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Cynics may consider that review of emergent stroke therapies in 2007 is likely to make for quick reading—it is certainly true that many high profile trials reported unexpected neutral outcomes. However, although these disappointments made for headline medical news, there were still a number of encouraging results of novel acute therapies.

The first "casualty" of the year was neuroprotection. The free radical trapping agent NXY-059 had been consistently shown to reduce infarct size and improve functional outcomes in published reports of animal models. The first phase III study in humans (SAINT) was positive, reporting a statistically significant improvement in global disability (Figure).[1] Unfortunately, the follow up SAINT II trial did not confirm this result (Figure).[2] This randomized placebo-controlled study of 3306 ischemic stroke patients up to 6 hours from ictus demonstrated no significant improvement in the primary end point of day 90 modified Rankin score (mRS). Subgroup analyses also failed to replicate the previous finding of reduced hemorrhagic transformation rate in patients treated with thrombolytic.

Although the result was disappointing, the trial itself was rigorous and it optimized statistical analyses to describe functional outcomes across the treatment groups. A clear message from the SAINT trials is that even large-scale meticulously planned trials are subject to the play of chance, and that initial positive results require verification with a second adequately powered study. These themes have been echoed in other acute stroke trials throughout the year.

As the European Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) confirmed safety and efficacy of intravenous thrombolysis in routine practice, the stroke community were already advancing knowledge on novel approaches to reperfusion. The second Desmoteplase in Ischemic Acute Stroke (DIAS II) study sought to build on the success of previous studies using the fibrin specific plasminogen activator desmoteplase.[3] The aim was to target therapy to those most likely to benefit by including only patients with perfusion-diffusion mismatch of at least 20% total infarct volume or equivalent CT-perfusion findings. In a cohort of patients 3 to 9 hours after event, placebo was tested against intravenous boluses of 90 μg/kg and 125 μg/kg desmoteplase. In contrast to previous results, no benefit was found from desmoteplase; in fact patients treated at highest dose showed a trend toward excess mortality.

The reasons for this neutral result remain unclear and may relate to the active agent, to the imaging based protocol, or to statistical underpowering—at 186 patients this was still a small trial. It seems unlikely that patients selected for persistence of penumbra 3 to 9 hours after stroke will show a greater response to thrombolysis than we achieve with rapid alteplase use. Groups of 60 patients are too small to confirm treatment effects comparable to those of alteplase when used under optimal conditions. The excess mortality in the higher desmoteplase dosage group seems unlikely to relate directly to desmoteplase as, of the 14 deaths, 9 were considered nonneurological and 9 occurred 1 week or later after treatment. Were the DIAS trialists simply victims of "significant" bad luck?

At present the future of desmoteplase is unclear. However, the evidence base for using penumbral imaging to target acute therapies continues to grow. The DEFUSE study successfully used MRI imaging to predict patients likely to benefit from tPA in the 3- to 6-hour time period,[4] a result confirmed in a recent analysis of pooled data from 5 European centers.[5]

Intraarterial delivery of thrombolytic has theoretical advantages over intravenous administration, including local delivery of agent and reduced systemic effects. It is almost a decade since the PROACT-II study first suggested efficacy of intraarterial thrombolysis.[6] A confirmatory trial was never completed, although many centers continued to use intraarterial lytics for patients ineligible for standard intravenous therapy. The MELT study (MCA Embolism Local fibrinolytic intervention Trial) helps reassure us that the intraarterial approach represents a viable treatment option.[7] This prospective trial randomized 114 patients, with confirmed occlusion of the M1 or M2 MCA segment and within 6 hours of event, to intraarterial urokinase or medical therapy. The trial was terminated early when intravenous tPA was licensed for clinical use in Japan. Although no difference was seen on primary end point (mRS 0 to 2; $P=0.345$; Figure), on prespecified secondary end point analysis an increase in patients showing excellent recovery was demonstrated (mRS 0 to 1; $P=0.045$; Figure) with no significant difference in mortality or hemorrhage.

Primary intracerebral hemorrhage (ICH) is a frustrating entity, with higher levels of mortality and disability than ischemic stroke and few proven therapies. Pilot results using the hemostatic agent recombinant factor VII (rFVII) had

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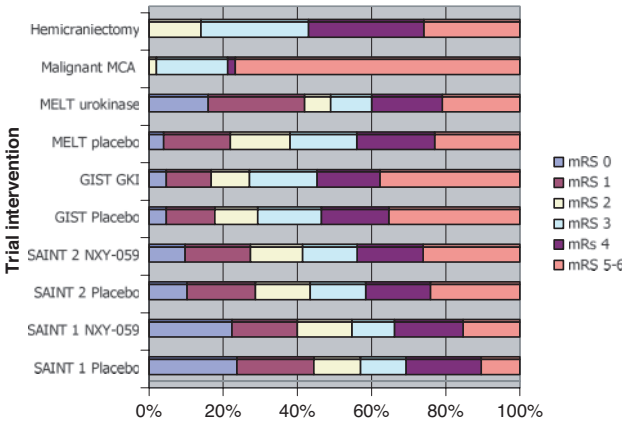

Figure. Functional outcomes in major stroke trials of 2007; for comparison results of both SAINT trials are presented.

suggested efficacy, therefore results of the phase III FAST trial were eagerly awaited.[8] In FAST, 821 patients diagnosed within 3 hours of onset were randomized to rFVII 20 μg/kg; 80 μg/kg or placebo. Despite a significant dose-dependent reduction in hematoma growth, no significant difference was seen in the main end point of the trial of death or severe disability at 90 days. These data seem counterintuitive: hematoma growth is known to be independently associated with poor outcome. Although this could represent further play of chance, analysis of trial subpopulations may offer explanation. According to baseline characteristics presented at the European Stroke Conference in 2007 (http://www.eurostroke.org/esc_gla_highlights.htm#oral%20presentation, accessed 24/10/07), more patients in the treatment arms had low conscious level, had evidence of left ventricular hypertrophy, and had intraventricular extension of hemorrhage–all powerful predictors of outcome. It should also be noted that unlike most acute stroke trials, FAST did not specify an upper age limit. It seems plausible that rFVII may only impact on outcomes in a younger, fitter cohort. We await publication of the full results so that we can consider all likely confounding influences.

The disappointing result of FAST must be balanced by promising work in other areas of ICH intervention. The INTERACT pilot study of blood pressure reduction has completed initial work demonstrating that rapid reduction of blood pressure to a target of 140/90 mm Hg is feasible and well tolerated. In recognition of the grave prognosis associated with intraventricular hemorrhage the CLEAR trials are testing local thrombolysis to aid clot resolution. Results to date are promising with a suggestion of markedly improved outcomes,[9] and a definitive trial is being planned.

Physiological monitoring is an important component of acute stroke unit care. However, there is little evidence to guide treatment when parameters become deranged. The Glucose in Stroke Trial (GIST) was the first multicenter study of acute glycaemic intervention.[10] Patients were randomized to treatment with a glucose-potassium-insulin infusion (GKI) to maintain euglycaemia (capillary blood glucose 4 to 7 mmol/L) or placebo. Treatment conferred no benefit either in terms of 90-day mortality or functional outcome measures (Figure). This neutral result does not necessarily signal the end of glycaemic control in acute stroke; at 933 patients the study population fell well short of the planned 2355 and although statistically significant, the mean difference in glucose between GKI and control (0.57 mmol/L) was clinically modest, probably less than can be achieved with insulin infusion.[11] Further trials targeting insulin therapy to patients with higher baseline sugars are ongoing.

Last year may have been disappointing for acute pharmacotherapy but was less so for nondrug intervention. The Wingspan stenting device was approved by the US Food and Drug administration in 2005 for use in intracranial stenosis. An NIH funded registry of 131 stenting outcomes reported a high degree of technical success (97%) and a low rate of early complications (4.6%).[12] Observational data have also been reported for the mechanical embolectomy device—the MERCI retriever. The Multi-MERCI study of 164 patient outcomes again reported high rates of successful recanalisation (57.8%) with few periprocedural complications (6.9%).[13] Although new tools for use in acute stroke are welcome, these results should be treated with some caution. Voluntary registries and single arm studies are likely to overestimate benefits from treatment. There is now an ethical and scientific need to build on these observational data with prospective randomized controlled trials comparing intervention with best medical therapy.

Malignant MCA infarction is a feared complication of ischemic stroke, with mortality approaching 80%. Decompressive hemicraniectomy has been practiced for many years with case-series suggesting potential for good outcomes but no adequately powered randomized controlled trials. Three recent European trials have compared hemicraniectomy to conservative management. Individually the trials provided a strong suggestion of benefit; however, it took this year's pooled analysis to finally prove efficacy. Compared with best medical treatment, numbers needed to treat to prevent death, severe disability, or moderate disability are 2, 2, and 4, respectively.[14] It is remarkable that in a complication of stroke previously considered fatal, intervention can leave a substantial proportion with slight disability only (Figure). Having now proven benefit, we must better define optimal timing and patient characteristics. In these studies the population were relatively young (mean age 43 years, maximal age 60 years) and intervention was rapid (less than 48 hours from stroke).

So perhaps there were fewer successful emergent therapies in 2007 than we dared to hope. Regardless, we have still strengthened the evidence base for acute stroke care. Trials would not be performed if we were already certain of the outcome, and the major trials of last year, both positive and neutral, have greatly added to our knowledge of stroke care and reconfirmed that large scale well conducted clinical trials are possible in acute stroke. Medicine advances incrementally; we should celebrate the opportunities that await as much as the successes we have achieved.

Disclosures

K.R.L was international principal investigator for the SAINT I trial and chaired the steering committee for the CHANT and SAINT I & II trials (AstraZeneca). He chaired the data monitoring committee for

DIAS, DEDAS, and DIAS-II trials (Forest, Paion). Both authors have participated in locally funded projects examining acute glycaemic control in stroke. Neither author has any specific conflict of interest in relation to the content of this article.

References

1. Lees KR, Zivin JA, Ashwood T, Davalos A, Davis SM, Diener HC, Grotta J, Lyden P, Shuaib A, Hardemark HG, Wasiewski WW. Stroke-Acute Ischemic NXY Treatment (SAINT I) Trial Investigators. NXY-059 for acute ischemic stroke. *N Engl J Med*. 2006;354:588–600.
2. Shuaib A, Lees KR, Lyden P, Grotta J, Davalos A, Davis SM, Diener HC, Ashwood T, Wasiewski WW, Emeribe U. SAINT II Trial Investigators. NXY-059 for the treatment of acute ischemic stroke. *N Engl J Med*. 2007;357:562–571.
3. Hacke W, Furlan A; for the DIAS-2 Investigators Results from the phase III study of desmoteplase in acute ischaemic stroke trial (DIAS 2) Presented at European Stroke Conference, Glasgow 2007.
4. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, Kakuda W, Lansberg MG, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP. DEFUSE Investigators. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Annals Neurol*. 2006;60:508–517.
5. Schellinger PD, Thomalla G, Fiehler J, Köhrmann M, Molina CA, Neumann-Haefelin T, Ribo M, Singer OC, Zaro-Weber O, Sobesky J. MRI-based and CT-based thrombolytic therapy in acute stroke within and beyond established time windows: an analysis of 1210 patients. *Stroke*. 2007;38:2640–2645.
6. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in acute cerebral thromboembolism. *JAMA*. 1999;282:2003–2011.
7. Ogawa A, Mori E, Minematsu E, Taki W, Takahashi A, Nemoto S, Miyamoto S, Sasaki M, Inoue T; for The MELT Japan Study Group. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. *Stroke*. 2007;38:2633–2639.
8. Mayer SA, Begtrup BK, Broderick JP, Davis SM, Diringer MN, Skolnick BE, Steiner T; on behalf of the FAST investigators. Randomized placebo-controlled, double-blind phase III study to assess rFVIIa efficacy in acute intracerebral hemorrhage: the FAST trial. Presented at European Stroke Conference, Glasgow 2007.
9. D Hanley; for the CLEAR IVH Investigative Team. Results of CLEAR IVH B; Dose-response for 3rd and 4th ventricular blood clearance. Presented at European Stroke Conference, Glasgow 2007.
10. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, Bamford JM, James OF, Alberti KG. GIST Trialists Collaboration. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol*. 2007;6:397–406.
11. Walters MR, Weir CJ, Lees KR. A randomised, controlled pilot study to investigate the potential benefit of intervention with insulin in hyperglycaemic acute ischaemic stroke patients. *Cerebrovasc Dis*. 2006;22:116–122.
12. Fiorella D, Levy EI, Turk AS, Albuquerque FC, Niemann DB, Aagaard-Kienitz B, Hanel RA, Woo H, Rasmussen PA, Hopkins LN, Masaryk TJ, McDougall CG. US multicenter experience with the wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. *Stroke*. 2007;38:881–887.
13. Flint AC, Duckwiler GR, Budzik RF, Liebeskind DS, Smith WS. MERCI and Multi MERCI Writing Committee. Mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and Multi MERCI Part I trials. *Stroke*. 2007;38:1274–1280.
14. K Vahedi, J Hofmeijer and E Juettler, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Bousser MG, van der Worp HB, Hacke W; and for the DECIMAL, DESTINY, and HAMLET investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol*. 2007;6:215–222.

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