Neuroprotection for Acute Stroke
Making Clinical Trials Work

Keith W. Muir, MD; Donald G. Grosset, MD

Background—With the exception of the National Institutes of Neurological Disorders and Stroke trial of recombinant tissue plasminogen activator, clinical trials in stroke have failed to show improved outcome. If further negative results such as those of recent large neuroprotective trials are to be avoided, trial methodology must be reevaluated.

Summary—Because there is little evidence from animal focal ischemia models for protection of white matter, glia, or subcortical neurons, the logical target population for initial clinical trials is patients with middle cerebral artery stroke involving cerebral cortex. Clinical differentiation of moderate to large middle cerebral stroke from lacunar stroke is possible with the Oxfordshire Community Stroke Project classification but less readily achieved by numerical stroke scales. Several imaging techniques can further distinguish middle cerebral stroke patients with a “penumbra” potentially amenable to intervention from those without a penumbra, in whom outcome appears already determined. The window for intervention may be better defined by imaging than by time alone. Shortened follow-up periods may reduce variation in outcome attributable to differences in provision of rehabilitation or secondary preventative treatments among centers, and imaging may provide useful surrogate end points.

Conclusions—Clinical trials restricted to patients with large middle cerebral stroke accompanied by radiological evidence of a penumbra should be an essential component of drug development. Slower recruitment may be offset by extended time windows and requirements for fewer patients. Imaging may define surrogate evidence of biological effect prior to embarking on a phase 3 program. (Stroke. 1999;30:180-182.)

Key Words: clinical trials ■ lacunar infarction ■ magnetic resonance imaging ■ neuroprotection ■ tomography, emission computed

Almost 3 years after the licensing of recombinant tissue plasminogen activator (rtPA) for ischemic stroke in the United States following the landmark National Institutes of Neurological Disorders and Stroke (NINDS) trial,1 the likelihood of additions to the limited therapeutic armamentarium seems increasingly distant. Wider experience has reinforced that the logistics of safe thrombolysis render rtPA suitable for only a minority of patients. The termination of both the ECASS II and ATLANTIS trials may well prevent wider licensing of rtPA and is likely to impede any anticipated reorganization of stroke services as a consequence of extended time windows for thrombolysis. Now, the high-profile failure of neuroprotective drug trials, notably those of tirilazad, lubezol, epliol, selfotel, endomab, and aptiganel,2 brings stroke physicians to a watershed. At this juncture, large parts of the pharmaceutical industry have paused to consider the commercial viability of continued neuroprotective drug development. While there are explanations for many of the trial failures, and aspects of preclinical and early clinical drug development could undoubtedly be improved, there is a need for clinicians to accept in large measure the responsibility for unsuccessful trial design.

Critical reevaluation of stroke trial methodology is required, or potentially beneficial treatments for our patients will be discarded, to remain only as pharmacological tools or to be diverted to “less difficult” clinical areas.

Clinical trial methodology in stroke has evolved considerably in the past decade: optimistic 48-hour time windows have been superseded by an appreciation of the need to treat early, usually within 6 hours; intravenous administration has replaced oral dosing to achieve high plasma (and, hopefully, brain) drug concentrations rapidly; the importance of full pharmacokinetic data in phase 2 trials is now appreciated; and methods for follow-up are now standardized around (albeit imperfect) scales of activities of daily living and disability.

However, current trials favor the inclusion of as broad a range of stroke pathologies as possible, within the boundaries of excluding those with very poor and very benign prognoses (eg, patients in a coma or with rapidly resolving deficits, respectively). While ideally it would be desirable for drug efficacy to be proven in all patient groups, this strategy fails to acknowledge either animal models or clinical data.

Animal models of stroke involve histological assessment after MCA occlusion, with resultant infarction of cortex,
basal ganglia and white matter. Almost all neuroprotectives work via receptor-mediated or intraneuronal mechanisms of uncertain relevance to gloa or white matter. Even in animal models where preischemic treatment is possible, significant protection is confined to the cerebral cortex for almost all drugs. Techniques for assessing axonal integrity require further development, and at present there are almost no in vivo data supporting the ability of drugs to rescue ischemic white matter. There is no a priori reason to expect efficacy of neuroprotective drugs across the full spectrum of clinical stroke syndromes: restricting inclusion to patients with strokes causing cortical ischemia is a logical step, which requires changes in clinical and radiological assessment in trials.

Clinical trials presently include a high proportion of patients with lacunar syndromes, involving damage to white matter tracts and subcortical nuclei, with no involvement of cortical neurones. Neuroprotection cannot therefore be anticipated in this group, which is pathophysiologically distinct from thromboembolic large-vessel disease. Moreover, the benign prognosis of lacunes (around 66% of patients with lacunar syndromes are independent at 6 months) means that inclusion of large numbers of these patients dilutes the number of end points in trials, necessitating a larger sample size. Can lacunar strokes be excluded by clinical criteria? The answer is certainly “yes,” but this requires a change in the approach to initial clinical evaluation. The reliance on numerical neurological impairment scales lends an unjustified pseudoscientific respectability to the determination of trial eligibility. Stroke scales were not designed to differentiate lacunar from cortical strokes, and since such scales emphasize motor function, lacunar strokes readily fulfill trial entry criteria. The Oxfordshire Community Stroke Project (OCSP) classification has been less popular with trialists because it lacks a numerical component, but unlike stroke scales, it is widely used clinically because its syndromic description is clinically meaningful. In practice, trials such as those of lubeluzole have often supplemented standard stroke scales with nonnumerical assessments for subgroup analyses. The OCSP provides a well-defined and familiar framework and proved valuable in the Chlomethiazole in Acute Stroke Study (CLASS), where benefit was seen in total anterior circulation strokes despite an overall negative result. The ongoing trial of chlomethiazole contrasts with the fate of lubeluzole, where subgroup analysis foundered on the qualitative and undefined “clinical global impression” of stroke severity. The CLASS results also highlighted limitations of the OCSP in the differentiation of lacunes from small MCA cortical strokes, indicating a need for further development to adapt to a trial setting. The unusually poor prognosis of small-vessel strokes in the NINDS trial also suggests a need for greater refinement of classifications in the hyperacute stroke patient. However, the OCSP is a practical means of tightening clinical entry criteria to ensure that only patients with moderate to large cortical MCA strokes are included—the patient group in whom there is a rationale for neuroprotection.

Imaging should now supplement clinical identification of patients with large MCA strokes, and it promises additional important benefits. Positron emission tomography (PET) has identified patterns of blood flow and metabolic derangements not detectable by clinical examination, with profound prognostic implications. Only around one third of patients presenting 5 to 18 hours after onset have evidence of an ischemic penumbra potentially salvageable by neuroprotectives (using a working definition of blood flow that is significantly reduced but not absent, and preserved metabolism): in these patients, clinical outcome is variable, therefore perhaps not fixed. In two thirds, PET indicates patterns associated with uniformly poor or good outcome (no residual flow or metabolism and spontaneous reperfusion, respectively). These patterns could not be predicted by clinical evaluation. More practical imaging modalities are now widely available and can provide similar identification of a penumbra, whether defined by blood flow (using HMPAO-single-photon emission CT [HMPAO-SPECT], perfusion-weighted MRI [pMRI], or xenon CT) or metabolic disturbance (diffusion-weighted MRI). Even CT, whose value is traditionally thought to be limited to exclusion of hemorrhage, identified very early low-density changes probably signifying irreversible tissue damage—the CT equivalent of severe ischemia without penumbra—in the ECASS trials. Phase 2 (and probably also ultimately phase 3) neuroprotective trials could, and should, further refine entry criteria by including only large MCA infarcts with imaging evidence of penumbra. This approach may also permit more flexible inclusion criteria. Defining an arbitrary time window for trial entry ignores evidence of wide interindividual variation in the duration of the penumbra. In ECASS there was no difference between the 0 to 3– to 3 to 6–hour cohorts with respect to the incidence of CT changes of irreversible ischemic damage, and cerebral blood flow studies further support the clinical observation that in some patients the penumbra is gone by 1 hour while in others it remains present at 24 hours or more. Redefinition of time windows by imaging may compensate for the higher proportion of patients excluded through absence of a penumbra.

In addition to determining trial eligibility, imaging also has potential as a surrogate end-point. While clinical end-points must ultimately define the value of new treatments, “proof of concept” for neuroprotection remains absent. The standard stroke trial end point, functional outcome at 3 months, is subject to numerous uncontrolled factors, including comorbid disease, secondary complications of stroke, adequacy of secondary prevention, social circumstances, and availability of physical, speech or occupational therapy. The larger the trial, the more “noise” generated by variation in these factors among centers. Shorter follow-up periods, although ignoring the role of neuronal plasticity in functional brain recovery after stroke, may enhance the ability to detect the effects of acute interventions by eliminating much of this noise. This should be supplemented by developing objective end points, such as comparing final infarct volume on conventional CT or MRI with the volume of initial ischemia (using the individual patients as their own controls) to serve as a surrogate marker for histological evidence in placebo-controlled human trials. Some trials (eg, citicholine) are beginning to explore this methodology.
The possible financial implications of restricted entry criteria for trial sponsors in the pharmaceutical industry—through the need to maintain a large trial network for longer periods, shorter patent life span, and restricted applicability of treatment to a subgroup of stroke patients—must be considered. However, this strategy may permit smaller phase 2 trials with longer time windows, enhance dose selection (potentially obviating the need for multiple phase 2 studies), and increase confidence in a biological treatment effect before proceeding to efficacy trials. Moderate or large MCA ischemic strokes account for around 50% of all cases, a substantial market in its own right.

In summary, we believe that the failure of neuroprotective trials to date demands reappraisal of methodology by clinicians. Stroke is so heterogeneous that it is naive to expect one intervention to help all patients, and in attempting to prove efficacy in all patients before showing it in any, we risk losing (and may already have lost) treatments that are highly effective for the specific pathophysiological derangements in better-defined patient groups. Selecting a target patient population consistent with a drug’s preclinical activity is feasible with clinical assessment, refined by imaging. It is vital to develop logical strategies to maximize the certainty that a drug has biological effects in the target population at the selected dose before proceeding to definitive clinical trials, which must continue to use functional outcome measures. The use of surrogate imaging markers after shorter follow-up is presently the best candidate strategy. In effecting changes of this type, the stroke trial culture developed over recent years must alter. Appropriate bridging trials using the methods suggested will reduce patient recruitment dramatically at each center, with increased effort required to apply clinical and imaging techniques stringently. Failure to address these issues now risks the premature abandonment of drugs in development for stroke, with the ultimate losers being our future patients.

References
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