LETTER

Intravenous thrombolysis in stroke after dabigatran reversal with idarucizumab: case series and systematic review

BACKGROUND

Idarucizumab can reverse the effect of the direct thrombin inhibitor dabigatran,[1] a non-vitamin K oral anticoagulant (NOAC) available for primary and secondary prevention of cardioembolic stroke due to non-valvular atrial fibrillation. Ischaemic stroke may happen despite ongoing anticoagulation, a contraindication to intravenous thrombolysis (IVT).[2] Thus, patients with ischaemic stroke while on dabigatran might be eligible for anticoagulation reversal with idarucizumab to allow IVT. Here, we report our case series and provide a systematic review to define outcomes of such treatment algorithm.

METHODS

Case series of patients undergoing IVT after dabigatran reversal was identified from our stroke registry (online supplementary file 1). Systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[3] and specified protocol (PROSPERO: http://www.crd.york.ac.uk/PROSPERO, registration no. CRD42017060274) (online supplementary file 2). Search strategy, performed on Cochrane Library, MEDLINE, EMBASE and PubMed, can be found in online supplementary file 1.

Data extraction and outcome assessment

All available data were collected (online supplementary file 1). According to National Institute of Health Stroke Scale (NIHSS) total score, stroke were divided into mild (1–4), moderate (5–15), moderate to severe (16–20) and severe (21–42 4). Unfavourable outcome was defined as an increase in NIHSS score or death. Additional outcomes included modified Rankin Scale (mRS) at follow-up, symptomatic intracerebral haemorrhage, systemic bleeding, allergic reactions to idarucizumab, recurrent stroke and venous thrombosis during post-acute phase.

Statistical analysis

Statistical analysis was performed with R software using stats packages. Descriptive statistics are presented for continuous variables as means, SD, medians and IQRs. Categorical variables are presented as counts and percentages. Multivariate logistic regressions were used for modelling the functional outcome.

RESULTS

Searching our stroke registry, from October 2015, among 627 stroke cases we detected two cases that met the inclusions criteria (online supplementary file 1). Databases search identified 188 articles. Only 24 articles fulfilled inclusion criteria and were included for revision,[4–26] all being case series or case reports (table 1).

Cohort characteristics

Overall, including ours, 55 cases of ischaemic stroke treated with IVT after reversal of dabigatran with idarucizumab were collected (43.6% women; mean age 74.35±11.32 years) (table 1). Mean dabigatran dosage was 247.69±38.43 mg. Personal history revealed hypertension in 23.26%, diabetes in 13.95%, dyslipidaemia in 6.98% and previous stroke in 11.63%. All individuals received anticoagulation reversal with idarucizumab and subsequent IVT according to the prescribing information. Prolonged activated partial thromboplastin time (aPTT) (>35 s) was found in 75.0% of cases (36/48), while prolonged TT (>20 s) was detected in 96.3% of patients (26/27). No correlation was found between aPTT prolongation and dabigatran concentrations.

Clinical and neuroradiological outcomes

At admission, seven patients had mild (NIHSS 1–4, 12.96%), 34 moderate (NIHSS 5–15, 62.96%), six moderate to severe (NIHSS 16–20, 11.11%) and seven severe stroke (NIHSS 21–42, 12.96%). Mean time from symptoms onset to IVT was 174.82±53.76 min. Overall, 45 patients (81.9%) benefited from treatment, with median NIHSS improvement of 5 points (IQR 3–10). No NIHSS variation was detected for four patients, and an unfavourable outcome was recorded in only six patients: four died, and two had NIHSS worsening, one of them developing a further stroke after 30 hours from first IVT.[5] Haemorrhagic transformation was asymptomatic in one patient, while three patients had clinical deterioration, leading to significant disability (n=1, mRS 5) or death (n=2, mRS 6). Overall, mRS score ≤2 at follow-up was reported in 56.76% of patients (n=21, available data for 37 patients). After stroke on dabigatran, 23 patients were prescribed the same drug (62.16%), while 8 patients increased dosage from 110 twice daily to 150 twice daily, and 13 patients changed prescription.

With univariate analysis, NIHSS at admission, mRS at admission and symptomatic intracranial haemorrhage all negatively impacted mRS at follow-up, but no factor was confirmed predictive of worse outcome with multivariate analysis (table 2).

Discussion

We systematically reviewed data on IVT after dabigatran reversal with idarucizumab, defining clinical course and outcomes.

Overall, 55 patients have been reported.[4–26] Moderate stroke prevailed (62.96% of patients), and IVT was performed within an early time window (mean 175 min). Blood clotting test, altered in up to 96% of patients, returned within limits soon after idarucizumab administration. Thus, IVT after dabigatran reversal with idarucizumab seems feasible in real-life setting and might then be considered for all patients suffering from a stroke while on dabigatran.

Moreover, the clinical improvement seen in 81.9% of patients, together with follow-up mRS <2 in 56% of patients, suggest that effectiveness IVT is preserved. An unfavourable outcome was registered for 10.9% of patients, all displaying known risk factors for worse outcome, including arterial occlusion of a major intracranial vessel, high NIHSS and haemorrhagic transformation.[27] Time to last dabigatran intake, dabigatran serum concentration, blood clotting examinations and time to treatment did not affect outcome. Thus idarucizumab reversal might be taken into account in all patients eligible for IVT with last dabigatran assumption within 24 hours, as well as in those with unknown dose timing and altered aPTT or TT, which can be used as point-of care methods if dabigatran concentrations cannot be determined.[28]

Compared with the existing systematic review,[4] we have been able to double included papers (24 vs 13) and enlarge the cohort of more than a third (55 patients vs 40). Moreover, in this systematic review, stroke severity increased, with moderate to severe stroke in 63% of cases (vs 10%[4]), and median time to IVT increasing to 173 min (vs 155 min[4]). Despite increasing stroke severity and time to IVT, the rate of favourable outcomes is higher than previously reported (81.9% vs 72%), suggesting that the treatment paradigm

Table 1 Demographic, laboratory and imaging characteristics of 55 patients with acute ischaemic stroke receiving IVT with tissue plasminogen activator

				Dabigatran				IVT		NIHSS				mRS					
N	Reference	Age and gender		Dose (mg)	Last intake (min)	Serum concentration	aPTT	Time to rtPA	rtPA dose	Admission	Outcome	Variation	Vessel occluded	Pre-stroke	At admission	At follow-up	ICH	Adverse events	Recommended anticoagulation
1	4	88	F	220	270	202.4	71	160	0.9	10	1	9	NA	NA	NA	NA	NA	No	Apixaban
2	4	67	M	300	338	183.7	77	247	0.9	4	0	4	NA	NA	NA	NA	NA	No	DAB
3	4	84	M	300	424	31.4	84	133	0.9	10	2	8	NA	NA	NA	NA	NA	Urinary infection	DAB
4	4	85	M	220	NA	43	36	95	0.9	7	2	5	NA	NA	NA	NA	NA	No	DAB
5	4	82	M	220	NA	172.2	52	123	0.9	18	7	11	NA	NA	NA	NA	NA	No	NA
6	5	85	M	NA	1020	NA	NA	167	0.9	30	Death	–	Tandem left ICA MCA occlusion	NA	NA	6	Yes	NA	NA
7	5	46	M	NA	60	NA	NA	178	0.9	5	18	–13	None	NA	NA	5	No	Contralateral M2 occlusion 30 hours after first IVT	NA
8	6	78	M	220	NA	NA	NA	NA	0.6	NA	0	0	NA	NA	NA	0	No	No	NA
9	6	84	M	220	NA	79	41.6	NA	0.9	9	4	5	NA	NA	5	NA	No	No	DAB 110 twice daily
10	7	71	F	300	NA	NA	29	210	0.9	9	NA	NA	NA	0	NA	1	No	No	DAB 150 twice daily
11	8	76	M	220	210	NA	73.3	150	0.9	11	1	10	None	NA	NA	NA	No	No	↑to DAB 150 twice daily
12	9	69	M	300	NA	74	39.2	197	0.9	12	1	11	NA	3	NA	3	No	No	NA
13	10	65	F	NA	NA	NA	31	210	0.9	19	1	18	Left MCA (M1)	NA	NA	NA	NA	NA	NA
14	11	75	F	300	90	74	NA	225	0.9	4	0	4	None	NA	NA	NA	No	No	NA
15	12	78	F	300	180	74	NA	210	0.9	4	0	4	None	NA	NA	NA	NA	NA	NA
16	13	75	M	220	NA	NA	39	NA	0.9	5	0	5	NA	NA	NA	NA	No	No	↑to DAB 150 twice daily
17	14	75	F	220	570	90	35.5	120	0.9	7	18	–11	Left PCA	NA	NA	NA	No	Pneumonia	Another NOAC, ie, rivaroxaban after 3–4 weeks
18	15	75	M	220	NA	NA	38		0.9	5	1	4	NA	NA	3	1	No	NA	DAB 110 twice daily
19	15	40	F	220	NA	NA	24.3	NA	0.9	12	1	11	NA	NA	4	0	No	NA	VKA
20	15	83	M	220	NA	NA	34.6	NA	0.9	4	2	2	NA	NA	2	1	No	NA	DAB 110 twice daily
21	15	76	M	220	NA	NA	73	NA	0.9	11	1	10	NA	NA	4	1	No	NA	↑to DAB 150 twice daily
22	15	67	F	300	NA	NA	26	NA	0.9	10	8	2	NA	NA	4	4	No	NA	Apixaban 5 twice daily
23	15	86	F	220	NA	NA	34.6	NA	0.9	5	2	3	NA	NA	2	1	No	NA	DAB 110 twice daily
24	15	86	F	220	NA	NA	45	NA	0.9	12	2	10	NA	NA	4	1	No	NA	Edoxaban
25	15	58	F	300	NA	NA	35.8	NA	0.9	3			NA	NA	3	NA	No	NA	Argatroban
26	15	53	M	300	NA	NA	25.9	NA	0.9	17	Death	–	NA	NA	5	6	No	Pneumonia DVT, PE	NA
27	15	75	F	220	NA	NA	35.6	NA	0.9	7	18	–11	NA	NA	5	5	No	NA	OAC not specified
28	15	80	M	220	NA	NA	59	NA	0.9	5	2	3	NA	NA	2	0	No	NA	DAB 110 twice daily
29	15	94	F	220	NA	NA	69	NA	0.9	6	0	6	NA	NA	4	0	No	NA	↑to DAB 150 twice daily
30	15	85	M	300	NA	NA	48	NA	0.9	7	1	6	NA	NA	3	1	No	NA	DAB 150 twice daily
31	15	78	F	220	NA	NA	84	NA	0.9	7	1	6	NA	NA	2	1	No	NA	↑to DAB 150 twice daily
32	15	84	F	220	NA	NA	25.6	NA	0.9	14	14	0	NA	NA	4	4	No	NA	ASA 100
33	15	77	M	220	NA	NA	43.6	NA	0.9	4	1	3	NA	NA	4	1	No	NA	↑to DAB 150 twice daily
34	15	54	M	300	NA	NA	26.1	NA	0.9	11	2	9	NA	NA	3	2	No	NA	DAB 150 twice daily
35	15	89	F	220	NA	NA	38.9	NA	0.9	5	2	3	NA	NA	2	2	No	NA	DAB 110 twice daily
36	15	90	F	220	NA	NA	37	NA	0.9	7	3	4	NA	NA	3	1	No	NA	DAB 110 twice daily
37	16	68	M	220	45	34.1	34	110	0.9	3	3	0	NA	NA	3	2	No	No	↑to DAB 150 twice daily
38	17	67	F	300	240	NA	NA	90	0.9	10	NA	NA	Right MCA (M3)	NA	NA	NA	No	NA	NA
39	18	76	M	220	540	NA	72.2	170	0.9	11	1	10	None	NA	NA	NA	NA	No	NA
40	19	71	M	300	109	NA	62	137	0.9	6	0	6	NA	NA	NA	NA	No	No	NA
41	20	66	F	300	200	NA	72	220	0.9	22	11	11	NA	NA	NA	4	NA	No	NA

Continued

Table 1 Continued

				Dabigatran				IVT		NIHSS				mRS					
N	Reference	Age and gender		Dose (mg)	Last intake (min)	Serum concentration	aPTT	Time to rtPA	rtPA dose	Admission	Outcome	Variation	Vessel occluded	Pre-stroke	At admission	At follow-up	ICH	Adverse events	Recommended anticoagulation
42	20	63	M	220	165	NA	46	215	0.9	22	19	3	NA	NA	NA	6	NA	Cerebral oedema	NA
43	20	78	F	300	180	NA	44	185	0.9	20	16	4	NA	NA	NA	5	Yes	NA	NA
44	20	73	F	300	205	NA	61	208	0.9	6	3	3	NA	NA	NA	0	NA	NA	NA
45	20	52	M	300	273	NA	58	285	0.9	28	2	26	NA	NA	NA	3	NA	NA	NA
46	20	75	M	220	160	NA	45	165	0.9	6	0	6	NA	NA	NA	0	NA	NA	NA
47	21	85	F	220	255	NA	32.2	303	0.9	17	0	17	No large vessel occlusion, several distal emboli	NA	NA	NA	No	No	DAB 110 twice daily
48	22	78	F	300	NA	NA	49	125	0.9	11	0	11	No large vessel occlusion	NA	NA	NA	No	No	DAB 150 twice daily
49	23	79	F	220	120	NA	50.7	120	0.6	34	6	28	NA	4	5	4	No	No	↑to DAB 150 twice daily
50	24	72	M	220	1050	NA	36.1	180	0.6	12	10	2	NA	NA	NA	NA	No	No	No
51	24	79	M	220	720	NA	24.6	173	0.6	12	12	0	NA	NA	NA	4	No	No	Rivaroxaban 15
52	25	57	M	220	NA	NA	41.2	93	0.9	22	7	15	Left MCA	0	4	3	No	Asymptomatic right popliteal artery occlusion	Rivaroxaban 15
53	26	74	M	220	145	NA	NA	135	0.9	16	0	16	Right MCA (M1M2)	0	NA	1	Yes (asymptomatic)	No	Rivaroxaban 15
54	Case 1	78	M	220	1200	NA	47	180	0.9	12	1	11	None	1	3	1	No	No	Apixaban
55	Case 2	85	M	220	180	NA	53	250	0.9	22	Death	–	Left MCA	3	5	6	Yes	HF, respiratory failure	NA
Overall (n=55)		74.35 ± 11.32	F 43.6%	247.69 ± 38.43	344.19 ± 318.68	96.16 ± 61.16	46.68 ± 16.79	174.82 ± 53.76	*Four had reduced rtPA	11.26 ± 7.22	4.22 ± 5.71	6.33 ± 7.6		1.57 ± 1.72	3.52 ± 1.04	2.39 ± 2.03	3 sICH 1 aICH		

aICH, asymptomatic intracerebral haemorrhage; aPTT, activated partial thromboplastin time; ASA, aspirin; DAB, dabigatran; DVT, deep vein thrombosis; HF, heart failure; ICA, internal carotid artery; ICH, intracerebral haemorrhage; IVT, intravenous thrombolysis; MCA, middle cerebral artery; mRS, modified Rankin Scale; N, patient consecutive number; NA, not applicable; NIHSS, National Institute of Health Stroke Scale; NOAC, non-vitamin K oral anticoagulant; PCA, posterior cerebral artery; PE, pulmonary embolism; rtPA, recombinant tissue plasminogen activator; sICH, symptomatic intracerebral haemorrhage; VKA, vitamin K antagonist.

Table 2 Univariate and multivariate analysis for functional outcome at follow-up (mRS)

	Univariate		Multivariate	
	HR (95% CI)	P values	HR (95% CI)	P values
Age	0.97 (0.91 to 1.02)	NS	1.01 (0.96 to 1.07)	0.64
Gender (male)	1.38 (0.34 to 5.67)	NS	1.02 (0.27 to 3.84)	0.97
Dabigatran dose	1.01 (0.99 to 1.03)	NS	–	NS
Dabigatran last dose	1 (0.99 to 1)	NS	–	NS
aPTT	0.97 (0.93 to 1.02)	NS	0.96 (0.92 to 1)	0.06
Time to rtPA	1.01 (0.99 to 1.03)	NS	–	NS
rtPA dose	0.36 (0 to 1645.06)	NS	–	NS
NIHSS at admission	1.16 (1.09 to 1.25)	<0.001	1.06 (0.95 to 1.19)	0.25
mRS at admission	3.26 (1.77 to 5.99)	<0.001	2.01 (0.9 to 4.47)	0.08
sICH	37.7 (4.61 to 308.56)	<0.01	12.27 (0.39 to 383.4)	0.14

aPTT, activated partial thromboplastin time; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; NS, not significant; rTPA, recombinant tissue plasminogen activator; sICH, symptomatic intracerebral haemorrhage.

might be considered also for all patients with acute ischaemic stroke, including those with moderate to severe stroke and longer time windows for IVT. Since at least 1% of patients eligible for IVT will be on NOAC,[28] the results of this systematic review, supporting safety and effectiveness of IVT after idarucizumab, might help clinicians in pursuing this treatment paradigm. Further data from patient registries, such as the Registry of Acute Stroke Under Novel Oral Anticoagulants-Prime (RASU-NOA-Prime, ClinicalTrials.gov: NCT02533960) will refine treatment paradigm and eligibility.

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