Advances in Emerging Therapies 2006

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The past year has seen further advancement toward the goal of effective and multifaceted stroke treatment. Encouraging evidence has emerged to support mechanical intervention for large artery occlusion, late and imaging-directed thrombolytic therapy, neuroprotectant strategies and decompressive surgery for large middle cerebral artery (MCA) stroke. We have seen important advances with regard to secondary preventative strategies.

The attraction of catheter-based reperfusion techniques is obvious. They may afford use of lower systemic doses of thrombolytic agents, while mechanical clot disruption and retrieval could obviate the need for drugs. This would not only be a particular advantage in those with elevated hemorrhage risk but may also improve the poor reperfusion rates after proximal carotid, basilar or M1 MCA occlusion. Although the MERCI trial[1] suggested benefit some 2 years ago, this position has been supported by a recent small series of 12 patients with basilar artery occlusion[2] of whom half underwent successful mechanical recanalization. Time to reperfusion was shorter in these patients and they were spared the risks of thrombolytic therapy. Preliminary data also suggest that catheter-based interventions can be applied more distally than hitherto considered possible, perhaps offering direct treatment for intracranial stenosis with reduced rates of stroke or vascular death compared with historical controls.[3] Although these techniques are hugely promising and may represent a real alternative for those with major stroke who are unsuitable for recombinant tissue plasminogen activator (rt-PA), we must recognize that conclusive randomized controlled evidence is lacking and benefit is unproven. Furthermore, such techniques will only aid those fortunate enough to be treated in a major center. While we consider these complex, costly and less readily available treatments, we should note that 2006 provided further evidence that intravenous thrombolytic therapy is safe but underused[4] and that it remains a valuable treatment for life-threatening conditions such as basilar artery occlusion.[5]

Trials such as ECASS III and the International Stroke Trial-3 are still testing whether the time window for thrombolytic therapy can be safely prolonged to 4.5 or perhaps 6 hours. Preliminary evidence suggests that use of magnetic resonance perfusion/diffusion scanning will allow us to stretch the window at least this far. MRI is the more widely studied modality but CT perfusion–imaging also identifies ischemic penumbra.[6] Recently published nonrandomized data[7] showed that favorable outcomes were more common after MRI guided rt-PA within 6 hours than in historical trial controls given rt-PA treatment or placebo after standard CT imaging. Reassuringly, the intracerebral hemorrhage rate was comparable to that after placebo.

The Desmoteplase study program suggests that this newer fibrin-specific thrombolytic may be effective up to 9 hours after ictus in patients with MRI perfusion/diffusion mismatch. The DIAS (Desmoteplase in Acute Ischemic Stroke) trial reported nearly 2 years ago,[8] but the DEDAS (Dose Escalation of Desmoteplase for Acute Ischemic Stroke) trial[9] and a combined analysis of the two[10] now appear to corroborate the initial findings: reperfusion rates and clinical outcomes were improved in such patients if treated with 90 to 125 μg/kg of desmoteplase. A further phase IIb study (DIAS II) seeks to replicate these results while allowing a choice of MRI or CT perfusion as entry criterion. By selecting those patients most likely to benefit from thrombolytic therapy, the investigators hope that the risk benefit ratio can be further refined, while also maximizing its use. However, we must remain cautious: the data supporting CT perfusion and MRI-guided rt-PA do not yet derive from randomized controlled trials, and the desmoteplase data are based on a tiny patient cohort. We are well aware of the limitations of small trials; even relatively large and rigorously controlled trials can give misleading results.

Reperfusion strategies have been the cornerstone of acute stroke treatment since introduction over a decade ago. Throughout this period a number of promising neuroprotectant drugs have been tried, tested and failed. The year 2006 appeared different; evidence emerged that NXY-059, a novel free radical trapping agent, may reduce poststroke disability and the rate of hemorrhagic transformation after rt-PA.[11] In line with expectations for this approach, the benefits seen were modest but by no means economically, clinically or statistically insignificant especially in light of potentially wide applicability. A lively debate ensued. A particular focus of attention was the novel analysis method used, which was geared to measure improvement in disability across the entire range of modified Rankin scores. It seems remarkable that such methods that increase rigor and trial power are still criticized in favor of less sensitive dichotomized approaches designed instead for treatments that could threaten to increase

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the proportion of disabled survivors. The neutral results of the confirmatory SAINT II trial that were recently announced in summary format suggest that intravenous administration of a free-radical–trapping agent may not be effective after all; we await publication of the full results. Despite this grave disappointment, the debate and the lessons learned will be of value in the future because rigorous science is a prerequisite to development of emerging therapies.

Complete MCA infarction is an evil among the stroke subtypes and is associated with brain edema, increased intracranial pressure and a risk of transtentorial herniation and death. Medical therapy does little to improve mortality rates, which reach 80%. Several case series and systematic reviews suggest that decompressive hemicraniectomy can reduce mortality,[12] perhaps to as low as 30%. However, a major concern has been that surgery may simply convert a fatal ischemic stroke event into a severely disabling one, with little hope of a favorable outcome. Some time ago, the DESTINY (Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery) trial[13] showed a significant mortality reduction in those with severe MCA stroke after surgery compared with standard conservative treatment (46.7% versus 88.2%), but the functional outcome data are only recently available.[14] These suggest that functional outcomes are improved with a higher proportion of patients having a modified Rankin Scale score of ≤3; a message reinforced by the recently concluded DECIMAL trial (Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarcts).[15] DECIMAL included 38 patients—slightly more than the 32 in DESTINY—and again showed a large mortality benefit and improved functional outcome after surgery; (52.8% absolute mortality risk reduction and 50% compared with 22% had a modified Rankin Scale score of ≤3 at 12 month). Hemicraniectomy should perhaps now be considered for patients with complete MCA infarction, and certainly the results of the combined analyses of these 2 trials are eagerly awaited.

Although these changes are encouraging, we took bigger strides with secondary prevention. Three large trials (ESPRIT, CHARISMA and SPARCL) have contributed usefully. ESPRIT[16] involved 2763 patients with recent stroke or transient ischemic attack and revealed, during a mean follow-up of 3.5 years, that the combination of aspirin and slow-release dipyridamole afford a 20% relative risk reduction in the rate of vascular death or nonfatal stroke or myocardial infarction. The surprising lack of increased bleeding complications is curious, and further claims of anti-inflammatory and nonplatelet-mediated benefits of dipyridamole have emerged.[17] The results of ESPRIT confirm those of ESPS 2[18] and have consolidated the position of aspirin and dipyridamole combination therapy as the antiplatelet strategy of choice for secondary prevention of stroke.

Regrettably, dual aspirin and clopidogrel therapy has had a less good year. The CHARISMA trial[19] compared aspirin and clopidogrel therapy versus aspirin alone among 15 603 patients, the majority of whom had established cardiovascular disease. In 27% of patients the trial entry criterion was previous cerebrovascular disease. Clopidogrel was no more effective than placebo in aspirin-treated patients with stable cardiovascular disease, but bleeding complications were increased. Trends toward benefit were apparent in those who entered the trial on account of stroke, and all-cause stroke appeared lower in the population as a whole. However, benefits only bordered on statistical significance before adjustment for multiple comparisons and do not support the combination as a routine treatment strategy.

We know that statin therapy reduces both the risk of stroke in patients with coronary artery disease and the risk of cardiac events in those who have had a stroke. It was not clear, however, whether statin therapy reduces the risk of recurrent stroke after an index cerebrovascular event. The SPARCL trial[20] randomized 4731 patients to high dose atorvastatin or placebo. Treatment led to a 16% relative risk reduction of recurrent stroke and to reductions in the rates of most other vascular complications. The incidence of hemorrhagic stroke was slightly higher but fatal intracerebral hemorrhage was unchanged. Thus, in contrast to results from the Heart Protection Study, where rate of recurrent stroke was unaltered by simvastatin treatment, the SPARCL trial confirms that risk of recurrent stroke is significantly reduced by statin therapy.

So what do these developments tell us? The cynics might say not much. We have long known that thrombolytic therapy is effective and more so the earlier it is given. We have also long suspected that the therapeutic window may be extended, that surgery may be of benefit in those with the most severe strokes, that aspirin and dipyridamole dual therapy is preferable to aspirin monotherapy and that statin therapy is of benefit after stroke. However, many questions have been answered and answered clearly. The publication of randomized controlled trials involving over 20 000 patients is hardly insignificant. These have clarified the roles of several treatment strategies. Our biggest disappointment is of course that the once shining star of neuroprotectant therapy burns a little less brightly, but even this provides testament to the ability of the stroke community to conduct the highest quality of randomized controlled trials. We hope this will continue into 2007 and beyond with the emergence of more promising therapies.

Disclosures

K.R.L. chairs the independent data monitoring committee for the ECASS-III (Boehringer Ingelheim) and DIAS-I, DEDAS and DIAS-II (Forest, Paion) trials; was principal investigator of SAINT-I and chairs the steering committee for the SAINT and CHANT trial program (AstraZeneca). He participated as an investigator, and J.D. as a subinvestigator, in the ESPRIT (academic), SPARCL (Pfizer) and CHARISMA (Sanofi) trials. Neither author has any conflict in relation to the content of this article, however.

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