Neuroprotection for Acute Stroke
Making Clinical Trials Work

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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
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evidence of wide interindividual variation in the duration of
penumbra. In ECASS there was no difference between the
vasal ganglia and white matter. Almost all neuroprotectives
work via receptor-mediated or intraneuronal mechanisms of
uncertain relevance to glia 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 antici-
pated 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 nu-
merical 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 empha-
size 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 refine-
ment 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 prog-
nostic implications. Only around one third of patients pres-
enting 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 metab-
olism and spontaneous reperfusion, respectively). These pat-
terns 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 emis-
sion CT [HMPAO-SPECT], perfusion-weighted MRI [pM-
RI], 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 irrevers-
ible 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– and 3 to 6–hour cohorts with respect to the incidence
of CT changes of irreversible ischemic damage, and cere-
bral blood flow studies further support the clinical observa-
tion 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 ab-
sence 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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