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A prospective naturalistic multicenter study on choice of parenteral medication in psychiatric emergency settings in Japan

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Abstract

Aim: To provide information about psychiatric emergency situations in Japan, we examined psychiatrists' preference among parenteral medication since intramuscular (IM)-olanzapine became available and clinical characteristics in patients given IM-olanzapine compared to those given other parenteral medication.

Methods: We conducted a naturalistic study proceeding over a 1-year period in 9 psychiatric emergency departments.

Results: Among 197 patients, the distribution of IM-injections (n = 89) was as follows: IM-olanzapine, 66 patients (74.2%), IM-levomepromazine, 17 patients (19.1%), IM-haloperidol, 5 patients (5.6%), and IM-diazepam, 1 patient (1.1%). The distribution of intravenous (IV)-injections (n = 108) was as follows: IV-haloperidol, 78 patients (72.2%), and IV-benzodiazepines (diazepam, flunitrazepam, or midazolam), 30 patients (27.8%). Advantages of IM-olanzapine over other parenteral medications in efficacy were found as follows: less frequent needs of an additional injection despite no difference in duration until a patient became cooperative for oral administration, and less

frequent needs of restraint after the injection. Furthermore, advantages of IM-olanzapine over other injections in safety were found as follows: less frequent appearance of extrapyramidal symptoms, no occurrence of ECG abnormality and other serious adverse events except a fall, less frequent needs of an adjunctive anticholinergic drug, and less frequent needs of another kind of drug additionally injected.

Conclusions: Olanzapine has rapidly become the first choice of intramuscular medication in psychiatric emergency situations since it became available in Japan, probably due to the advantages in both efficacy and safety. This study reflecting psychiatric emergency practice in Japan may contribute to periodic international comparison of psychiatric emergency practice.

KEYWORDS
agitation, benzodiazepine, haloperidol, olanzapine, schizophrenia

1 | INTRODUCTION

In psychiatric emergency settings, intramuscular (IM)/intravenous (IV) medications are indispensable measures against patients' extremely severe excitement and refusal to take an essential medicine. In a retrospective chart review, the availability of a rapidly disintegrating formulation of an atypical antipsychotic for emergent use reportedly did not reduce the use of IM antipsychotics or of seclusion or restraint in an acute inpatient psychiatric setting.[1] In the latest international survey among 21 countries consisting of 20 European countries and India, the distribution of parenteral medication use has been reported as follows: haloperidol and lorazepam, 15 countries; second-generation antipsychotics, 13 countries; zuclopenthixol, 12 countries; low potency antipsychotics, 9 countries; intravenous medication, 3 countries.[2] In Japan, among first-generation antipsychotics, the use of IM-levomepromazine has gradually decreased due to concerns about side effects, whereas IM/IV-haloperidol has dominated practice in psychiatric emergency. In 2012, IM-olanzapine became available as the first atypical (second generation) antipsychotic drug except long-acting injectable antipsychotics in Japan. Accumulated evidence suggests that short-acting intramuscular formulations of second-generation antipsychotics are as effective as IM-haloperidol, and superior to IM-haloperidol in short-term tolerability.[3] Thus, the choice of parenteral medication in psychiatric emergency settings has been changing. In this naturalistic study proceeding over a 1-year period in 9 psychiatric emergency departments, we examined psychiatrists' preference among parenteral medication since IM-olanzapine became available to provide information about psychiatric emergency situations in Japan, and clinical characteristics in patients given IM-olanzapine compared to those given other parenteral medication.

2 | METHODS

2.1 | Design

This was a naturalistic study proceeded over a 1-year period (June 1, 2014 to May 31, 2015) in 9 psychiatric emergency departments. All study protocols were approved by the institutional review board of Juntendo University School of Medicine and each institutional review board. The approved protocol did not require informed consent from patients, as the protocol was not different from ordinary practice, and as the data remained anonymous and were analyzed in aggregate.

2.2 | Clinical settings

In each area, psychiatric emergency patients requiring hospitalization are hospitalized under the responsibility of each of these hospitals. Most of the patients from these hospitals were behavioral emergencies and about 60% of them were brought in by the police. All were involuntary admissions, being an immediate danger to themselves or others, according to the 2014 Law Concerning Mental Health and Welfare for the Mentally Disabled. Details of the clinical setting are described elsewhere.[4] Psychiatrists attending this study have referred to Guidelines for Psychiatric Emergency Treatment 2009 edited by the Japanese Association for Emergency Psychiatry, but prescription was left to their discretion to a certain extent.

2.3 | Patients

Patients who required IM/IV medications at the time of admission or during emergency hospitalization due to extremely severe agitation and refusal to take an essential medicine were included. IM medication was chosen when there was little possibility of complication of somatic disease or abnormal physiological conditions. IV medication was chosen when uncooperative patients were required to receive CT, MRI, or lumbar puncture, or when uncooperative patients were required to receive fluid therapy due to dehydration, hypokalemia, or elevation of serum muscle enzymes such as creatine phosphokinase.[4]

2.4 | Data collection

Patient's demographic and clinical characteristics such as age, sex, ethnicity, body mass index, diagnosis according to DSM-5, substance

dependence, smoking, duration from onset, history of medication, timing of injection, reason for injection, the Global Assessment of Functioning (GAF) were recorded.

The primary outcome was the frequency distribution for various kinds of IM/IV medication. Kinds and the initial dose of IM/IV medication, kinds of additional injection during the first 3 days after the initial injection, and adjunctive anticholinergic drug were recorded. Data of assessment using the Excited Component for Positive and Negative syndrome scale (PANSS-EC: Excitement, Hostility, Tension, Uncooperativeness, and Poor impulse control; score range 5-35)[5] and the Calming Agitation-Evaluating Scale (ACES: 1 = marked agitation, 2 = moderate agitation, 3 = mild agitation, 4 = normal, 5 = mild calmness, 6 = moderate calmness, 7 = marked calmness, 8 = deep sleep, 9 = unarousable)[6] were collected. The permission of using ACES was obtained from Eli Lilly and Company (Indianapolis, USA). The timing of assessment was as follows: at the time of an initial injection, 30 min, 60 min, 90 min, 1 day, 2 days, and 3 days after the initial injection. The use of restraint or seclusion after the initial injection and time to becoming cooperative to take medicine were recorded.

Vital signs and the Drug-induced Extrapyramidal Symptom Scale (DIEPSS)[7] were also recorded at the time of an initial injection, 30 min, 60 min, 90 min, 1 day, 2 days, and 3 days after the initial injection. Electrocardiogram and any serious adverse events were recorded after injections.

2.5 | Statistical analysis

Data were collected on standardized forms and statistical analyses were performed using SPSS version 23-J software (IBM Japan, Tokyo, Japan). Differences between categorical variables in patient demographics and clinical characteristics were calculated using Fisher's exact test. Differences between sequential variables were calculated using the unpaired *t* test (with Welch correction if applicable). If data were not sampled from Gaussian distributions, a non-parametric test (Mann-Whitney test) was used. To test for the effects of treatment on changes in PANSS-EC, a 5 (IM-olanzapine, IM-levomepromazine, IM-haloperidol, IV- haloperidol, and IV-benzodiazepine) $\times$4 (0, 24, 48, and 72 time point) repeated-measures analysis of variance (ANOVA) was used. Missing values were handled using the method of last-observation-carried-forward (LOCF). All statistical tests were 2-tailed. Values of $P < .05$ were regarded as statistically significant.

3 | RESULTS

3.1 | The distribution of initial injections

During the study period, 4 252 patients admitted to the 9 psychiatric emergency departments. Among these, 197 patients received IM/IV medication (4.6%) were included in the study. Baseline characteristics of 197 patients were as follows: the mean age, 47.1 (SD 16.4); the proportion of men, 41.6%; Schizophrenia spectrum, 68.0%; substance dependence, 8.1%; drug-naïve, 23.4%; the mean score of PANSS-EC, 25.3 (SD 6.7). As a reason for the injection, "Marked agitation" was the most frequent (69.5%), followed by "Refusal of oral administration" (22.8%) and "Uncooperativeness for CT/MRI" (6.1%).

Among 197 patients receiving parenteral medication, 89 patients (45.2%) received IM-injections and 108 patients (54.8%) received IV-injections. The distribution of IM-injections among 89 patients was as follows: IM-olanzapine, 66 patients (74.2%), IM-levomepromazine, 17 patients (19.1%), IM-haloperidol, 5 patients (5.6%), and IM-diazepam, 1 patient (1.1%). IM-levomepromazine was used only in 3 hospitals. There were no patients receiving 2 kinds of injections at the same time. The distribution of IV-injections among 108 patients was as follows: IV-haloperidol, 78 patients (72.2%), and IV-benzodiazepines (diazepam, flunitrazepam, or midazolam), 30 patients (27.8%). Thus, olanzapine and haloperidol were the first choice as an IM- and an IV-injection, respectively, among most psychiatrists in emergency situations. Details are shown in Table 1. There were no significant differences in baseline characteristics among groups, except the item of "Uncooperativeness for CT/MRI" as a reason for the injection in which the rate of IV-benzodiazepine was significantly higher than others.

3.2 | The follow-up data up to 72 hours after the initial injection: additional injections, seclusion, or restraint

As shown in Table 2, patients given IM-levomepromazine less frequently required an additional injection and an additional injection of another kind of drug followed by IM-olanzapine. In contrast, 86% and 70% of patients whose initial injection was IV-haloperidol and IV-benzodiazepine, respectively, received additional injection. In particular, 59% of patients whose initial injection was IV-haloperidol required IV-benzodiazepine, and 80% of patients whose initial injection was IV-benzodiazepine required IV-haloperidol. Nevertheless, there was no significant difference in duration until patients became cooperative for oral administration among groups. Repeated-measures ANOVA revealed a significant main effect of time course ($F = 126.159$, $P < .0001$), but no significant main effect of treatment ($F = 0.911$, $P = .46$) or interaction between time course and treatment ($F = 1.427$, $P = .19$) on PANSS-EC. Thus, IM-levomepromazine and IM-olanzapine appeared to be superior to IV-haloperidol and IV-benzodiazepine in terms of monotherapy.

In all, 136 patients who received an injection at the time of admission had not been restricted/secluded at the time of the injection. Among 61 patients who received an injection during hospitalization, 46 patients had been already restricted/secluded at the time of the injection: restraint, 23 patients, and seclusion, 23 patients. The rates of restraint after injection were very high in patients with IM-levomepromazine (100%), IV-haloperidol (81%), and IV-benzodiazepine (67%) in contrast with IM-olanzapine (36.4%), whereas the rate of seclusion in patients with IM-olanzapine was the highest among groups.

TABLE 1 Baseline characteristics of patients receiving parenteral medication for agitation

	Total	Olanzapine IM	LPZ IM	Haloperidol IM	BZ IM	Haloperidol IV	BZ IV	*P*
Number of patients (%)	197	66 (33.5)	17 (8.6)	5 (2.5)	1 (0.5)	78 (39.6)	30 (15.2)	
Age, y	47.1 (16.4)	47.0 (16.3)	40.5 (15.9)	46.8 (15.8)	66	48.2 (16.9)	47.5 (16.1)	.55
Men, n (%)	82 (41.6)	24 (36.4)	5 (29.4)	4 (80.0)	0	36 (46.2)	13 (43.3)	.16
Asian, n (%)	197 (100)	66 (100)	17 (100)	5 (100)	1	78 (100)	30 (100)	
Body mass index	22.5 (4.5)	22.0 (4.3)	22.1 (3.5)	22.8 (2.2)	24.3	23.1 (5.0)	21.9 (4.3)	.61
Diagnosis, n (%)								
Schizophrenia spectrum	134 (68.0)	47 (71.2)	10 (58.8)	3 (60.0)	0	56 (71.8)	18 (60.0)	.42
Bipolar disorders	20 (10.2)	7 (10.6)	1 (5.9)	2 (40.0)	0	5 (6.4)	5 (16.7)	.08
Depressive disorders	9 (4.6)	4 (6.1)	0	0	1	3 (3.8)	1 (3.3)	.49
Other	34 (17.3)	8 (12.1)	6 (35.3)	0	0	14 (17.9)	6 (20.0)	
Substance dependence, n (%)	16 (8.1)	5 (7.6)	2 (11.8)	0	0	5 (6.4)	4 (13.3)	1.00
Smoking, n (%)	55 (27.9)	15 (22.7)	3 (17.6)	3 (60.0)	0	27 (34.6)	7 (23.3)	.15
Duration from onset, y	12.7 (11.7)	11.8 (10.9)	8.1 (8.8)	12.6 (7.8)	0.08	14.7 (12.8)	12.3 (11.9)	.25
Drug-naïve, n (%)	46 (23.4)	12 (18.1)	6 (35.3)	1 (20.0)	1	18 (23.1)	8 (26.7)	.28
Timing of an injection, n (%)								
At the time of admission	136 (69.0)	41 (62.1)	9 (52.9)	3 (60.0)	0	58 (74.4)	25 (83.3)	.09
During a hospitalization	61 (31.0)	25 (37.9)	8 (47.1)	2 (40.0)	1	20 (25.6)	5 (16.7)	
Reason for an injection, n (%)								
Refusal of oral administration	45 (22.8)	23 (34.8)	2 (11.8)	2 (40.0)	0	14 (17.9)	4 (13.3)	.32
Marked agitation	137 (69.5)	41 (62.1)	15 (88.2)	3 (60.0)	1	58 (74.4)	19 (63.3)	.10
Uncooperativeness for CT/MRI	12 (6.1)	1 (1.5)	0	0	0	4 (5.1)	7 (23.3)	.0004[a]
Other	3 (1.5)	1 (1.5)	0	0	0	2 (2.6)	0	
GAF	19.9 (9.8)	20.5 (11.3)	19.4 (12.9)	26.4 (8.6)	20	19.0 (7.9)	20.1 (9.2)	.53
ACES (median)	1.0	1.0	1.0	1.0	2	2.0	1.0	.08
PANSS-EC	25.3 (6.7)	25.1 (7.0)	28.5 (6.9)	27.0 (4.6)	26	24.7 (6.5)	25.1 (7.0)	.31
Systolic blood pressure (median), mm Hg	136.0	138.0	122.5	150.5	160	135.5	128.0	.26
Diastolic blood pressure (median), mm Hg	84.0	86.0	81.5	90.0	120	83.0	81.0	.60
Heart rate (median), bpm	90	92	93	95	87	88	92	.57

ACES, the Calming Agitation-Evaluating Scale; BZ, benzodiazepine; GAF, the Global Assessment of Functioning; LPZ, levomepromazine; PANSS-EC, the Positive and Negative Syndrome Scale Excited Component Data represent mean (SD) or n (%), unless otherwise indicated.
[a]IV-benzodiazepine group vs other groups.

Extrapyramidal symptoms were significantly less frequent in patients whose initial injection was IM-olanzapine than those in other patients. Consequently, the frequency of an adjunctive anticholinergic drug in patients with olanzapine was significantly lower than other groups. ECG abnormality was as follows: 2 patients with QTc prolongation (IV-haloperidol) and 1 patient with non-sustained ventricular tachycardia (IV-benzodiazepine followed by IV-haloperidol). Other serious adverse events were as follows: a fall, 1 patient with IM-olanzapine (2%); oversedation, 2 patients with IM-levomepromazine (12%); severe parkinsonism, 1 patient with IV-haloperidol; elevation of serum creatine phosphokinase, 1 patient with IV-haloperidol; respiratory inhibition, 1 patient with IV-haloperidol followed by IV-benzodiazepine. Thus, IM-olanzapine appeared to be the safest among parenteral medication in terms of extrapyramidal symptoms, ECG abnormality, and other serious side effects in psychiatric emergency situations.

4 | DISCUSSION

Before IM-olanzapine was available in Japan, parenteral haloperidol was considered a first-line treatment option by experts of the Japanese Association for Emergency Psychiatry.[8] The present study showed IV-haloperidol was still the most frequent, but it was followed by IM-olanzapine with a small difference (39.6% vs 33.5%). Also, IM-levomepromazine was considered a first-line treatment option by 24% of the experts before IM-olanzapine was available, but the present study showed that it became less frequent (8.6%).

TABLE 2 Outcomes of patients receiving parenteral medication for agitation

	Total (n = 197)	Olanzapine IM (n = 66)	LPZ IM (n = 17)	Haloperidol IM (n = 5)	BZ IM (n = 1)	Haloperidol IV (n = 78)	BZ IV (n = 30)	*P*
Initial dose, median (mg/day)		10	25	5	DZ, 10	10	FZ (n = 25), 2 DZ (n = 5), 10	
Additional injection, n (%)	113 (57.4)	19 (28.8)	3 (17.6)	2 (40.0)	1	67 (85.9)	21 (70.0)	<.0001[a]
Day 1								
The same drug, n (%)	11 (5.6)	1 (1.5)	0	0	1	9 (11.5)	0	
Another drug, n (%)	77 (39.1)	5 (7.6)	1 (5.9)	1 (20.0)	1	46 (59.0)	24 (80.0)	
Day 2								
The same drug, n (%)	49 (24.9)	15 (22.7)	2 (11.8)	2 (40.0)	1	27 (34.6)	2 (6.7)	
Another drug, n (%)	5 (2.5)	0	0	0	0	0	5 (16.7)	
Day 3								
The same drug, n (%)	37 (18.8)	8 (12.1)	1 (5.9)	2 (40.0)	0	25 (32.1)	1 (3.3)	
Another drug, n (%)	4 (2.0)	0	0	0	0	0	4 (13.3)	
Duration until a patient become cooperative for oral administration (median), h	19	21	24	24	29	18	18	.97
Adjunctive anticholinergic drug, n (%)	19 (9.6)	1 (1.5)	0	3 (60.0)	0	15 (19.2)	0	.004[a]
Seclusion after an injection, n (%)	56 (28.4)	31 (47.0)	0	1 (20.0)	1	13 (16.7)	10 (33.3)	<.0001[a]
Total time of seclusion for the first 3 days (median), h	72	72				58	68	.15
Restraint after an injection, n (%)	125 (63.5)	24 (36.4)	17 (100)	1 (20.0)	0	63 (80.8)	20 (66.7)	<.0001[a]
Total time of restraint for the first 3 days (median), h	72	72	59			72	68	.11
Duration until seclusion/restraint is over (median), d	11	12	7			14	8	.40
Appearance of ECG abnormality, n (%)	3 (1.5)	0	0	0	0	2 (2.6)	1 (3.3)	.39
Any serious adverse events, n (%)	6 (3.0)	1 (1.5)	2 (11.8)	0	0	3 (3.8)	0	.09
Extrapyramidal symptoms (DIEPSS)								
Any symptoms, n (%)	59 (29.9)	12 (18.1)	5 (29.4)	3 (60.0)	1	29 (37.1)	9 (30.0)	.01[a]
Parkinsonism, n (%)	59 (29.9)	12 (18.1)	5 (29.4)	3 (60.0)	1	29 (37.1)	9 (30.0)	.01[a]
Akathisia, n (%)	9 (4.6)	4 (6.1)	0	0	0	4 (5.1)	1 (3.3)	.49
Dystonia, n (%)	8 (4.1)	4 (6.1)	0	0	0	2 (2.6)	2 (6.7)	.45
Dyskinesia, n (%)	7 (3.6)	4 (6.1)	0	0	0	2 (2.6)	1 (3.3)	.23
Length of hospitalization (media), d	59	63	59	85	46	59	42	.28

ACES, the Calming Agitation-Evaluating Scale; BZ, benzodiazepine; DZ, diazepam; FZ, flunitrazepam; GAF, the Global Assessment of Functioning; LPZ, levomepromazine; PANSS-EC, the Positive and Negative Syndrome Scale Excited Component.
Data represent mean (SD) or n (%), unless otherwise indicated.
[a]IM-olanzapine group vs other groups.

Thus, we found that IM-olanzapine has become the first choice of IM-injection among most psychiatrists in emergency situations in Japan. Simultaneously, advantages of IM-olanzapine over other parenteral medications in efficacy were also found as follows: less frequent needs of an additional injection despite no difference in duration until a patient became cooperative for oral administration or no difference in the reduction of PANSS scores, and less frequent needs of restraint after the injection. The rate of seclusion in patients administered IM-olanzapine was the highest, but that of restraint was the second lowest next to IM-haloperidol. Effects of IM-olanzapine on agitation might have been sufficient so that the rate of patients who required restraint was smaller than rates in other injection groups. Another explanation is that physicians might have chosen IM-olanzapine in patients without physical concerns. Without physical management such as keeping venous lines, the necessity of restraint becomes low. As shown in Table 2, the rate of restraint during the first 3 days after the initial injection was almost the same as that of an additional injection in the IV-haloperidol

group (80.8% vs 85.9%), and the IV-benzodiazepine group (66.7% vs 70.0%). An intravenous injection is usually chosen in a patient with physical concerns, such as pathophysiological abnormality like dehydration and potential physical complications, with physical management including keeping a venous line. To prevent a patient from removing the venous line, restraint is often used. The coincidence could be explained in such a way. Meanwhile, the relationship could not be found between the rate of restraint/seclusion during the first 3 days after the initial injection and that of an additional injection in the IM-olanzapine group (36.4%/47.0% vs 28.8%) and the IM-levomepromazine group (100%/0% vs 17.6%).

Advantages of IM-olanzapine over other injections in safety were found as follows: less frequent appearance of extrapyramidal symptoms, no occurrence of ECG abnormality and other serious adverse events except a fall, and less frequent needs of an adjunctive anticholinergic drug. These advantages in both efficacy and safety may have made IM-olanzapine the first choice in psychiatric emergency situations in such a brief period of 2 years since it became available in Japan.

The first finding based on a double-blind randomized trial of IM-olanzapine and IM-haloperidol in the treatment of acute agitation was published in 2001, in which superiority of IM-olanzapine to IM-haloperidol in both of efficacy and safety is suggested.[9] Since then, advantages of IM-olanzapine over other parenteral medication have been reported,[10] whereas no significant differences in efficacy and safety between IM-olanzapine and IM-haloperidol[11,12] or inferiority of IM-olanzapine to IM-haloperidol plus promethazine in efficacy[13] have been reported. The superiority of IM-olanzapine to IM-haloperidol in safety has also been reported.[14-16] Thus, accumulated evidence based on randomized controlled trials suggests the superiority of IM-olanzapine to IM-haloperidol in short-term tolerability although advantages in efficacy are controversial. A recent meta-analysis showed that while there was no significant difference in PANSS-EC scores after 2 h between IM-olanzapine and IM-haloperidol, IM-olanzapine outperformed IM-haloperidol in the ACES after 2 h, and that compared with IM-haloperidol, IM-olanzapine was associated with fewer side effects, including anticholinergic use, akathisia, extrapyramidal symptoms, and dystonia, and marginally less QT prolongation compared with IM-haloperidol.[17] The present findings are compatible to such evidence.

This study has several limitations. Nine out of 108 hospitals with psychiatric emergency wards all over Japan joined this survey, so findings might not necessarily represent the average of Japanese psychiatric emergency settings. However, all psychiatric emergency wards in Japan are managed according to the same law and the same public insurance, so the difference in quality between 9 psychiatric emergency wards in the study and those of other hospitals may not have been so great. Second, due to naturalistic design, selection bias may have influenced the results. Third, the number of patients for each treatment was various, so analysis may have been underpowered. A strength is reflecting real practice. Non-pharmaceutical support is another strength. This naturalistic multicenter study reflecting psychiatric emergency in Japan may contribute to periodic international comparison of psychiatric emergency practice.

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CONFLICT OF INTEREST

Kotaro Hatta has received lecture honoraria from Dainippon-Sumitomo, Eli Lilly, Eisai, GlaxoSmithKlein, Janssen, Meiji Seika, MSD, Ono, Otsuka, Pfizer, Takeda, and Tanabe-Mitsubishi within the last 3 years. Fumiyoshi Morikawa has received lecture honoraria from Daiichi-Sankyo, Eisai, Eli Lilly, Janssen, Mochida, Ono, Otsuka, and Yoshitomi. Atsushi Imai has received lecture honoraria from Sumitomo-Dainippon. Kiyoshi Fujita has received lecture honoraria from Eli Lilly, Janssen, Meiji Seika, Novartis, Otsuka, Sumitomo-Dainippon, and Yoshitomi. Aiko Fujita has received lecture honoraria from Janssen and Otsuka. Takuya Ishizuka has received lecture honoraria from Daiichi-Sankyo, Eli Lilly, Janssen, Meiji Seika, Otsuka, and Takeda. Yasuhiko Sudo has received lecture honoraria from Meiji Seika and Otsuka. Chie Usui has received honoraria for Shionogi and Pfizer. Yoshio Yamanouchi has received honoraria for Sumitomo-Dainihon and Otsuka. Shigemasa Katayama, Kijiro Hashimoto, Takayuki Abe, Hiroyuki Nakamura, and Toyoaki Hirata declare that they have no conflicts of interest.

DATA REPOSITORY

Supporting information Data S1.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

All study protocols were approved by the institutional review board of Juntendo University School of Medicine and each institutional review board.

INFORMED CONSENT

The approved protocol did not require informed consent from patients, as the protocol was not different from ordinary practice, and as the data remained anonymous and were analyzed in aggregate.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

n/a.

ANIMAL STUDIES

n/a.

AUTHOR CONTRIBUTION

KH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: All authors. Acquisition of data: SK, FM, AI, KF, AF, TI, TA, YS, and KiH. Analysis and interpretation of data: All authors. Drafting the article: KH. All authors have approved the final version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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