22	89.7	1.5	14-1	joint	R. knee	mild	3.75	120	60	effective	effective	effective
					14-2	joint	L. ankle	moderate	2.47	120	60	effective	effective	effective
					14-3	joint	R. ankle	moderate	2.58	120	60	effective	effective	effective
					14-4	joint	R. ankle	moderate	2.23	120	60	effective	excellent	excellent
					14-5	joint	L. ankle	moderate	1.32	120	60	effective	effective	effective

* HA, hemophilia A; HB, hemophilia B. ** HA patient showed FVIII inhibitor titer and HB patient showed FIX inhibitor titer.

Table 3. Time-course of hemostatic efficacy of MC710

Evaluation time point	Bleeding episodes	Hemostatic efficacy: excellent	effective	partially effective	ineffective	Efficacy rate: excellent + effective	[two-tailed 95% CI]
8h after 1st dosing	21	2	16	2	1	18 (85.7%)	[63.7 - 97.0%]
24h after 1st dosing or 8h after 2nd dosing	21	6	13	0	2	19 (90.5%)	[69.6 - 98.8%]
8h after last dosing (*primary endpoint*)	21	3	16	0	2	19 (90.5%)	[69.6 - 98.8%]

Table 4. Subpopulation analysis (regimen, subjects, and bleeding episodes)

Background	Subpopulation	Category	Bleeding episodes	Hemostatic efficacy (*primary endpoint*): excellent	effective	partially effective	ineffective	Efficacy rate: excellent + effective	[two-tailed 95% CI]
a) Treatment regimen	Pattern of dosing (1st / 2nd)	60 μg/kg / -	3	0	3	0	0	3 (100.0%)	[29.2 - 100.0%]
		120 μg/kg / -	7	2	5	0	0	7 (100.0%)	[59.0 - 100.0%]
		60 μg/kg / 60 μg/kg	1	0	1	0	0	1 (100.0%)	N.C.
		120 μg/kg / 60 μg/kg	10	1	7	0	2	8 (80.0%)	[44.4 - 97.5%]
b) Subjects background	Hemophilia type	HA inhibitor	11	1	9	0	1	10 (90.9%)	[58.7 - 99.8%]
		HB inhibitor	10	2	7	0	1	9 (90.0%)	[55.5 - 99.7%]
	Age	< 19 years old	7	0	6	0	1	6 (85.7%)	[42.1 - 99.6%]
		≥ 19 years old	14	3	10	0	1	13 (92.9%)	[66.1 - 99.8%]
	FVIII inhibitor titer	< 5 BU/mL (low-titer)	3	0	3	0	0	3 (100.0%)	[29.2 - 100.0%]
		≥ 5 BU/mL (high-titer)	8	1	6	0	1	7 (87.5%)	[47.3 - 99.7%]
	FXI inhibitor titer	< 5 BU/mL (low-titer)	7	1	6	0	0	7 (100.0%)	[59.0 - 100.0%]
		≥ 5 BU/mL (high-titer)	3	1	1	0	1	2 (66.7%)	[9.4 - 99.2%]
c) Bleeding episode characteristics	Bleeding site	joint	16	3	11	0	2	14 (87.5%)	[61.7 - 98.4%]
		muscle	3	0	3	0	0	3 (100.0%)	[29.2 - 100.0%]
		subcutaneous	2	0	2	0	0	2 (100.0%)	N.C.
	Bleeding severity	mild	7	0	7	0	0	7 (100.0%)	[59.0 - 100.0%]
		moderate	13	3	9	0	1	12 (92.3%)	[64.0 - 99.8%]
		severe	1	0	0	0	1	0 (0%)	N.C.
	Time from bleeding to 1st dosing	≤ 3 h	8	2	5	0	1	7 (87.5%)	[47.3 - 99.7%]
		> 3 h, ≤ 5 h	13	1	11	0	1	12 (92.3%)	[64.0 - 99.8%]

N.C., Not calculated.

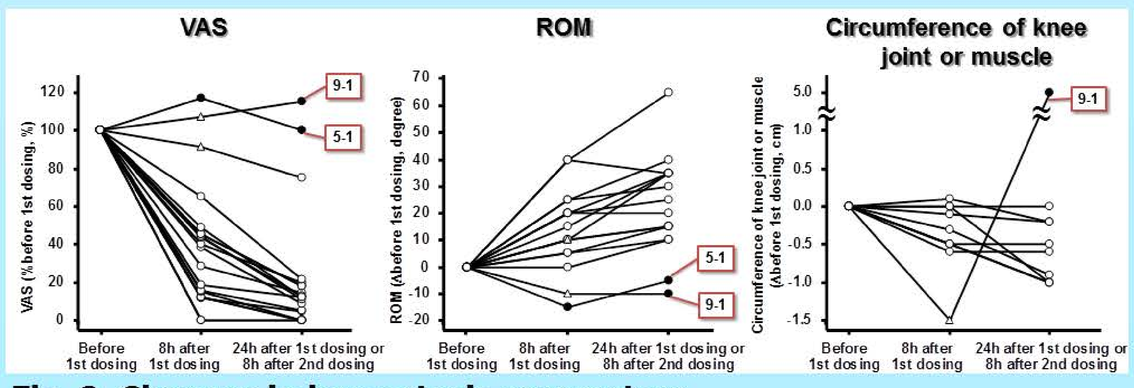

Fig. 2. Changes in hemostasis parameters

x-x, Episode No.; ○, excellent or effective; △, partially effective; ●, ineffective.

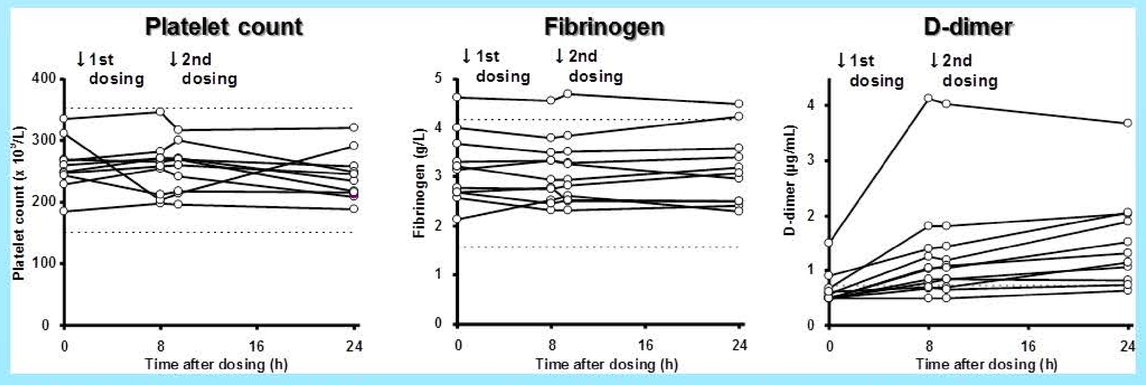

Fig. 3. Changes in DIC parameters (subjects with two dosings)

The normal ranges of healthy control (---) for platelet count were defined as 350 (upper limit) and 150 (lower limit) x10⁹/L, for fibrinogen as 4.15 (upper limit) and 1.55 g/L (lower limit), and for D-dimer as 0.72 μg/mL(upper limit).

Conclusion

MC710 has sufficient (strong and long-lasting) hemostatic efficacy with one or two administrations at 8 h intervals for different types of bleeding, and has acceptable safety with a total dose up to 180 μg/kg for the treatment regimen. MC710 is thus expected to be a safe and efficacious novel bypassing agent for controlling bleeding in hemophilia patients with inhibitors, and a viable alternative to other commercially available bypassing agents.

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