Intravenous Thrombolysis in Acute Ischemic Stroke After Idarucizumab Reversal of Dabigatran Effect: Analysis of the Cases From Taiwan

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Background: Asians with atrial fibrillation carry a higher risk of ischemic stroke than non-Asians even under treatment of nonvitamin K antagonist oral anticoagulants. The purpose of the study was to observe the feasibility of intravenous thrombolytic therapy after administering a reversal agent, idarucizumab, in dabigatran-treated patients with acute ischemic stroke in Taiwan. *Methods:* Dabigatran-treated patients with acute ischemic stroke who received intravenous recombinant tissue plasminogen activator (rt-PA) after idarucizumab reversal were enrolled in the retrospective nationwide study. The clinical data, treatment course, and outcomes were recorded. Stroke severity was evaluated using the National Institutes of Health Stroke Scale (NIHSS) score. Any intracerebral hemorrhage (ICH) after rt-PA was detected by neuroimaging studies. *Results:* Ten dabigatran-treated patients (6 men, mean age 71.10 ± 7.96 years) with acute ischemic stroke were included. Before stroke, the mean CHA_2DS_2-VASc score was 4.50 ± 1.57 and 8 patients (80%) received dabigatran 110 mg twice daily. All patients were treated with 5 g idarucizumab, following which the activated partial thromboplastin time normalized. Intravenous rt-PA (mean dose .78 mg/kg) was initiated a mean time of 11.11 minutes after idarucizumab infusion. The NIHSS score improved significantly after thrombolysis (16.0 ± 6.67 at admission to 9.38 ± 4.75 at discharge, $P = .016$). ICH developed in 3 patients (30%). Two of them were asymptomatic and 1 patient suffered from symptomatic ICH leading to mortality. *Conclusion:* Our data reconfirmed the feasibility of intravenous rt-PA for Asian stroke patients after reversal of dabigatran effect with idarucizumab.

Key Words: Ischemic stroke—atrial fibrillation—idarucizumab—dabigatran

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Introduction

Nonvitamin K antagonist oral anticoagulants (NOACs) are widely prescribed for stroke prevention in atrial fibrillation (AF). While the occurrence of stroke is greatly reduced with NOAC treatment, approximately 1%-2% of AF patients still develop acute ischemic stroke.[1] Asian patients have a higher risk of ischemic stroke than non-Asians even treated with the same dose of NOAC. In the Randomized Evaluation of Long-Term Anticoagulation Therapy study, the absolute rates of ischemic stroke were numerically higher in Asians than in non-Asians in dabigatran 110 mg bid (2.05% versus 1.14% per year) and 150 mg bid (1.12% versus .81% per year) groups, respectively.[2] Similarly, in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF trial, there was a trend toward higher risk of stroke or systemic embolism in the East Asian patients compared with the remaining study population irrespective of rivaroxaban or warfarin treatment.[3] Among the NOACs, the real world data in Asia showed that the risk of ischemic stroke was similar in AF patients, regardless of whether they were treated with dabigatran, rivaroxaban, or apixaban.[4,5] Thus, management of acute ischemic stroke in patients who are taking NOACs becomes an important issue for Asian patients.

Idarucizumab is a humanized monoclonal antibody which binds dabigatran and rapidly reverses its anticoagulant effect. The effect of idarucizumab has been shown in the RE-VERSE AD study and Asian clinical study.[6,7] Recent studies, in dabigatran-treated patients who developed acute ischemic stroke, found that intravenous thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) could be performed after administering idarucizumab.[8-10] However, most studies about the clinical experiences of using such treatment in acute ischemic stroke were from the Western countries. In this nationwide study, we report the real world experience with idarucizumab used before intravenous rt-PA for acute ischemic stroke in Taiwan. Our study has important clinical implications for Asian patients who have a higher stroke and bleeding risk than non-Asians.

Methods

We retrospectively collected the data of dabigatran-treated patients with acute ischemic stroke who received intravenous thrombolytic therapy with rt-PA after administering idarucizumab from May 2016 to May 2018 in Taiwan. The patients' demographic data, vascular risk factors, previous disease history, stroke severity, laboratory results, initial brain computed tomography (CT) results, and clinical outcome at discharge were collected. The estimated glomerular filtration rate at admission was calculated from the Modification of Diet in Renal Disease equation. The time from admission to idarucizumab injection and the time from the end of idarucizumab injection to start of intravenous rt-PA were recorded. The stroke severity at admission and during follow-up or at discharge was evaluated using the National Institutes of Health Stroke Scale (NIHSS) score by the in-charged neurologists. Routine neuroimaging studies including CT or magnetic resonance imaging were performed at around 24 hours after rt-PA to assess any occurrence of intracerebral hemorrhage (ICH). The neuroimaging studies could be done earlier if there were new neurological symptoms or signs. Symptomatic ICH was defined as ICH that causes at least a 4-point increase of the NIHSS score or mortality. The study was approved by the Institutional Review Board in each hospital where the patients were enrolled. Continuous variables were presented as means ± standard deviations and categorical variables were presented as numbers and percentages. Wilcoxon signed-rank test was used to compare the changes of NIHSS score before and after rt-PA treatment. A 2-tailed P value $< .05$ was considered significant.

Results

Overall, 10 dabigatran-treated patients (6 men, mean age 71.10 ± 7.96 years) who developed acute ischemic stroke, were included in this study. Table 1 shows the demographic and clinical characteristics of these patients. All patients had hypertension and the estimated glomerular filtration rate at admission was 72.39 ± 17.34 (48.8-105.4) mL/min/1.73m^2. Seven patients (70%) had a previous history of ischemic stroke or transient ischemic attack and the mean time interval from the last event to the current stroke was 2.5 years (13 months-5 years). The CHA_2DS_2-VASc score was 4.50 ± 1.57. AF was the indication for dabigatran use in all patients and 2 (20%) patients had paroxysmal AF. Eight patients (80%) were treated with dabigatran 110 mg twice daily and the other 2 patients used 150 mg twice daily. Table 2 summarizes the clinical course, treatment, and outcome results of these patients. The time from last intake of dabigatran to admission was 9.67 hours and the time of idarucizumab administration after admission was 64.20 ± 34.06 minutes. All patients were treated with a standard dose of 5 g idarucizumab. The activated partial thromboplastin time (aPTT) before reversal was 30.55 ± 5.72 seconds and normalized after idarucizumab (26.82 ± 1.77 seconds). Intravenous rt-PA was initiated 11.11 ± 4.91 minutes after completion of idarucizumab administration. The mean dose of rt-PA given was .78 mg/kg and ranged from .6 (n = 2), .7 (n = 3) to .9 mg/kg (n = 5). Mechanical thrombectomy after thrombolytic therapy was performed in 1 patient (10%). In 8 patients with complete data (Fig 1), the NIHSS score improved significantly after thrombolysis (16.0 ± 6.67 at admission to 9.38 ± 4.75 at discharge, $P = .016$). ICH developed after intravenous thrombolytic therapy in 3 patients (30%). Two of them were asymptomatic. The

Table 1. *Baseline demographic and clinical characteristics of cases from Taiwan, Japan, and Hong Kong*

Case no.	Sex	Age	BW (kg)	HTN	DM	Creatinine at admission (mg/dL)	eGFR (mL/min/1.73m^2)	Previous IS	Previous CAD	Previous HF	CHA_2DS_2-VASc score
1	Male	79	57.6	Yes	No	.89	87.6	Yes	No	No	5
2	Male	72	70	Yes	Yes	1.16	57	No	No	No	3
3	Female	60	44	Yes	No	.85	68	No	No	Yes	3
4	Female	75	n.a.	Yes	No	.71	84	Yes	Yes	Yes	7
5	Male	64	61	Yes	No	.97	77.9	Yes	No	No	3
6	Female	78	59	Yes	No	.9	64.4	Yes	No	No	6
7	Male	57	82	Yes	No	1.0	81.9	No	No	Yes	2
8	Female	68	65	Yes	No	.6	105.4	Yes	Yes	No	6
9	Male	79	71	Yes	No	1.4	48.9	Yes	No	No	5
10	Male	79	63.4	Yes	No	1.1	48.8	Yes	No	No	5
Percentage or mean ± SD	Male 60%	71.10 ± 7.96	63.67 ± 9.91	100%	10%	.96 ± .22	72.39 ± 17.34	70%	20%	30%	4.50 ± 1.57
Japan	Male	57	n.a.	Yes	Yes	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Hong Kong	Female	78	n.a.	Yes	Yes	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

BW, body weight; CAD, coronary artery disease; DM, diabetes mellitus, eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; IS, ischemic stroke; n.a., not available; SD, standard deviation.

first asymptomatic case (case no. 7) was a 57-year-old male patient with an initial NIHSS score of 9. After idarucizumab reversal and rt-PA (.9 mg/kg) treatment, the patient was referred to a tertiary center where mechanical thrombectomy was performed at the right middle cerebral artery successfully. Follow-up magnetic resonance imaging on the second day showed the right frontal infarction with asymptomatic small hemorrhagic transformation. The second asymptomatic case (case no. 9) was a 79-year-old male patient with an initial NIHSS score of 23. After idarucizumab reversal and rt-PA (.9 mg/kg) treatment, follow-up CT at 1 day after stroke onset showed small focal hemorrhage in the left frontal lobe. The patient with symptomatic ICH (case no. 6) was a 78-year-old female with an admission NIHSS score of 24. She suffered from consciousness deterioration with large hemorrhagic transformation 10 hours after rt-PA and died 34 hours after stroke onset. The detailed clinical course of this case was published previously as a case report.[11] In the 9 patients who survived to discharge, NOACs were restarted in 7 patients from 14 to 21 days after stroke. Dabigatran 150 mg bid was restarted in 3 patients and the other 4 patients received a factor Xa inhibitor, either rivaroxaban (n = 2), apixaban (n = 1), or edoxaban (n = 1).

Discussion

In recently published expert opinion and guideline,[12,13] intravenous rt-PA is suggested as a treatment option in patients with acute ischemic stroke anticoagulated with dabigatran after using the specific reversal agent, idarucizumab. However, the recommendation was only based on limited data from the Western countries. In Germany, a series of 19 dabigatran-treated patients received intravenous rt-PA for acute ischemic stroke after idarucizumab.[8] Fifteen of the 19 patients had improved NIHSS scores and none of these patients developed ICH. In New Zealand, 6 patients received rt-PA for acute ischemic stroke after idarucizumab reversal and 1 patient developed symptomatic ICH.[9] In the Czech Republic, 13 similar patients received rt-PA for acute ischemic stroke.[10] ICH occurred in 2 (15.4%) patients and 2 (15.4%) other patients developed recurrent ischemic stroke at 21 and 25 hours after the end of thrombolytic therapy. In Asia other than Taiwan, there were only 2 case reports from Hong Kong and Japan.[14,15] The demographic data and clinical outcomes of the 2 patients were summarized in the Tables 1 and 2. Both cases had improved clinical outcomes without major bleeding complications. Our study is the first report of a case series in Asia. Compared with the 19 cases from Germany,[8] the age was similar (75.3 ± 14.6 years versus 71.10 ± 7.96 years), but the NIHSS score at admission of our patients was higher (8.0 ± 3.89 versus 16.0 ± 6.67). Our observations have some unique clinical implications specifically for Asian patients. First, the European guideline suggested that rt-PA can be administered directly in

Table 2. *Clinical course, treatment, and outcome of cases from Taiwan, Japan, and Hong Kong*

Case no.	Time from last intake of dabigatran to admission (h)	Time from admission to idarucizumab (min)	Time from the end of idarucizumab injection to start rt-PA (min)	aPTT before idarucizumab (s)	aPTT after idarucizumab (s)	rt-PA dose (mg/kg)	ICH	NIHSS score at admission	NIHSS score at follow-up or discharge
1	12	133	10	24.6	n.a.	.6	No	12	12
2	2.5	90	10	36.1	n.a.	.7	No	12	10
3	24	41	17	n.a.	n.a.	.7	No	12	2
4	6	63	8	25.6	n.a.	.9	No	26	n.a.
5	7	25	n.a.	32.9	27.6	.9	No	16	10
6	16	28	19	26.8	n.a.	.9	Yes (S)	24	n.a. (mortality)
7	9	32	17	25.1	23.8	.9	Yes (A)	9	6
8	1.5	50	5	29.5	29.1	.6	No	19	16
9	9	79	8	42.9	26.2	.9	Yes (A)	23	14
10	n.a.	101	6	31.5	27.4	.7	No	7	5
Mean ± SD	9.67 ± 6.59	64.20 ± 34.06	11.11 ± 4.91	30.55 ± 5.72	26.82 ± 1.77	.78 ± .12		16.0 ± 6.67	9.38 ± 4.75
Japan	n.a.	39	rt-PA was given after idarucizumab infusion for 15 min	41.3	n.a.	n.a.	No	22	7
Hong Kong	2 h before onset	n.a.	rt-PA was given 10 min after the start of idarucizumab injection	50.7	29.5	.6	No	34	improved

A, asymptomatic; aPTT, activated partial thromboplastin time; n.a., not available; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; S, symptomatic; SD, standard deviation.

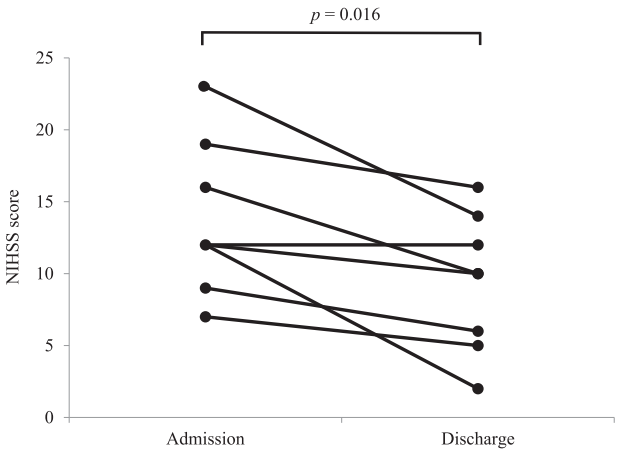

Figure 1. *The changes of the NIHSS score at admission and discharge. NIHSS, National Institutes of Health Stroke Scale.*

NOAC-treated patients if the NOAC plasma level is below the lower limit of detection or the last NOAC intake is >48 hours in patients with normal renal function.[13] For patients who do not meet the above criteria, rt-PA can be given after reversal of anticoagulant effect. The recently published Japanese consensus suggested that rt-PA can be given directly in dabigatran-treated patients if the last dosing time is >4 hours and the level of aPTT is <1.5 times of the baseline value. For patients who are regarded as ineligible due to the above criteria, rt-PA can be considered after intravenous administration of idarucizumab or use mechanical thrombectomy directly without pretreatment by idarucizumab or thrombolysis if thrombectomy can be quickly performed.[16] In fact, aPTT is the most commonly used coagulation assay in patients treated with dabigatran. But a normal aPTT result could not completely rule out the presence of dabigatran in plasma because it is not able to quantitatively measure dabigatran blood concentration. More accurate tests, such as diluted thrombin time or ecarin clotting time are unavailable in most hospitals in Taiwan and other Asian countries. Furthermore, the clinical experiences in Taiwan showed that the information of last NOAC dosing time obtained by history taken from patients or families is usually not very accurate. Therefore, for safety reasons, we suggested giving idarucizumab routinely to dabigatran-treated patients before thrombolytic therapy even if the aPTT is normal. Second, Asian patients have a higher risk of symptomatic ICH after rt-PA treatment for acute ischemic stroke.[17] The adequate dose of rt-PA for Asians is still controversial. Although a randomized clinical trial showed the low-dose rt-PA (.6 mg/kg) was less effective compared to the standard-dose (.9 mg/kg) in reducing mortality and disability at 90 days after stroke, low dose rt-PA carried a lower risk of ICH.[18] The standard rt-PA dose suggested in Taiwan is .9 mg/kg. However, in the real-world clinical practice, neurologists may choose a lower rt-PA dose after considering patients' clinical conditions, such as old age, fragility, and other bleeding risk features. The 3 cases in our series with ICH after thrombolysis all received .9 mg/kg rt-PA. In Asian patients with ischemic stroke where dabigatran treatment is reversed, a lower dose of rt-PA (<0.90 to ≥ .60 mg/kg) may be safer even if idarucizumab is used. However, this observation is based on a small number of patients in our series and may need confirmation with larger studies. Recently, direct mechanical thrombectomy without idarucizumab and thrombolysis in these patients was proposed as another reasonable treatment in hospitals that are capable of performing such procedure immediately.[16] However, there have been no clinical trials showing a better outcome in mechanical thrombectomy without thrombolysis than thrombolysis only. The availability of mechanical thrombectomy is also a challenge in most Asian countries. Therefore, we favored the American guideline's suggestion that if patients are eligible for thrombolysis, they should receive rt-PA first even if mechanical thrombectomy is being considered.[19]

In conclusion, our real world experiences reconfirm that idarucizumab is a feasible strategy to allow beneficial treatment with intravenous thrombolytic therapy for dabigatran-treated patients who present with acute ischemic stroke. For Asian patients, routine reversal with idarucizumab and using lower rt-PA dose may be considered. Since factor Xa inhibitor-treated patients carry a similar risk of ischemic stroke, the availability of a reversal agent for factor Xa inhibitors should be expedited.

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