hardly conclusive. Are these results sufficient to support continuation of a large phase III development programme? Thankfully, the sponsor’s view was affirmative. With the need so enormous, and the potential benefit suggested (although not proven) by these phase II results, the effort is indeed justified despite the substantial uncertainty. In a few months, we will learn whether tarenflurbil will be the first anti-amyloid intervention to be efficacious in a pivotal trial.

The best news is that several other promising anti-amyloid programmes are moving forwards, despite the methodological difficulties of seeing clear efficacy in phase II studies. Further, biomarker techniques are improving, allowing more rational selection of drug doses to target secretases; these advances should increase the likelihood that such programmes will succeed. The realistic possibility that pharmacological control over the amyloid cascade will be achieved, and the enormous effort this would have on world health, should continue to drive these efforts.

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While working at Georgetown University, I was a site investigator for the Myriad Pharmaceuticals phase III trial of tarenflurbil. I was not involved in the Phase II trial, and I have never been a consultant to Myriad.


Cilostazol shows promise as an alternative to aspirin for patients with ischaemic stroke

The most widely prescribed antiplatelet drug to reduce the long-term risk of major vascular events in patients who have had arterial ischaemic stroke is aspirin. Aspirin is reasonably safe and affordable but has only modest effectiveness; the reduction in relative risk (RRR) of major vascular events is only about 13% (95% CI 6–19%). Aspirin also might not be safe to use in populations that are at high risk of intracerebral haemorrhage (eg, Asians).

Among the alternative antiplatelet drugs, dipyridamole is not more effective than aspirin (∼2%, ∼18% to 12%) and clopidogrel might only be marginally more effective than aspirin (8.7%, 0.3–16.3%); the combination of aspirin and extended-release dipyridamole is more effective than aspirin alone (18%, 9–26%) but is more likely to cause headache. Cilostazol is an antiplatelet drug that has been shown to reduce the risk of major vascular events compared with placebo (39%, 9–59%) in a randomised trial of 1095 Japanese patients with ischaemic stroke. However, the burning question is: how does cilostazol compare with another “gold standard” antiplatelet drug, such as aspirin, and not just with a placebo? In this issue of The Lancet Neurology, Huang and colleagues report the results of a randomised, double-blind, pilot trial that compared cilostazol with aspirin in 720 patients from China with recent (within 1–6 months) ischaemic stroke.

Compared with standard-dose aspirin (100 mg per day), random assignment to cilostazol (100 mg twice per day) was associated with a reduction in the relative risk of the primary outcome—recurrent stroke—by 38% (95% CI –26% to 70%) after an average of little more than a year on treatment. These results are consistent with the expected outcome, based on a previous comparison of cilostazol with placebo (ie, a RRR of about 25% with cilostazol vs aspirin), but they are also consistent with cilostazol being up to 26% less effective than aspirin and 70% more effective than aspirin, in relative terms. The extremely wide confidence intervals around the point estimate of the RRR show the small number of patients randomised, their moderate risk profile (patients who were at the highest risk of recurrent stroke—those in their first month after ischaemic stroke—were excluded), and the short follow-up. Unfortunately, the trial design did not include sample-size calculations or the more statistically robust

http://neurology.thelancet.com Vol 7 June 2008 469

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See Articles page 494
outcome event—the composite of stroke, myocardial infarction, or vascular death.

The authors are understandably excited by the smaller number of symptomatic intracerebral haemorrhages in patients in the cilostazol group (n=1) versus those in the aspirin group (n=5), and by the possibility that finding brain microbleeds on MRI gradient echo T2 sequences might identify the patients who are at greatest risk of antiplatelet-associated intracerebral haemorrhage. However, caution is required in the interpretation of these results because the number of intracerebral haemorrhages was extremely small (and so the results are imprecise and only hypothesis-generating), and the diagnostic and prognostic usefulness of brain microbleeds is uncertain.6

Although the results are prone to random error, they are unlikely to be substantially influenced by bias: selection bias in treatment allocation was minimised by the concealed randomisation process, which resulted in baseline comparability of the treatment groups; performance bias was minimised by otherwise equal treatment of the two groups during the trial; attrition bias is unlikely because only 1·3% of patients were lost to follow-up; and detection bias is unlikely because the assessment of outcome events was made by investigators who were blinded to the treatment allocation.

The trial results are, therefore, likely to be internally valid and biologically plausible. Cilostazol not only inhibits platelet aggregation by selectively blocking phosphodiesterase type 3 (an enzyme that breaks down cyclic AMP) but it also inhibits the production of thromboxane B2 and the release of platelet-derived growth factor by activated platelets. Cilostazol also has a vasodilatory action and a favourable effect on plasma lipid profiles; moreover, it increases the distance that patients with peripheral arterial disease can walk7 and might be comparable or superior to clopidogrel for the prevention of subacute coronary artery stent thrombosis and restenosis.8,9

The implications of these results for clinicians are that they offer hope for a safer antiplatelet drug that is at least as effective as aspirin in use in patients with ischaemic stroke. The implications of these results for researchers are the need to explore the external validity of these pilot study results in a phase III randomised trial that compares cilostazol with aspirin (or with the new gold standard of antiplatelet therapy, pending the results of the PROFESS trial10) in a large number of high-risk patients with recent ischaemic stroke from a wide range of nations and ethnic groups.

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