Treating ischaemic stroke with intravenous tPA beyond 4.5 hours under the guidance of a MRI DWI/T2WI mismatch was safe and effective

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ABSTRACT

Purpose Clinical trials have provided evidence that treating patients with acute ischaemic stroke (AIS) beyond 4.5 hours was feasible. Among them using MRI diffusion-weighted imaging/fluid attenuation inversion response (DWI/FLAIR) mismatch to guide intravenous tissue plasminogen activator (tPA) was successful. Our study explored the outcome and safety of using DWI/T2-weighted imaging (T2WI) mismatch to guide intravenous tPA therapy for patients with AIS between 4.5 hours and 12 hours of onset.

Method This was a retrospective study. Records of 1462 AIS patients with the time of onset of <12 hours were reviewed. Those had MRI rapid sequence study and had hyperintense signal on DWI but normal T2WI and received intravenous tPA up to 12 hours of onset were included in the analysis. Their demographics, risk factors, post-tPA complications, National Institutes of Health Stroke Scale (NIHSS) scores and outcome were recorded and analyse. χ^2 was used to compare the intergroup variables. SAS was used to perform statistical calculation. A p<0.05 was considered statistically significant.

Results Of 1462 identified, 601 (41%) patients were entered into the final analysis. Among them, 327 (54%) had intravenous tPA within 4.5 hours of onset and 274 (46%) were treated between 4.5–12 hours. After intravenous tPA, 426 cases (71%) had >4 pints of improvement on NIHSS score within 24 hours. Postintravenous tPA, 32 (5.32%) cases had haemorrhagic transformation. 26 (4.33%) were asymptomatic ICH and 4 (0.67%) died. At 90 days, 523 (87%) achieved a modified Rankin scale of 0–2.

Conclusion Using MRI DWI/T2WI mismatch to identify patients with AIS for intravenous tPA between 4.5 hours and 12 hours was safe and effective. The outcome was similar to those used DWI/PWI or DWI/FLAIR mismatch as the screening tool. However, obtaining DWI/T2WI was faster and avoided the need of contrast material.

Intravenous recombinant tissue plasminogen activator (tPA) is now an internationally recognised evidence-based effective treatment for patients with acute ischaemic stroke (AIS).[1 2] The treatment window for intravenous tPA was expanded to 4.5 hours from 3 hours of onset based on the findings from the European Cooperative Acute Stroke Study III.[3 4] However, everyone's penumbra is different because of different collaterals, cerebral blood flow reserve and tolerance to ischaemia. Even presenting within the currently recommended treatment time window, each patient's potentially salvageable penumbra varies. Relying on MRI multimodal imaging to define the imaging time window and tissue penumbra, it was feasible that certain selected number of patients could still benefit from delayed intravenous tPA.[5–8] We have demonstrated that rapid MRI sequence-guided intravenous tPA in patients with AIS beyond the acute phase of presentation was safe and effective.[9–13] The current research compared the safety and efficacy between the time window and tissue window-guided intravenous tPA therapy.

METHODS

From November 2007 to February 2018, data of all stroke patients came through the fast stroke triage 'green pathway' and received intravenous tPA were reviewed. Data recorded included: demographics, stroke onset time, risk factors, time to intravenous tPA treatment, MRI diffusion-weighted imaging (DWI) and T2-weighted imaging (T2WI) sequences, follow-up brain images, National Institutes of Health Stroke Scale (NIHSS) scores, any adverse events and 90-day outcome.

Patient selection

Clinical criteria: age 18–80 years, onset to presentation <12 hours, clinically diagnosed AIS with the following neurological deficits (aphasia, motor deficit, visual defect and sensory loss) lasting >1 hour, NIHSS score 4–24, CT excluded intracranial haemorrhage (ICH) and showed no early signs of infarction. Patient or family consented to treatment.

Patient would be excluded clinically with history of ICH, stroke within 3 months,

bleeding disorders within 6 months, platelets <100 000/mm,[3] glucose level <50 mg/dL (2.7 mmol/L) or >400 mg/dL (22.2 mmol/L), severe organ failure or pregnant, systolic blood pressure >185/110 mm Hg and on warfarin with International Normalized Ratio (INR) >1.5.

MRI exclusion criteria: DWI and T2WI or fluid attenuation inversion response (FLAIR) showed high signal indicative of brain infarction, any signs of previous or new haemorrhagic changes, or cerebral amyloid angiopathy.

Brain imaging requirement

CT: CT of head was done as the screening imaging test. CT scan by Phillip was 64-slice spiral CT with a slice thickness at 10 mm, 120 kV, 130 MA.

MRI was done simultaneously with the preparation of intravenous tPA and await for lab results and patient's consent. GE 1.5 T HDXT Twinspeed was used. Fast spin echo (FSE) was used for T2WI, with time repetition (TR) at 4000 ms, time of echo (TE) 102.0 ms/Ef, field of view (FOV) 24 cm×18 cm, matrix 320×224, number of excitations 2 (NEX 2), thickness of 6 mm, distance of each layer at 1 mm; DWI: TR=6000 ms, TE=96 ms, b value at 0/1000 s/m m^2; Three dimensions-time of flight-magnetic resonance angiography (3D-TOF-MRA): TR27 ms, flip angle of 20°, thickness at 1.4 mm and bandwidth of 25.

Imaging reading and interpretation

Three experienced neuroradiologists performed all the readings before and after intravenous tPA therapy. Presence of DWI changes but no T2WI or FLAIR changes were used as the standard to diagnose ischaemic stroke with possible treatment opportunity.

Intravenous tPA therapy

Intravenous tPA was given in standard recommendation: 0.9 mg/kg, with 10% intravenous push over 1 min and remaining dose in intravenous drip over 1 hour. Any antithrombotics would be allowed to start 24 hours post intravenous tPA. A follow-up CT or MRI of head was done at 24 hours, 7 days and 90 days.

Efficacy and safety evaluation

NIHSS was used to evaluate neurological function prior to intravenous tPA and at 24 hours and 7 days post-treatment.[14] Modified Rankin scale (mRS) and Barthel Index (BI) was used to evaluate functional outcome at 90 days.[14] An improvement of NIHSS score of 8 or a score of 0–1 on NIHSS score was considered good neurological recovery. A BI of ≥95 was indicative of good function outcome.[3] Symptomatic ICH was defined as any worsening of NIHSS score of ≥4 from ICH.

Statistical analysis

SAS V.8 was used to perform the statistical analysis. A p<0.05 was considered statistically significant. χ^2 was used to compare variables between the two treatment groups. The outcome was compared by the multiple logistic regression analysis.

RESULTS

Of 1462 identified, 1036 (70%) were male. Their average time from onset to hospital was 5.96±2.36 hours. After rapid multimodal imaging study was completed, 601 patients (428 men and 173 women) received intravenous tPA between 1 hour and 12 hours of onset (table 1, figure 1). They were divided into two groups: intravenous tPA ≤4.5 hours and intravenous tPA between 4.5 hours and 12 hours (table 2). Of 274 patients treated between 4.5 hours and 12 hours, 76 were wake-up strokes. Their mean NIHSS score at baseline was 10.98±4.10, 7.08±4.93 at 24 hours and 5.68±4.96 at day 7 postintravenous tPA. After intravenous tPA, 426 cases (71%) had >4 pints

Table 1 Multimodal imaging screening on 1462 patients presented with the different time window

Item	Total	≤4.5 hours	4.5h~12 hours	P value
Age	1462	59.25±9.46 (n=433)	59.17±8.59 (n=1029)	0.175
Male (%)		68.82 (298/433)	66.18 (681/1029)	0.505
Hypertension (%)		76.67 (332/433)	79.79 (821/1029)	0.536
Atrial Fibrillation (%)		8.78 (38/433)	7.87 (81/1029)	0.578
Diabetes (%)		9.70 (42/433)	9.33 (96/1029)	0.732
Stroke location (left/right)		228/205	491/538	0.425
CT screening		433 (433/1462, 29.6%)	1029 (1029/1462, 70.4%)	–
CT excluding				
Acute stroke	592 (592/1462, 40.5%)	83 (83/433, 19.2%)	509 (509/1029, 49.5%)	–
MRI screening	870 (870/1462, 59.5%)	350 (350/870, 40.2%)	520 (520/870, 59.8%)	–
Patients treated based on MRI				
Finding	601 (601/870, 69.1%)	327 (327/601, 54.4%)	274 (274/601, 45.6%)	–
	601/1462, 41.1%	327/433, 75.5%	274/1029, 26.6%	–

*More patients treated ≤4.5 hours*2=50.26, p=0.0001.
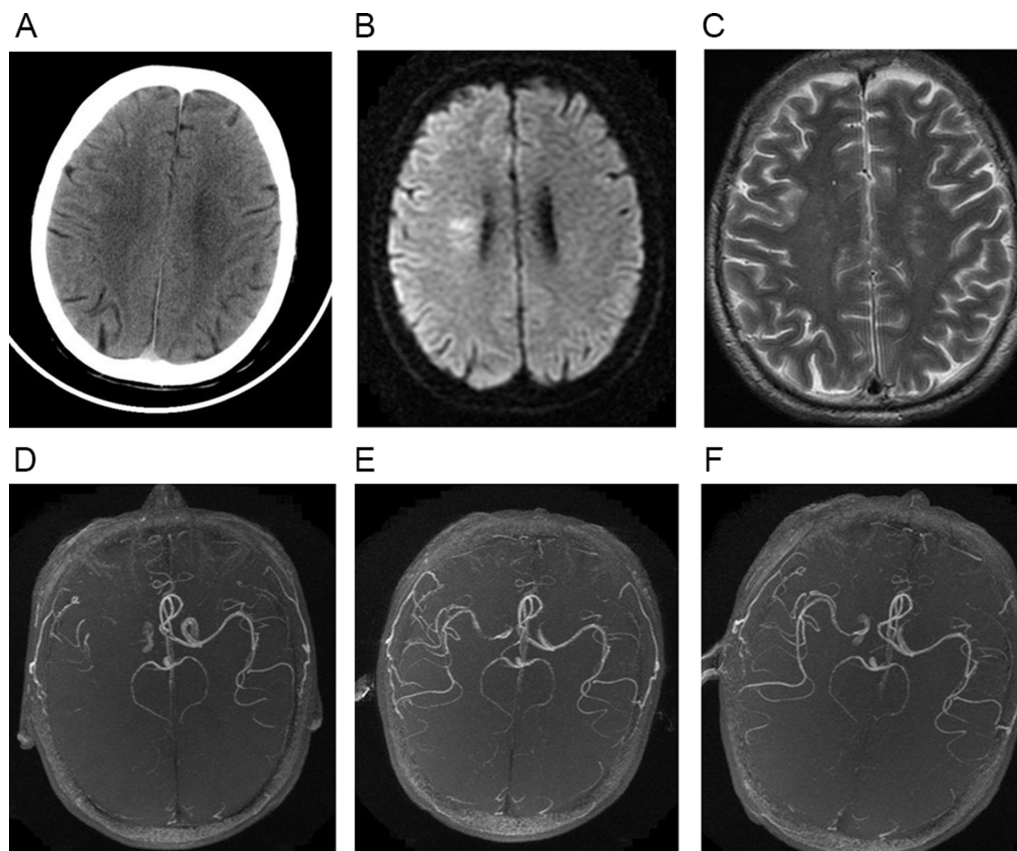
Figure 1 Male patient, 68 years old, 11 hours into left haemiparesis and dysarthria. (A–D Before intravenous tPA, CT of head showed right corona radiate and high frontal are hypodensity. DWI high signal, T2W was negative, 3D-TOF-MRA showed severe right MCA stenosis; (E–F) 24 hours postintravenous tPA, MRA showed reanalysed right MCA. DWI, diffusion-weighted imaging; MCA, middle cerebral artery; T2W, T2-weighted imaging; tPA, tissue plasminogen activator.

of improvement on NIHSS score within 24 hours. On multimodal MRI, the mean area of lesion in two groups were: ≤4.5 hours: 1.8 cm×1.9 cm=3.42 cm^2, 4.5–12 hours: 1.9 cm×2.0 cm=3.8 cm^2, without significant statistical difference (p<0.05).

Postintravenous tPA CTH detected haemorrhagic transformation in 32 (5.32%) cases. Among them, 6 (1.00%) was symptomatic ICH and took place between 6 hours and 1 week postintravenous tPA. 26 (4.33%) were asymptomatic ICH. At 90 days, 523 (87.02%) achieved an mRS of 0–2, 74 (12.31%) had mRS 3–5 and 4 (0.67%) died. Table 3 listed the logistic regression analysis for the two groups comparing the functional outcome. When using mRS of 0–1 as the good come to perform predictive factor analysis, we found that low blood glucose level and low onset NIHSS

Table 2 Baseline NIHSS score and outcome of 601 treated with intravenous tPA

	≤4.5 hours (n=327)	4.5 hours~12 hours (n=274)	P value
Baseline NIHSS	10.86±4.83	10.98±4.10	0.182
24 hours NIHSS	6.73±4.27	7.08±4.93	0.626
7 day NIHSS	5.05±4.23	5.68±4.96	0.515
Arterial stenosis (%)	26.90 (88/327)	25.91 (71/274)	0.534
Recanalisation (%)	42.05 (37/88)	38.57 (27/70)	0.415
Asymptomatic ICH (%)	3.98 (13/327)	4.74 (13/274)	0.324
Symptomatic ICH (%)	0.92 (3/327)	1.09 (3/274)	0.526
Death (%)	0.72 (2/327)	0.73 (2/274)	0.583
90-day mRS (0 or 1) or NIHSS improved ≥8 (%)	86.85 (284/327)	85.04 (233/274)	0.679
90-day BI (≥95) (%)	83.20 (272/327)	80.29 (220/274)	0.541

BI, Barthel Index; ICH, intracranial haemorrhage; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

Table 3 Standard time window: predictive factor analysis for good outcome (mRS 0–1)

	Monofactor		Multifactor*	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (year)	0.99 (0.97 to 1.02)	0.656	0.97 (0.94 to 1.01)	0.097
Gender	0.99 (0.53 to 1.87)	0.984	0.60 (0.27 to 1.33)	0.208
Hypertension	0.45 (0.23 to 0.87)	0.018	0.65 (0.29 to 1.46)	0.299
Diabetes	1.21 (0.55 to 2.66)	0.633	2.73 (0.92 to 8.11)	0.072
Hyperlipaemia	0.97 (0.55 to 1.71)	0.905	1.04 (0.51 to 2.10)	0.919
AF	2.41 (0.54 to 10.73)	0.248		
Stroke	0.40 (0.05 to 3.22)	0.389		
SBP/5 mm Hg	0.93 (0.87 to 0.99)	0.033	0.94 (0.87 to 1.03)	0.180
DBP/5 mm Hg	0.94 (0.84 to 1.05)	0.241		
FBG (mmol/L)	0.86 (0.77 to 0.97)	0.011	0.81 (0.70 to 0.95)	0.009
GHb	0.90 (0.77 to 1.05)	0.186		
TG (mmol/L)	1.20 (0.91 to 1.58)	0.206		
TC (mmol/L)	0.66 (0.52 to 0.85)	0.001	0.62 (0.36 to 1.05)	0.073
LDL-C (mmol/L)	0.73 (0.55 to 0.97)	0.032	1.25 (0.69 to 2.29)	0.465
UA (μmol/L)	1.00 (1.00 to 1.00)	0.849		
Fg	1.01 (0.72 to 1.41)	0.977		
Hcy (μmol/L)	0.98 (0.96 to 1.01)	0.200		
Admission NIHSS	0.80 (0.75 to 0.86)	<0.001	0.79 (0.73 to 0.85)	<0.001
DTN (hour)	1.00 (0.74 to 1.36)	0.996	1.13 (0.78 to 1.65)	0.515

*Adjusted age, gender, hypertension, diabetes, hyperlipaemia, TOAST, SBP, FBG, TC, LDL-C, admission NIHSS and DTN.
AF, atrial fibrillation; DBP, diastolic blood pressure; DTN, door-to-needle time; FBG, fasting blood glucose; Fg, fibrinogen; GHb, glycosylated haemoglobin; Hcy, homocysteine; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressur; TC, total cholesterol; TG, triglyceride; TOAST, design of the trial of Org 10172 in acute stroke treatment; UA, uric acid.

score were good predictors in monofactor and multifactor analysis (table 4).

DISCUSSION

With the advent of new CT and MRI technology, it is now possible to perform rapid multimodal imaging study to evaluate AIS patients with late presentation. To use imaging technique to identify the presence of a penumbra and guide the treatment has actually been successfully studied in three intra-arterial thrombectomy trials that treated AIS patients with an onset between 6 hours and 24 hours.[15–17] The results from these three trials have been written into the new AIS care guidelines.

Recently published results from two trials examined the outcome of using intravenous tPA in patients with wake-up AIS under the multimodal imaging guidance.[18 19] In MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset-WAKE UP trial,[18] 254 patients with DWI/FLAIR mismatch received intravenous tPA compared with 249 who receive placebo. However, treatment group had 10 deaths (4.1%), while placebo group had 3 (1.2%, p=0.07). Intravenous tPA group also had 2% of symptomatic intracranial hemorrhage (sICH) comparing with 0.4% in the placebo group. In the intravenous thrombolysis in unwitnessed stroke onset: MR WITNESS trial, 80

had intravenous tPA at median of 11.2 hours (9.5–13.3) from the onset of their strokes. One had sICH (1.3%) and three had symptomatic oedema (3.8%). At 90 days, about 39% treated with intravenous tPA had mRS between 0 and 1 at 90 days. The similar mRS scores between the two treatment groups at 90 days illustrated that mismatch on MRI at a later presentation offers the same opportunity of thrombolysis as those presented early.

Patients in our series treated between 4.5 hours and 12 hours had good outcome and no death. About 1% had sICH. Our series achieved mRS 0–1 in about 85% treated if there was a MRI/T2W mismatch. WAKE UP and MR WITNESS trials[15] used MRI DWI/FLAIRE mismatch to identify penumbra. In our series, DWI/T2W images were used to define penumbra, which was faster and as accurate comparing with WAKE UP and MR WITNESS trials. Close to 50% of 601 patients in our study had intravenous tPA within 4.5–12 hours under the DWI/T2W guidance. Obtaining T2W images (50 s) were about 100 s faster than obtaining FLAIR. The negative findings on T2W was indicative of the likelihood of delayed damage to blood–brain barrier (BBB) so that cytotoxic oedema has not taken place yet. It also indicated that since BBB might still be intact, the chance of developing subsequent haemorrhagic transformation by delayed thrombolysis

Table 4 Predictive factor analysis for good outcome (mRS 0–1) in patients with the extended time window

	Monofactor		Multifactor*	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (year)	0.99 (0.96 to 1.03)	0.603	1.00 (0.95 to 1.05)	0.960
Gender	0.78 (0.32 to 1.90)	0.583	1.00 (0.31 to 3.26)	0.998
Hypertension	0.58 (0.24 to 1.41)	0.232	0.63 (0.20 to 1.96)	0.425
Diabetes	1.23 (0.38 to 3.98)	0.722	3.93 (0.63 to 24.55)	0.143
Hyperlipaemia	1.02 (0.46 to 2.25)	0.965	0.77 (0.28 to 2.16)	0.626
AF	0.90 (0.09 to 8.94)	0.928		
Stroke	0.54 (0.06 to 4.65)	0.575		
SBP/5 mm Hg	0.93 (0.85 to 1.02)	0.137	0.96 (0.84 to 1.09)	0.481
DBP/5 mm Hg	0.95 (0.82 to 1.11)	0.507		
FBG (mmol/L)	0.84 (0.73 to 0.97)	0.014	0.84 (0.69 to 1.01)	0.064
GHb	0.86 (0.65 to 1.12)	0.251		
TG (mmol/L)	0.96 (0.69 to 1.34)	0.813		
TC (mmol/L)	0.71 (0.49 to 1.02)	0.062	0.52 (0.22 to 1.24)	0.137
LDL-C (mmol/L)	0.83 (0.55 to 1.25)	0.365	1.65 (0.66 to 4.15)	0.286
UA (µmol/L)	1.00 (1.00 to 1.00)	0.262		
Fg	0.66 (0.34 to 1.29)	0.223		
Hcy (µmol/L)	1.00 (0.91 to 1.10)	0.999		
Admission NIHSS	0.76 (0.68 to 0.86)	<0.001	0.78 (0.68 to 0.88)	<0.001
DTN (hour)	0.84 (0.69 to 1.04)	0.106	0.94 (0.71 to 1.24)	0.661

*Adjusted age, gender, hypertension, diabetes, hyperlipaemia, TOAST, SBP, FBG, TC, LDL-C, admission NIHSS and DTN.
AF, atrial fibrillation; DBP, diastolic blood pressure; DTN, door-to-needle time; FBG, fasting blood-glucose; Fg, fibrinogen; GHb, glycosylated haemoglobin; Hcy, homocysteine; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid.

was unlikely.[13] In acute stroke, every second counts in order to save the brain cells. Therefore, T2W image is a faster and reliable imaging sequence for rapid evaluation of a penumbra and identify a mismatch beyond 6 hours.

Like in WAKE UP and MR WITNESS trial, our series also proved that offering intravenous tPA under the guidance of rapid multimodal MRI of brain was safe and effective. With its ability to evaluate the cerebral blood flow, metabolism, tolerance of ischaemia and collaterals, multimodal MRI can identify those patients with AIS presented late (4.5–12 hours) for intravenous tPA just like those presented within the recommended time window (<4.5 hours).

The presence of a penumbra under brain ischaemia beyond 24 hours has been well reported in the literature.[20] Multimodal imaging studies in patients presented within the time window of 4.5 hours can also be useful. In AIS patients with a stroke from MCA occlusion presented early but DWI/T2W shows no mismatch, it is likely that the damage is more extensive and chance of haemorrhagic conversion could be high. Therefore, MRI helped identify those not suitable for intravenous tPA even they presented <4.5 hours.

CONCLUSION
Using DWI/T2W imaging can reliably identify patients with AIS who may benefit from intravenous tPA between

4.5 hours and 12 hours of onset of their stroke. However, such benefit still needs to be confirmed in future trials that compare DWI/T2W to DWI/FLAIR and DWI/PWI in those present to emergency room beyond 6 hours of onset.

REFERENCES

1. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581–7.
2. The NINDS t-PA Stroke Study Group. Generalized Efficacy of t-PA for Acute Stroke. *Stroke* 1997;28:2119–25.
3. Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317–1329.
4. Shobha N, Buchan AM, Hill MD, *et al*. Thrombolysis at 3-4.5 hours after acute ischemic stroke onset–evidence from the Canadian Alteplase for Stroke Effectiveness Study (CASES) registry. *Cerebrovasc Dis* 2011;31:223–8.
5. Lees KR, Bluhmki E, von Kummer R, *et al*. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010;375:1695–703.
6. Hjort N, Butcher K, Davis SM, *et al*. Magnetic resonance imaging criteria for thrombolysis in acute cerebral infarct. *Stroke* 2005;36:388–97.
7. Li YH, Li MH, Zhao JG, *et al*. MRI-based ultrafast protocol thrombolysis with rt-PA for acute ischemia stroke in 12-hour time window. *J Neuroimaging* 2011;21:332–9.
8. Ebinger M, Scheitz JF, Kufner A, *et al*. MRI-based intravenous thrombolysis in stroke patients with unknown time of symptom onset. *Eur J Neurol* 2012;19:348–50.
9. Zhao Z, Bai Q, Sui H, *et al*. Fast multimode MRI based emergency assessment of hyperacute stroke thrombolysis. *Neurol Res* 2009;31:346–50.
10. Bai Q, Zhao Z, Li Y, *et al*. The application of fast multiparametric protocol MRI-based thrombolysis with rt-PA hyperacute cerebral infarction. *Neurol Res* 2008;30:344–7.
11. Bai Q, Zhao Z, Fu P, *et al*. Clinical outcomes of fast MRI-based trombolysis in wake-up strokes compared to superacute ischemic strokes within 12 hours. *Neurol Res* 2013;35:492–7.
12. Bai Q, Zhao Z, Sui H, *et al*. Comparison of fast MRI-based individual thrombolysis therapy for patients with superacute infarction. *J Stroke Cerebrovasc Dis* 2014;23:e263–9.
13. Bai Q, Zhao Z, Sui H, *et al*. Susceptibility-weighted imaging for cerebral microbleed detection in super-acute ischemic stroke patients treated with intravenous thrombolysis. *Neurol Res* 2013;35:586–93.
14. Sui HJ, Yan CG, Zhao ZG, *et al*. Prognostic Value of Diffusion-Weighted Imaging (DWI) Apparent Diffusion Coefficient (ADC) in Patients with Hyperacute Cerebral Infarction Receiving rt-PA Intravenous thrombolytic Therapy. *Med Sci Monit* 2016;22:4438–45.
15. Lansberg MG, Christensen S, Kemp S, *et al*. Computed tomographic perfusion to Predict Response to Recanalization in ischemic stroke. *Ann Neurol* 2017;81:849–56.
16. Albers GW, Marks MP, Kemp S, *et al*. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N Engl J Med* 2018;378:708–18.
17. Nogueira RG, Jadhav AP, Haussen DC, *et al*. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *N Engl J Med* 2018;378:11–21.
18. Thomalla G, Simonsen CZ, Boutitie F, *et al*. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. *N Engl J Med* 2018;379:611–22.
19. Schwamm LH, Wu O, Song SS, *et al*. Intravenous thrombolysis in unwitnessed stroke onset: MR WITNESS trial results. *Ann Neurol* 2018;83:980–93.
20. Donnan GA, Howells DW, Markus R, *et al*. Can the time window for administration of thrombolytics in stroke be increased? *CNS Drugs* 2003;17:995–1011.