Introduction to the ACNR Stroke Series

In the last decade or so there have been radical changes in acute ischaemic stroke care, which have been at least partly driven by a need to provide access to early intravenous thrombolysis. Whilst this remains the only proven treatment, there are now many other promising approaches to achieving early reperfusion, including mechanical clot extraction and a variety of adjunctive methods, including renewed interest in neuroprotection by cooling. It seems highly likely that at least some of these treatments will be a part of our stroke units of the future. In this article, Phil White gives us a clear and concise overview of the key treatments tested recently or under evaluation, and shows that the rapid development of acute stroke care will continue to make it one of the most exciting aspects of acute neurology in the coming years.

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Clotbusting: Beyond Intravenous Thrombolysis for Ischaemic Stroke

Summary

- It is anticipated that more effective drug therapies (than tPA) will be available within five years.
- More use of advanced imaging techniques in hyperacute stroke within the NHS is a priority.
- IA Thrombectomy with modern technology looks promising but remains under clinical trial investigation.
- If endovascular approaches are proven then major stroke service reconfiguration would be required in a relatively short time frame.

Introduction

Over recent years, stroke has risen up the healthcare agenda in the UK. In terms of the need for neuroimaging, CT remains the mainstay but there is a strong need for more advanced brain imaging in many cases (such as CTaCTP) and MRI availability is indicated 24/7 for a minority of patients (see Figure 1). This review will briefly discuss emerging ‘new’ drugs, Neuroprotection (with EuroHYP-1 and IL-IRA), Plasmin, Ultrasound enhanced thrombolysis and endovascular treatment including the various recent and ongoing randomised clinical trials.

Approximately 50% of acute ischaemic strokes (AIS) are caused by large artery occlusion (LAAO). IV rtPA (IVT) administered within 4.5 hours of onset of symptoms is the only unequivocally proven treatment.1 Lees et al examined the relationship between stroke onset to start of treatment (OTT) with IV tPA treatment as assessed by day 90 modified Rankin score. The interaction was demonstrated to be statistically significant and the benefit from treatment decreased as OTT increased and no confirmed benefit was seen after 270 min2 (see figure 2). The current UK target for IVT treatment for stroke is 10%, already exceeded as rate of 11.8% was reported in Sentinel Stroke National Audit Programme report – Royal College of Physicians December 2013. In the near future, it is likely that 20-25% of patients will be eligible for IVT.

New Drugs

Desmoteplase is a genetically engineered highly fibrin-specific thrombolytic agent, similar to a substance found in the saliva of a vampire bat Desmodus rotundus. In contrast to alteplase, it has higher fibrin selectivity. It has minimal neurotoxicity (cf. rtPA has been linked with neurotoxicity in pathologic conditions, especially cell injury induced by activation of excitatory amino acid receptors). A clinical trial programme, Desmoteplase in Acute Ischaemic Stroke (DIAS), has been investigating the safety and efficacy of desmoteplase.3

Three studies (Dose Escalation Study of Desmoteplase in Acute Ischaemic Stroke (DEDAS), Desmoteplase in Acute Ischaemic Stroke (DIAS), and Desmoteplase in Acute Ischaemic Stroke-2 (DIAS-2)) have been completed and two large randomised, double-blind, placebo-controlled, phase III trials are ongoing at >200 sites worldwide (DIAS-3 and 4) and another in Japan (DIAS-J). The objective of DIAS-3 and DIAS-4 is to determine whether patients (NIHSS (National Institute of Health Stroke Scale) 4-24, age 18-85 years) with major artery occlusions without extensive ischaemic brain damage can be safely and effectively treated up to nine-hours after onset with desmoteplase. These trials are using CTA or MRA to image arterial occlusion and also evidence of ischaemic oedema for patient selection.4

Argatroban is a short-acting direct thrombin inhibitor that selectively inhibits free and clot-associated thrombin. Combined with IV tPA, it has been shown to be safe in patients with moderate neurological deficits due to proximal intracranial arterial
occlusions and may produce more complete recanalisation than tPA alone. A RCT of Argatroban With tPA for Acute Stroke (ARTSS-2) is an ongoing double blind phase IIb Multi-centre Safety/Efficacy Study. The purpose is to estimate the overall treatment benefit (improvement in disability) among stroke patients treated with tPA who are randomised to receive low-dose argatroban, high-dose argatroban or neither. The study started in October 2011 and the estimated study completion is December 2015.

Tenecteplase. A randomised trial of 75 patients who received alteplase (0.9mg per kilogram of body weight) or tenecteplase (0.1mg per kilogram or 0.25mg per kilogram) less than six hours after the onset of ischaemic stroke found tenecteplase to be superior to alteplase with respect to reperfusion and clinical improvement at 24 hours. Longer term clinical benefit was also shown, particularly with the higher dose of tenecteplase. The higher dose of tenecteplase was better than the lower dose for all imaging and efficacy outcomes. Furthermore, there was no increase in the incidence of intracranial haemorrhage with tenecteplase. However, a significant number of patients eligible for thrombolysis on the basis of standard clinical assessment and non-contrast CT were not included in this study because patient selection was based on CTP and CTA. Therefore, extrapolation of these results to all patients eligible for thrombolysis is not possible and although encouraging will need confirmation through larger trials.

Neuroprotection
Neuroprotection aims to prevent salvageable neurones in the penumbral region of the infarct from dying. A considerable number of treatments and agents have been unsuccessfully trialed in the past but hypothermia, ebselen (a glutathione-peroxidase mimic that is a free radical scavenger), statins, DP-β9 and IL-1RA are all under current investigation. We will concentrate on two that are under clinical trial in the UK.

European Stroke Research Network for Hypothermia (EuroHYP)-1
Inducing therapeutic hypothermia is used routinely in patients with cardiac arrest to limit neurologic deficit. It has shown significant efficacy in animal models of cerebral ischaemia. Various mechanisms proposed include preventing formation of free radicals, slowing cellular metabolism, reducing glutamate release and diminishing protein kinase C activity.

EuroHyp-1 is an ongoing open, randomised, phase III, multicentre clinical trial in 20 different European countries testing the effect of inducing hypothermia in 1500 awake adult acute ischaemic stroke patients to determine whether systemic cooling to a target temperature of 34 to 35°C, started within six hours of symptom onset and maintained for 24 hours,
improves functional outcome at three months. Cooling is performed with an intravenous infusion of 20ml/kg cold normal saline (@ 4°C) over 30-60 minutes followed by either surface or endovascular cooling to 34 to 35°C, maintained for 24 hours. Shivering will be prevented and treated with medication and all patients will receive the best medical treatment including intravenous thrombolysis, if indicated. A pragmatic trial is required as there are both safety concerns (mainly pneumonia risk increased with prolonged cooling and immobility) and tolerability concerns (prolonged shivering) with this therapeutic strategy as well as unproven efficacy.

IL-1RA
Intekeulin-1 receptor antagonist (IL-1RA) is another putative neuroprotective agent that has shown promising effects in animal studies. It is a naturally occurring competitive antagonist to the IL-1 receptor and targets the neuronal injury (inflammation as well as excitation) of the injured neurons. A meta-analysis of all pre-clinical ischaemia studies demonstrated that IL-1RA produced a 30% reduction in infarct volume in over seventeen studies. The efficacy improved with higher doses, central administration and early treatment. IL-1RA has been tested in a phase II clinical stroke trial and shown to be safe and well tolerated. The clinical outcome improved compared to placebo at three months. However, a phase III multicentre clinical trial is required to confirm its therapeutic benefits. This is in set up stage in the UK.

Plasmin
Plasmin is a direct-acting thrombolytic agent, which has to be administered via a catheter locally into the thrombus where it initiates thrombolysis but remains protected from antiplasmin. Once within the circulation, α2-antiplasmin rapidly neutralises it preventing haemorrhage at distant sites of vascular injury, making it potentially safer than tPA. Its' intravenous administration is safe but not effective as it gets neutralised in seconds. Plasmin has been shown to be safe in patients with peripheral arterial or graft occlusion, and efforts are now being directed towards stroke therapy. A dose-ranging study performed in a rabbit model of two-hour, thrombin-induced MCA occlusion showed that plasmin induced early recanalisation in all animals within 10 minutes after discontinuation of 3.2, or 1mg infusions. Control saline infusion failed to induce recanalisation in all rabbits. (1) A phase 1/2a clinical trial of Plasmin (Human) Administered Into the middle cerebral artery of Stroke Patients' is currently ongoing. Plasmin is administered through a catheter into the thrombus within nine hours of stroke onset to determine the safety of escalating doses of Plasmin (Human) and to look at its clinical effectiveness. Approximately 40 patients have enrolled so far and the estimated completion is March 2014.

Ultrasound enhanced thrombolysis
rtPA Thrombolysis can be potentiated using ultrasound, which delivers mechanical pressure waves to the clot and exposes more ultrasound waves to the clot and exposes more thrombus surface to the rtPA. The international multicentre phase II CLOTBUST trial (n=126) showed that in patients with acute ischaemic stroke, the combination of rtPA plus two hours of continuous transcranial Doppler (TCD) increased recanalisation rates, with better functional outcomes compared with rtPA alone. Administration of microbubbles may also enhance the effect of ultrasound on thrombolysis by reducing the threshold of the ultrasound waves needed to induce acoustic cavitation.

A multicentre international study TUCSON determined the dose of new more stable lipid microspheres, which can be safely administered with rtPA and TCD. Another development is an ultrasound transducer incorporated within a catheter, which can also deliver the intra-arterial rtPA. Known as the EKOS NeuroWave catheter, it uses 1.7–2.1 MHz pulsed-wave ultrasound with the emitting power of 400 mW, and is now being tested in randomised trials.

Mechanical clot disruption/removal
Endovascular stroke treatment (EST) has been shown to have higher probability of recanalisation (approx. 80%) than intravenous rtPA (approx. 46%). Recanalisation is most commonly assessed using the Thrombolysis in Cerebral Infarction classification (TICI). Grade 0 = no antegrade flow beyond point of arterial occlusion; grade 1 = contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run; 2a = The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction; however, the rate of entry of contrast into the vessel distal to the obstruction or its rate of clearance from the distal bed, or both, are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel (e.g., the opposite cerebral arterial or the arterial bed proximal to the obstruction); less than two-thirds of the entire vascular territory is visualised; for example, in a patient with an M1 segment occlusion, the M1 may have normal flow but at least M2 segment remains occluded; grade 2b = same as TICI 2a, except flow is seen into two-thirds or more of the expected vascular tree but is slower than normal; for example, in a patient with an M1 segment occlusion, all M2 branches proximally are open with areas of small segmental distal occlusion or slow flow; grade 3 = Complete perfusion; antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as that from an uninvolved other bed of the same vessel or the opposite cerebral artery (See Figure 4).

However, improved recanalisation may not be associated with a better clinical outcome. Indeed, neutral randomised controlled trials (RCTs) of endovascular stroke treatment; SYNTHESIS Expansion, IMS-III and MR RESCUE were recently published together in the New England Journal of Medicine.
strate LAO before randomisation. Only 165/181 patients allocated to EST.

NIHSS. Also, no vascular imaging such as CTA was performed to demonstrate (and it was delayed by 22 minutes on average in the IVT arm); any proven best medical therapy was withheld from half the participants.

This trial aimed to determine if the clinical superiority of endovascular therapy as compared with intravenous t-PA. The trial showed no significant difference in the clinical outcomes between the two groups (see Figure 4) and was stopped early due to the crossing of a prespecified futility rule.

EST used was IA t-PA or any approved thrombectomy device, IA t-PA alone was used in 138 patients, Merci device in 95 patients, Penumbra in 54, EKOS in 22. Modern technology for thrombectomy, a Stentriever, was used as primary device in only five patients, and in a further eight as a bailout after MERCI/ Penumbra/other had failed.

Again the trial has multiple major limitations. Only 282 (43%) patients had imaging confirmed large artery occlusion (LAO). Although IV rTPA was started at a mean of 121 minutes following stroke onset, EST was not started until a mean of 249 minutes (and mean procedural time was also prolonged at ~90 minutes)! Also, good reperfusion (TICI 2b or 3) was achieved in only 44% of patients with an M1 occlusion, and at a similar or lower rate for other sites of occlusion. This is far worse than in current technology trials. This is significant as results of two trials published recently in the Lancet both found that stent retrievers are clinically superior to older thrombectomy devices.23,24 Also, to date, we don’t know that lower dose bridging IV tPA as used in IMS-III EST arm is as effective as full dose used in control arm (the on-going ENCHANTED trial should clarify this).

In the IMS-III patients who did have CTA confirmed LAO prior to randomisation, there was an 8.7% absolute difference in clinical good outcome for IVT and IAT compared with IVT alone even bearing in mind obsolete EST used in IMS-III, which was statistically significant, p=0.0114 on van Elteren test used for primary analysis (Figure 5). There were no statistically significant differences in the clinical outcomes between the two groups (see Figure 4) and was stopped early due to the crossing of a pre-specified futility rule.

The study had multiple serious limitations including the fact that proven best medical treatment was withheld from half the participants (and it was delayed by 22 minutes on average in the IVT arm); any ischaemic stroke patients could be included, with no lower limit for NIHSS. Also, no vascular imaging such as CTA was performed to demonstrate LAO before randomisation. Only 165/181 patients allocated to EST group got EST and not all of those 165 had LAO. Most patients in the EST group only got loco-regional infusion of t-PA and fragmentation of the thrombus with a micro-guidewire (109). Only 56 patients (31%) then went on to have EST with a thrombectomy device and modern stent retrievers were used infrequently (13%). Crucially, EST was performed on average over an hour later than IV tPA therapy. Last, but not least, data on recanalisation rates and time to recanalisation were not presented nor was any formal Rankin shift analysis performed based on pre stroke baseline.

**IMS-III:** Interventional Management of Stroke (IMS) III trial was a phase III RCT that aimed to investigate if combined treatment with IV tPA followed by EST is more effective than IV tPA alone.22 This is perhaps the key clinical question in hyperacute stroke treatment.

The primary outcome measure was a modified Rankin scale score of two or less at 90 days. 656 patients with NIHSS 8 or higher were randomised. 434 patients were randomised to EST after bridging (low-dose) IV t-PA and 222 patients to full dose IV t-PA. The trial showed no significant difference in the clinical outcomes between the two groups (see Figure 4) and was stopped early due to the crossing of a prespecified futility rule.

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**SYNTHESIS expansion:** This trial aimed to determine if the clinical efficacy of endovascular treatment (EST) was better than the current standard medical care. Between Feb 2008-April 2012, 362 patients were randomised. 181 were allocated IV tPA up to 4.5 hours from symptom onset and the other 181 allocated EST up to six hours from symptom onset. Primary outcome was survival free of any appreciable disability (modified Rankin score of 0 or 1) at three months. Designed to verify or refute a difference of 15% between the proportions of patients with a favourable outcome in the two treatment arms, this study failed to show the superiority of endovascular therapy as compared with intravenous t-PA.23

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There are many ongoing RCTs, including: a) publicly funded academic trials such as MR CLEAN in Netherlands, THRACE in France, PISTE in UK;
b) academic industry funded trials- REVASCAT in Spain, EXTEND IA in Australia, Alberta run THERAPY trial; c) company driven trials such as SWIFT PRIME (Covidien), and several more are in set up. Most of those named have begun recruitment and in MR CLEAN and THRACE it is far advanced.

Conclusion

There are grounds to anticipate that within five years we will have IV drug therapies for acute stroke that are both somewhat more effective than rtPA and where some benefit beyond 4.5h in readily identifiable subgroups of patients will have been demonstrated. This will represent incremental but important improvements in medical therapy for acute stroke. To identify (stratify) such patients will probably require much wider use of acute vascular imaging and/or MRI. The role of adjunctive ultrasound should be clarified. Thrombectomy trials that address the relevant clinical questions are ongoing. It is very possible that within five years modern thrombectomy may be proven to be of benefit when added to IVT for some groups of patients. It is very probable that the clinical benefit of early thrombectomy when thrombolytic drugs are contraindicated will also be demonstrated. Together these imaging and therapeutic advances are likely to drive major service reconfiguration in acute stroke services.

REFERENCES


trace2=rank=2


