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Icatibant promotes patients' behavior modification associated with emergency room visits during an acute attack of hereditary angioedema

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SUMMARY Hereditary angioedema due to C1-inhibitor (C1-INH) deficiency (HAE-C1-INH) induces an acute attack of angioedema. In 2018, icatibant available for self-possession and subcutaneous self-administration was licensed for on-demand treatment in addition to intravenous C1-INH administration in Japan. We retrospectively evaluated the percentage of attacks in critical parts at emergency room (ER) visits and the time until visiting ER for C1-INH administration before and after the initial prescription of icatibant. The percentage of attacks in critical parts at ER visits before the prescription was 69.2%, but that was 80.0% when patients visited ER for additional C1-INH administration after the self-administration of icatibant. The time from the onset of an acute attack to visiting ER for the additional treatment after the self-administration of icatibant significantly increased from 6.2 h to 19.2 h ($p < 0.001$). Icatibant, therefore, promoted the patients' behavior modification associated with ER visits for C1-INH administration during an acute attack of HAE-C1-INH.

Keywords C1-inhibitor, emergency room, hereditary angioedema, icatibant, Japan

Hereditary angioedema caused by C1-inhibitor (C1-INH) deficiency (HAE-C1-INH), which induces excess bradykinin production resulting in an unpredictable and recurrent acute attack of angioedema, is a rare autosomal dominant disease. The worldwide prevalence of HAE-C1-INH is 1 case per 50,000 inhabitants (*1-4*). Due to low awareness of the disease, the delay from the initial symptom of the disease to its diagnosis has been reported to be long (mean duration of 13.8-15.6 years in Japan) (*5,6*). Because HAE-C1-INH can be potentially life-threatening when severe edema develops in the upper respiratory tract and can cause unbearable abdominal pain resulting from gastrointestinal edema, the guideline of the World Allergy Organization and the European Academy of Allergy and Clinical Immunology recommends that attacks should be treated as early as possible (*7-9*).

Since 2009, there have been several approved on-demand drugs for self-possession and self-administration which enable early treatment, mainly in the European Union and the United States of America. Patients in these countries can usually select the most appropriate self-administration drug for each acute attack instead of considering whether to visit a healthcare institution for on-demand treatment (*10-15*). In Japan, on the other hand, intravenous administration of plasma-derived human C1-INH concentrate (Berinert P®, CSL Behring, King of Prussia, PA, USA) was approved in 1990 for on-demand treatment. However, self-administration of the drug has not been allowed, and it must be injected only in a healthcare institution such as emergency room (ER) by a healthcare professional. Icatibant (Firazyr®, Takeda Pharmaceutical Company, Tokyo, Japan), licensed in Japan in November 2018, is a selective bradykinin B2 receptor antagonist for subcutaneous self-administration for on-demand treatment. A number of studies and clinical trials have evaluated the medical efficacy of the drug (*14-16*). In the specific Japanese situation, however, evaluating the patients' behavior modification during an acute attack before and after the initial prescription of icatibant is also considered worthwhile from the point of quality of life, because it has not been reported in this aspect. The aim of this study was therefore to retrospectively evaluate the change in the percentage of attacks in critical parts at ER visits and the time from the onset of an acute attack

Table 1. Number of ER visits for C1-INH administration due to an acute attack before and after the initial prescription, and after the self-administration of icatibant

Pt. No.	Age	Sex	Description of icatibant in 2019	Number of ER visits before and after the initial prescription of icatibant			
				Before		After [particularly after the self-administration of icatibant]	
				All attacks	Attacks in critical parts	All attacks	Attacks in critical parts
1	49	F	January	5	0	1 [1]	1 [1]
2	44	F	January	1	0	1 [0]	1 [0]
3	42	F	January	33	25	39 [4]	35 [3]
4	41	M	March	0	0	0 [0]	0 [0]
5	40	F	March	57	39	55 [9]	43 [8]
6	78	M	March	0	0	0 [0]	0 [0]
7	69	F	March	4	2	3 [1]	3 [1]
8	35	F	April	7	6	7 [0]	3 [0]
9	38	F	April	2	2	4 [0]	4 [0]
10	41	F	May	1	1	0 [0]	0 [0]
11	50	F	May	4	3	9 [0]	0 [0]
12	69	M	May	3	3	1 [0]	0 [0]
			Total	117	81 (69.2%)	120 [15]	90 (75.0%) [12 (80.0%)]

Abbreviations: C1-INH, C1-inhibitor; ER, emergency room; Pt. no., patient number; M, male; F, female.

until visiting ER for C1-INH administration during an acute attack before and after the initial prescription, and after the self-administration of icatibant in patients with HAE-C1-INH in Japan.

Our study enrolled 12 patients with HAE-C1-INH (3 males, 9 females; mean age, 49.7 years at their inclusions) who had been prescribed icatibant for the first time between January and May 2019 at the Juntendo University Hospital in Tokyo, Japan. We conducted the study procedures in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Juntendo University (No. 25-325). Written informed consent was obtained from the patients.

We evaluated the number of ER visits for C1-INH administration due to an acute attack, the percentage of attacks in critical parts at the ER visits, the time from the onset of an acute attack to an ER visit, and the use of icatibant before visiting ER for each 9-month period before and after the initial prescription of icatibant. Because angioedema of the throat, tongue, mouth and neck can potentially lead to suffocation and an abdominal attack can cause severe abdominal pain, we defined angioedema occurring in these parts as attacks in critical parts.

The number of ER visits for C1-INH administration before and after the initial prescription of icatibant was 117 and 120, respectively (Table 1). Within the 120 ER visits after the initial prescription, the number of ER visits for the additional treatment after the self-administration of icatibant was 15.

The percentage of attacks in critical parts at ER visits before and after the initial prescription was 69.2% (81 cases) and 75.0% (90 cases), respectively (Table 1). In particular, ER visits for the additional treatment after the self-administration of icatibant showed a larger

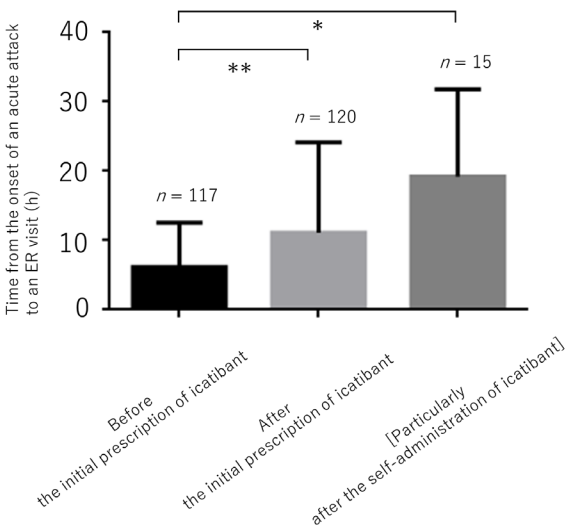

Figure 1. Time from the onset of an acute attack to an emergency room visit. The time from the onset of an acute attack to an ER visit was significantly increased from 6.2 ± 6.3 h to 11.1 ± 13.0 h after the initial prescription of icatibant ($p < 0.05$) and further extended to 19.2 ± 12.1 h after the self-administration of icatibant ($p < 0.001$), when patients needed to visit ER for C1-INH administration due to an acute attack. $^{*}p < 0.001$, $^{**}p < 0.05$. C1-INH, C1-inhibitor; ER, emergency room; h, hour; *n*, number.

percentage of attacks in critical parts (80.0%).

The time from the onset of an acute attack to an ER visit significantly increased from 6.2 ± 6.3 h to 11.1 ± 13.0 h after the initial prescription ($p < 0.05$), and especially 19.2 ± 12.1 h when patients needed to visit ER for the additional treatment after the self-administration of icatibant ($p < 0.001$) (Figure 1).

Early treatment through self-administration during an acute attack of HAE-C1-INH has been reported to reduce the need for an ER visit (*11*). However,

the number of ER visits for C1-INH administration before and after the initial prescription of icatibant did not significantly change in this study. We speculated that the causes were closely associated with the past treatment approach for HAE-C1-INH in Japan. Over many years, patients have depended heavily on the C1-INH administration for on-demand treatment in a healthcare institution and relied deeply on the treatment. Second, many patients in Japan might feel anxious when performing the self-administration, as well as patients in other countries (*17*).

After the initial prescription of icatibant, on the other hand, the percentage of attacks in critical parts at ER visits increased. In particular, the patients who visited ER for additional C1-INH administration after the self-administration of icatibant showed a larger percentage (Table 1). It suggests that patients suffered from acute attacks in more critical parts, when patients needed to visit ER for the additional treatment after the self-administration of icatibant.

In this study, the prescription of icatibant significantly increased the time from the onset of an acute attack to an ER visit (Figure 1). In addition to the efficacy of the drug, the possession itself might affect the time until an ER visit after the initial prescription, because a previous study reported that patients who carried icatibant with them gained confidence in managing their conditions associated with HAE-C1-INH attacks (*17*). Moreover, the time from the onset of an acute attack to an ER visit was further extended when patients needed to visit for additional intravenous C1-INH administration after the self-administration of icatibant (Figure 1). It suggests that the self-administration of icatibant could significantly prolong time to an ER visit, when patients who remained suffering from symptoms even after the self-administration of the drug visited ER for the additional treatment.

Japanese government, unfortunately, had to declare a state of emergency due to the Coronavirus Disease 2019 in April 2020, forcing us to break off data collection at that time, when patients' ER visiting behavior could be considered to be affected, and redefine the study duration for each 9-month period before and after the initial prescription. Furthermore, the number of ER visits due to acute attacks in the enrolled patients varied, but patients 3 and 5 (Table 1) made frequent visits to the ER. However, there was no significant correlation between the number of ER visits and the time from the onset to an ER visit (data not shown). We hope that more patients with HAE-C1-INH will be enrolled in a longer observational study.

In conclusion, when patients with HAE-C1-INH needed to visit ER for C1-INH administration in addition to the self-administration of icatibant due to an acute attack, they suffered from acute attacks in more critical parts, and the time from the onset of an acute attack to an ER visit was significantly extended.

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