Recommendations for Clinical Trial Evaluation of Acute Stroke Therapies

Stroke Therapy Academic Industry Roundtable II (STAIR-II)

Abstract—The development of therapies for acute ischemic stroke has achieved a few notable successes and, unfortunately, many unsuccessful efforts. Many valuable lessons for the future assessment of new acute stroke therapies can be gleaned from the positive and negative prior trials. Phase I and II trials must be carefully designed and implemented to derive relevant, valuable information needed to proceed to phase III trials with promising interventions. The phase III trial should evaluate drug efficacy in an appropriately targeted stroke population evaluated by a meaningful and reliable outcome measure. Combinations of various types of stroke therapies will likely be increasingly assessed in future trials that are designed and implemented by cooperative efforts between the pharmaceutical industry, government agencies, academic advisors and clinical investigators. The chances for future success in demonstrating efficacy with acute stroke therapies will be enhanced by carefully conceived, scientifically based clinical trials. The recommendations contained in this document may help to focus attention on how to achieve the goal of developing an expanding number of a effective and safe acute stroke therapies. (*Stroke*. 2001;32:1598-1606.)

Key Words: clinical trials ■ stroke, acute ■ therapy

The development of new therapies for acute ischemic stroke remains difficult, time consuming, and expensive. The process requires a carefully coordinated plan that encompasses an understanding of the fundamental mechanisms underlying focal ischemic brain injury, the development of drugs that act on these processes, preclinical evaluation of these drugs in appropriate animal models, and, finally, evaluation in well-designed clinical trials. Although there have been many pivotal efficacy trials, only 3 have yielded results that have been considered positive because of a clinically and statistically significant outcome.[1–3] However, many valuable lessons can be gleaned from both negative and positive studies.

The Stroke Therapy Academic Industry Roundtable (STAIR) met previously to discuss the preclinical issues for the optimal development of new acute stroke therapies. This group made a series of specific recommendations about performing preclinical assessments of potential stroke therapies that would support recommendations for introducing novel of new therapies into man for the treatment of acute stroke.[4] The group reconvened to discuss various aspects of the design of clinical trials for promising new acute stroke drugs, focusing on the design of both initial and pivotal clinical trials of single and combination therapies for acute ischemic stroke.

Importance of Phase I/II Trials in Acute Stroke

Rigorously designed phase 3 (pivotal efficacy) trials are required to evaluate the clinical benefit of potential therapies for acute ischemic stroke. Prior to the design of these large-scale studies, smaller phase I (initial first in man studies without therapeutic benefit, typically with healthy subjects and defining maximally tolerated doses) and phase II (dose range–finding studies exploring efficacy or surrogate end points in patients with the potential to benefit from treatment) trials are necessary to define both the safety profile of a given therapy and to establish a dose range for efficacy.[5] Late phase II studies usually address an hypothesis of biological activity of a drug (proof of concept) but are not usually sufficiently powered to determine conclusive efficacy.[6]

All phase III trials of neuroprotective agents for acute stroke and many of the thrombolytic/recanalization studies conducted thus far have been negative with regard to the primary outcome measure. Methodological flaws in the phase I and phase II trials on which these were based and suboptimal design or execution may have contributed to the negative results. The logical extension of these arguments is that a definitive statement regarding lack of efficacy for some of these agents is, therefore, not possible. Did the trial not succeed because the study was not sufficiently powered or the therapeutic window was not adequately defined so that a drug effect could be detected with a reliable degree of certainty? Or did the trial not succeed because the drug does not work in man? The parameters listed in Table 1 should be considered and addressed in phase I and II studies in order to proceed to phase III. Although the phase I and II portions of a drug development program may not be able to adequately

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TABLE 1. Considerations for Designing Phase IIb Stroke Trials

1. Route of administration
2. Dose range
3. Duration of treatment
4. Time from stroke onset to initiation of treatment (a key variable)
5. Pharmacokinetic profile
6. Side effects and their frequency (with attention to side effect management)
7. Interactions with other commonly used medications
8. Drug distribution to the proposed site of action
9. Refinement and identification of the target population (eg, drugs without preclinical evidence of activity in white matter ischemia should not be studied in patients with subcortical stroke or even large cortical events with attendant subcortical injury)
10. Obtain evidence measurement of therapeutic activity by evaluation of clinical and/or surrogate markers (hints of potential effectiveness)

address all of these issues, as much information as possible should be obtained before proceeding to phase III. Clinical inclusion/exclusion criteria should be selected with the expectation that patients treated in phase II will be similar to those enrolled in phase III. Examples of such criteria should include time to treatment, the age range of patients to be studied, minimal/maximal ranges of neurological deficit severity, stroke subtype, and concomitant medications. Placebo-controlled, blinded, randomized trials are necessary, even at this early stage.

End Points in Phase IIb Studies

Selection of the primary study end point(s) is among the most important considerations in the design of phase II and phase III studies. The choice depends on both the disease under study and the drug's expected mechanism of action and effect.[7] Several end points can be included in these phase II studies. For example, recanalization therapies administered within 3 hours may be more likely to return patients to near normal, whereas these same treatment administered later may be unlikely to completely reverse the patient's neurological deficit. Thus, a modified Rankin scale score of 0 or 1 was a more appropriate treatment goal in the NINDS rt-PA Stroke Trial, in which treatment was given within 3 hours of the stroke, compared with the ECASS II and PROACT II studies, in which therapy was initiated up to several hours later.[2,8]

Study end points should be easy to measure, reproducible, valid, clinically meaningful, and resistant to bias.[9] They should also detect clinically relevant differences with the smallest possible sample size. This is problematic for phase II studies in which the power of an end point to detect a treatment effect may be limited.

End points for phase II trials can be selected on the basis of previously positive studies, such as the NINDS rt-PA Stroke Trial. Unfortunately, there are no positive neuroprotective trials to provide such vital information. Positive data for neuroprotection has primarily come from animal model studies, in which the usual outcome measure is infarct size in the middle cerebral artery (MCA) territory, commonly evaluated within 1 week after the onset of experimental ische-

mia.[10] It would be advantageous to have information about the natural history of placebo-treated patients, and this information should be available through pooling of control data derived from previous clinical trials of similar patients. These data could be made available through a common, industry-supported database. Caveats about the pooling and use of such data are, however, warranted, because many variables that may affect outcome are likely to also play a role in the placebo response rates, eg, time window, clinical characteristics, or stroke severity.

Measurements of Drug Activity

The phase IIb study should select an end point most likely to reflect the activity of the treatment under consideration, recognizing that this may not always be the most clinically relevant measure. The goal is to optimize the chance of detecting a biological effect with as few patients as possible. The most sensitive measure might be clinical or radiographic, although later efficacy trials will require measurement of a clinically meaningful outcome.[11] For example, measurement of cerebral infarction volume by CT at 24 hours or at 3 months after stroke was not as sensitive as the various clinical end points in the NINDS rt-PA Stroke Trial, although the magnitude of the effect of treatment on infarct size was in the same direction as the measured clinical effects.[12] The reasons for this discrepancy are complicated but illustrate the limitations of using imaging end points as surrogate markers of outcome in efficacy trials.

One way to identify sensitive end points for acute stroke therapy trials is to explore existing databases derived from prior studies. This approach was recently employed with the NINDS rt-PA Stroke Trial database using Classification and Regression Tree (CART) methodology.[13] This method attempts to select measure(s), either clinical or radiographic, that best separate 2 treatment groups. A list of the most sensitive end points from Part A of the NINDS trial was then tested in Part B of the trial to determine which would require the fewest number of patients to detect significant differences. This approach may be most applicable to future recanalization studies in which therapy is initiated within 3 hours from onset. The selected measures may or may not be applicable to recanalization studies with interventions at later time points and, similarly, may or may not be applicable to neuroprotective trials. Another approach to selecting a trial end point measure would be to use a global outcome that incorporates several accepted and validated scales. This approach was used in Part B of the NINDS rt-PA Stroke Trial but was in part based on positive findings in Part A. It may be possible to combine the methodology of CART and the global outcome approach to develop end points with the greatest sensitivity for phase IIb trials, although this remains speculative.

Types of End Points

Impairment scales (eg, the NIH Stroke Scales, Canadian Neurological Scale, Scandinavian Stroke Scale, and the European Stroke Scale) may be the most sensitive to change and have the greatest capacity to differentiate between treatment groups, which makes them particularly useful for phase

II studies. Subsections or modified versions of these scales emphasizing cortical dysfunction may be preferred for studies of drugs that primarily affect gray matter and the cerebral cortex, although this concept remains to be validated.

In addition to measurements of impairment (body dimension), measures reflecting disability (activities dimension) and handicap (participation dimension) should always be included in phase II and phase III trials, even if they are not the primary outcome measures. Scales such as the Barthel Index, Rankin scale, and Stroke Impact Scale reflect these other levels of functioning. Experience gained in the use of these scales in early clinical development and the data obtained can then be used to estimate with greater precision sample sizes that may have a greater possibility to detect a drug effect in a phase III trial.

In vivo evaluation of ischemic damage or activity can be assessed by determining the extent of cytotoxic edema by diffusion-weighted MRI (DW-MRI) in relation to extent of hypoperfusion on perfusion-weighted MRI (PW-MRI) or by infarct size on delayed CT scan.[14] The comparison of DW- and PW-MRI images may help select patients who might benefit from treatment by providing a radiographic index of the extent of the penumbra, currently inferred on the basis of the amount of time elapsed from the onset of stroke symptoms. Additionally, the evolution of ischemic lesion volume on DW-MRI at baseline to T2 lesion volume on days 30 to 90 may provide a measure of drug effect in a relatively small sample size.[14] This concept is being explored but has not yet proved to be a superior tool for the selection of patients for inclusion and evaluation in stroke trials.[15]

The change in infarct size from a baseline CT or MRI is likely to be a better approach than measuring the final differences in infarct volume between treatment groups. Obtaining a baseline CT volume early after an acute stroke is difficult and thus limits this approach; DW-MRI overcomes this limitation and thus offers the possibility of determining a change in volume from baseline. Another limitation of this approach is that previous studies suggest there may be only moderate correlations between imaging end points and functional outcome. For example, the NINDS rt-PA trial demonstrated that the relationship between CT volume of infarction and clinical outcome was weak.[12] The most convincing surrogate outcome measure in multiple sclerosis (MS) drug trials has been MRI-measured plaque volume.[16] MS involves small multiple white matter lesions in scattered locations rather than a local critical mass of acute brain injury (often gray and white matter) causing stroke-related symptoms in stroke. The correlation coefficients relating lesion volume with disability measures in MS were only 0.23 to 0.33 versus 0.31 to 0.54 in acute stroke.[17]

Other markers of ischemic injury may be plasma levels of various substances released into the circulation from injured brain, including neuron-specific enolase, S-100, and thrombomodulin, among others. For thrombolytic therapy or mechanical recanalization, ultrasound or angiographic findings with contrast angiography, MR angiography, or CT angiography may provide surrogate markers of in vivo drug activity by measuring rates of recanalization.

Concept of Surrogate Measures

Surrogate measures should be easy to perform and reproducible, should not interfere with other necessary treatments or assessments, and should be sensitive to changes induced by therapeutic intervention. As reviewed above, detection of biological activity, the so-called proof-of-concept in phase IIb trials, is encouraged before proceeding to phase III studies. Thus, the ideal surrogate marker of drug activity (ie, indicator of biological activity as opposed to functional outcome) should not only provide an assessment of a therapy's direct impact on the targeted pathological process ischemia, but may also accelerate drug development and reduce cost.

PROACT-I provides a good example of how a surrogate outcome might be employed in a phase IIb trial.[18] In this study, recanalization of the M1 and M2 segments of the MCA at 2 hours after initiation of treatment was the primary end point. The use of a radiographic marker for recanalization is a surrogate for clinical outcome, because opening of an occluded blood vessel may ultimately correlate with an improved clinical outcome, as was demonstrated in PROACT-II.[2] The use of this surrogate also demonstrates a potential problem with surrogates in that recanalization rates at delayed time periods may not correlate with a favorable clinical outcome. The use of surrogate markers of drug activity could also be considered in neuroprotection trials, for example, concentrating on the changes in the radiographic extent of ischemic injury.

Duration of Follow-Up

Duration of follow-up for clinical end points (functional outcome) does not need to exceed 3 months in typical phase IIb trials, and shorter periods may be possible. A shorter time period will likely reduce variation in clinical outcome due to subsequent events unrelated to the study and thus permit a chance to accurately assess functional outcome and safety of drug treatment.

Publication

Investigators should seek agreement with the sponsoring organizations to ensure timely review of the data and publication of the results, regardless of whether the outcomes are positive or negative, because the results can provide insight into acute stroke and help to refine future acute stroke therapy trials. Medical journals should encourage the publication of negative trials so that the information contained in these trials is publically disseminated. A well-thought-out publication policy can help to focus the agreement of timely publication and appropriate authorship.

Phase III Clinical Trials

Large, pivotal, efficacy trials are required to provide convincing evidence of benefit, to better define the safety and tolerability profile, and to ultimately form the basis of the dossier required for review and approval by regulatory authorities. Such large phase III trials are a critical step in the process of successful drug development and must be designed with great care. Currently, only 3 phase III clinical trials in acute ischemic stroke have demonstrated statistically significant benefits in favor of the intervention.[1–3] Two of these

TABLE 2. Considerations for Designing Phase III Acute Stroke Trials

1. Dose selection based on preclinical and phases 1 and 2 data
2. Time window for initiation of drug
3. Patient selection based on mechanisms of action
4. Outcome measures: one type of primary outcome or a global assessment
5. Severity of stroke population to be studied
6. Length of follow-up period
7. Use of surrogate markers to provide support of drug efficacy
8. Prespecification of covariate analyses
9. Fostering of appropriate and effective relationships between sponsors, academicians, and investigators

successful acute stroke treatment trials had a very narrow time window to enrollment: 3 hours in both the NINDS rt-PA Stroke Trial and the North American Ancrod trial. Three other intravenous rtPA trials with longer time windows (5 to 6 hours) did not achieve the prespecified primary end point, despite a trend toward efficacy, supported by a recent meta-analysis of thrombolytic trials.[8,19,20] The third positive acute stroke trial, PROACT-II, initiated intra-arterial therapy with prourokinase within 6 hours of stroke onset in a modest number of highly selected stroke patients, all of whom had angiographic documentation of a proximal MCA occlusion.[2] Many phase III trials of neuroprotectants have been carried out, but none have demonstrated a significant beneficial effect as measured by the primary outcome measure.[21] None of these neuroprotective trials were limited to a 3-hour window after stroke onset, with the typical upper time limit for enrollment being 6 to 8 hours or even longer after stroke onset. Additionally, none of the neuroprotective trials were restricted to a homogeneous population of stroke patients, as was the case in PROACT-II. Many valuable lessons for designing better acute stroke trials in the future can be derived from both the few positive trials and the large number of negative trials. These lessons should be used in combination with information obtained from the phase II trial(s) of new agents to optimally design phase III trials that have a high likelihood of delivering unambiguous results (ie, demonstrating a treatment effect if the agent is active or, conversely, establishing lack of efficacy for inactive agents).

A number of important decisions must be made when considering how to best design, organize, and perform a phase III acute stroke trial. These considerations are presented in Table 2. Importantly, the design of a phase III trial should take into account the mechanism of action for the drug being studied. For example, it is becoming apparent that the mechanisms associated with the development of ischemic injury in white matter are distinct from those associated with gray matter insult.[22] If a neuroprotective drug does not have a protective effect on white matter ischemic injury, then patients with small-vessel, subcortical strokes that are primarily confined to the white matter are not likely to benefit. The phase III trial for this drug should exclude patients with subcortical strokes who can be identified by clinical criteria, brain imaging, or both.[23] For thrombolytic trials, drugs designed to restore circulation in medium to large cerebral vessels or the microcirculation are less likely to be of benefit if blood flow has already been restored. Therefore, vascular imaging techniques such as xenon-enhanced CT, perfusion CT, CT angiography, single-photon emission CT, and perfusion MRI/MR angiography may be useful to identify patients with compromised microcerebral or macrocerebral blood flow in future thrombolytic trials.[24,25] Ultrasound techniques may be useful for identification of patients with medium- or large-vessel obstruction in a clinical trial.[26]

The time window chosen for patient enrollment and the dose(s) to be given are key elements in trial design for phase III. The time window for patient enrollment should reflect data from preclinical models and experience from the phase II trial(s). It has been hypothesized that it is difficult to extrapolate the observed time window for drug effects from animal stroke models to stroke patients. However, if the drug to be studied in a phase III trial reduces infarct size only shortly after stroke onset in permanent occlusion rat models, only a restricted time window should be considered for a human trial. If there are additional positive data using a longer time window in nonhuman primates, this would also be reassuring that a longer time window might be appropriate for a phase III trial. If in the phase II trial there is suggestive evidence of clinical or imaging benefit within a selected time window for initiating therapy, then selecting a similar time window for phase III is supported. As a general rule, a phase III trial should be designed so as to choose a time window that enrolls patients as soon as possible after stroke onset to maximize the chances for detecting a treatment benefit.[27] If the drug is shown to have clinical benefit in a phase III trial with a short window, it would be ethical and clinically meaningful that subsequent studies could be done to determine whether a more delayed time window in appropriately selected patients is efficacious. Once the time window for enrollment has been chosen, investigators should be strongly encouraged to enroll patients as quickly as possible after stroke onset. One mechanism to assure that a more even distribution occurs over the allotted time window is to employ forced stratification of enrollment by time. This approach was successfully used in the NINDS rt-PA Stroke Trial and is an optimal model for use in other trials attempting to balance randomization within an allowed window of treatment time. Irrespective of drug mechanism of action, it is highly likely that the earlier the initiation of therapy the more likely that clinical improvement will occur. Incentives to investigators can be considered to enhance early enrollment, or the trial can be designed with stratification by time of enrollment.

As with time window considerations, the dose(s) of drug to be used in a phase III should reflect data concerning the tolerability, safety, and efficacy of the agent in preclinical and preliminary human studies. Ideally, the dose(s) to be tested should achieve plasma and central nervous system levels in animals that are within the predicted levels of efficacy and are shown to have a tolerable safety profile in phase I and II studies. Consideration should be given to studying >1 dose in the phase III trial to help define a dose-response relationship and to possibly identify a minimally effective dose.

Another important consideration is selection of an appropriate patient population for phase III trials. A lower age limit of 18 years is commonly used but may be reconsidered in light of the drug's mechanism of action. The upper age limit can be determined on the basis of data concerning tolerability, pharmacokinetic handling, and metabolism of the drug. Adequate numbers of patients of both sexes should be enrolled. A vital consideration is the range of baseline stroke severity to be included in the trial. Recent trial results demonstrate that patients with very mild baseline deficits (eg, National Institutes of Health Stroke Scale (NIHSS) scores of <6 to 7) have a high rate of spontaneous improvement to normal or near normal by 90 days.[28,29] Additionally, severely affected patients with NIHSS scores >20 to 22 had a very low rate of full recovery when treated within the 3-hour time window used in the NINDS rt-PA Stroke Trial, although these patients still had a better outcome than patients treated with placebo.[11] Patients with severe baseline deficits may become functionally independent if treated with an acute therapy but are unlikely to have a full recovery. Including stroke patients with very mild or very severe stroke will likely make detection of treatment effects difficult, because the mildly affected patients will likely have a large placebo response rate and the severely affected patients may have only a small therapeutic effect. Therefore, the likelihood of detecting a clinical benefit would be increased if study enrollment is limited to patients with moderate baseline deficits (NIHSS scores between 7 and 22).

Stroke subtypes may also be an important consideration, depending on the intervention's mechanism of action. For example, as discussed previously, if the mechanism of action of the drug to be studied precludes white matter effects, then patients with-small vessel, subcortical white matter strokes should be excluded by clinical and/or imaging criteria. Patients with brain stem strokes may be difficult to assess by the commonly used impairment scales, as these were designed primarily for use in the setting of hemispheric strokes. Patients with primary intracerebral hemorrhage should usually be excluded or removed a priori from the intention to treat analysis unless there is reason to believe that the intervention would be both safe and efficacious in this group. Covariate analyses should be specified a priori for important variables such as baseline severity; age; concomitant use of rtPA; use of heparin; development and management of medical complications such as fever, hyperglycemia, blood pressure management, or electrolyte disturbance; poststroke antithrombotic therapy; concomitant drug use; and the intensity of poststroke rehabilitation. Standardized management of likely side effects of the study medication should be included in the study design.

Choosing the most appropriate end point and when it should be measured are vital issues for phase III trial design. In prior trials, measures of impairment, disability, and handicap have been used. All 3 types of end points have advantages and disadvantages. Choosing how to define a positive outcome with a particular rating scale can also be difficult. For example, with the modified Rankin scale (a global disability measure), the difference between a score of 1 versus 2 may be subtle, (ie, no significant disability versus slight disability).[30] In the ECASS-II trial,[8] the primary outcome measure was the proportion of patients who achieved a modified Rankin scale score of 0 to 1 at 90 days. The difference between the rtPA- and placebo-treated patients was not significant. However, a post hoc analysis that used a modified Rankin score of 0 to 2 as the definition of a successful outcome demonstrated a significant difference in favor of the rtPA group. Thrombolysis administered later after stroke onset may, therefore, be less likely to return patients to normal or near-normal function but still may reduce death or dependency. The GAIN trials[31] of a glycine antagonist used a trichotomy analysis, which avoids some limitations associated with selecting a single division of a functional outcome scale (ie, the Barthel Index).

As discussed, one potential way of avoiding reliance on a single outcome measure is to use the global statistic approach.[32] With the global statistic, simultaneous testing of treatment effects on multiple, predefined outcome measures is performed. This type of analysis was used in the second part of the NINDS rt-PA trial and evaluated treatment effects on 4 outcome measures: the modified Rankin scale, the Barthel Index, the Glasgow Outcome Scale, and the NIHSS.[1] Although each individual outcome measure demonstrated a significant difference, the global test showed the most robust treatment difference between rtPA and placebo patients. In addition to clinical scoring scales, imaging end points could be included among the outcome measures used in the global test. In future phase III stroke therapy trials, careful consideration should be given to using the global test as the primary outcome measure with individual decisions about what specific outcome measures should be included for the drug to be used in the trial.

Currently, 90 days after stroke onset is typically used as the primary end point to measure outcome. Choosing an earlier time for evaluating the primary end point of the trial may help to avoid confounding effects unrelated to the study drug, such as late medical complications, recurrent stroke, or imbalances in the use of prolonged rehabilitation services and other interventions that might alter the long-term outcome of stroke. Follow-up studies can be performed to evaluate late treatment effects. For drugs that primarily have restorative effects after acute stroke, a 90-day end point may be insufficient and a more delayed time point more appropriate.

Combination Therapy Trials

The potential benefits of combination therapy are to achieve a synergistic effect of 2 or more drugs and/or to reduce toxicity by decreasing the dose(s) of the medications. The risk is of untoward toxicity due to drug-drug interactions. Both the scientific and practical complexities of designing stroke trials are compounded by the requirements of a combination therapy trial. For the purposes of this discussion, it is assumed that appropriate outcome measures have been established and that any proprietary issues have been resolved. From a design standpoint, the pharmacological properties of the drugs to be tested are then critical, with the design of the phase III combination study predicated on obtaining critical preclinical, phase I, and phase II clinical data.

It can be difficult to predict the combined efficacy and toxicity of drugs given in combination. A variety of preclinical study designs could be used to address the problem. The most rigorous, but also the most costly and labor intensive, would be to vary the dose of each drug in combination (ie, each dose of drug 1 would be given with each dose of drug 2, with the ranges determined by dose effect studies with each drug given alone). A second design is to pick the maximally effective dose of one drug and then test this in combination with varying doses of the second drug. Again, serum levels could be used to help choose an appropriate dosage range in phase I studies. Depending on the drugs to be studied, issues related to the duration of treatment and dosing intervals (both relative to the onset of cerebral ischemia and relative to each other) would also need to be established. There may be a need to evaluate both the maximal degree of neuroprotection that can be achieved and/or the maximal duration of the treatment window.

Typically, clinical dose escalation studies (phase I) are performed to identify the highest tolerable dose of the drug to be tested. In these studies, the dose is increased until significant toxicity develops. In preclinical studies, it is useful to have carefully determined the relationships between drug dose, plasma/tissue concentration, and efficacy. The design of clinical dose-escalation studies is simplified if preclinical studies show a plateau in benefit at higher doses. In this case, a phase I clinical study, carried out to test the safety and tolerability, can simply increase the dose until the theoretical serum/tissue level is reached, thus narrowing the dosage range for phase II studies. A phase II study would then be carried out to determine that a plateau in response had been reached (ie, to determine whether there is a consistent biological response to the intended regimen). If that is the case, erring on the side of choosing too high a dose would have limited or no effect on efficacy. In contrast, an inverted U– or bell-shaped dose-response curve indicates that there is diminishing benefit after a maximally efficacious dose is reached, usually because higher doses produce toxic side effects. Depending on the shape of the curve, this may require a narrow dosing range. These phase II studies may be facilitated by the use of innovative "adaptive" designs or other novel statistical approaches.[33,34]

The discussion thus far has focused on the case in which 2 novel drugs are to be tested in combination. From a practical standpoint, the problem of study design is somewhat simplified when one of the agents has already been demonstrated to be efficacious on the basis of phase III human trial data. This drug regimen then becomes the standard therapy, with the second drug an "add on." In preclinical, phase I, and phase II studies, the dose of the proven drug is held constant and the dose-escalation is carried out only for the second medication. However, possible issues related to dosing intervals and the duration of therapy remain, as well as drug-drug interactions with regard to metabolism, pharmacokinetics, and pharmacodynamics.

Another scenario may occur in which 2 drugs have individually been assessed in phase III studies but neither has proven efficacious (or in which human data are available for at least one of drugs to be studied). The goal of combined therapy would be to seek a synergistic effect of the combination that could not be detected when each drug was tested separately. If critical preliminary data are missing, they need to be obtained before the combination therapy study can be conducted. However, the design of the combination study should be facilitated by the availability of the extensive data obtained for the individual phase III studies.

Finally, the probable mechanism(s) of action of the drugs needs to be considered. For example, one potential avenue of therapy might be to administer a putative neuroprotective agent in combination with, before, or after a thrombolytic drug. For rtPA, the dose and timing have been provisionally established and constitute the standard therapy. A combination of 2 neuroprotective agents acting through differing mechanisms represent another potential therapy. For example, a glutamate antagonist could be coupled with a free radical scavenger. This type of trial would represent a formidable undertaking, but by careful attention to the principles discussed above, a rationale study design should be possible.

Preliminary preclinical and clinical studies of combination therapy have been completed or are in progress. Lyden and colleagues[35] have studied the combination of a glutamate antagonist (MK-801) plus a gamma-aminobutyric acid type A agonist (muscimol) in rats after cerebral embolism. When given 5 minutes after the onset of ischemia, reduced doses of the 2 drugs given in combination appeared to be neuroprotective; however, more detailed dose-response data needed to be obtained. In a second study,[36] this combination of neuroprotectives appeared to extend the time windows of the drugs compared with either given alone and blocked toxic vacuolization seen in the retrosplenial and cingulate cortex after MK-801 treatment. Thus, increased efficacy with decreased toxicity may be possible by using different neuroprotective agents together.

There are several potential reasons for considering combining a thrombolytic drug with a neuroprotective agent. First, neuroprotective therapy initiated before or during the administration of a thrombolytic might extend the time period that the ischemic penumbra remains salvageable, leading to a higher proportion of patients with better outcomes.[36,37] A preliminary phase II study would be complex in that both the dose and timing (before or after initiation of tPA) of the neuroprotective agent would need to be systematically varied (the dose and timing of tPA are based on the NINDS trial). Diffusion/perfusion MRI, MR angiography, and other imaging technologies may prove helpful in a phase II study in selecting patients likely to benefit from this approach and for providing preliminary biological efficacy data.[38]

Another potential reason to combine a thrombolytic with a neuroprotective agent would be to extend the time window for intravenous tPA beyond the 3-hour limit that is based on the currently available data. The coadministration of a neuroprotective agent could lead to a reduced deficit and better outcomes with longer treatment window.[39] This approach would need to overcome concerns of increasing bleeding complications with increasing intervals between the onset of stroke symptoms and the administration of a thrombolytic. Therefore, the first approach would be favored initially.

A third target of combined thrombolytic and adjunctive therapy is secondary "reperfusion" injury.[40] The mechanism(s) of this injury are uncertain, but may include microvascular occlusion, inflammation, the release of cytokines, the generation of oxygen free radicals, apoptosis, and other forms of delayed neuronal death. Preliminary laboratory data suggest that combination therapy aimed at reducing reperfusion injury may extend the period of effective thrombolysis.[41] The issues related to the design of phase II and then phase III clinical studies are similar to those previously discussed.

Two preliminary clinical studies of the combination of tPA and a neuroprotective agent have been reported. The first was a study of lubeluzole and tPA.[42] A suggestion of benefit was observed in patients with a major clinical stroke syndrome. Although there was no benefit of the combination, the study was halted prematurely by the sponsor because of issues unrelated to the progress of the trial. The second was a safety study of clomethiazole and tPA in 200 patients.[43] Nevertheless, these data suggest that the combination appeared safe and that the conduct of a study of this type is feasible. The FDA has generally wanted pivotal phase III combination studies to include a factorial design. The successful design of these phase III studies of combination therapies will depend on the adequacy of preclinical, phase I, and phase II data, as well as the ethics of randomizing patients to the placebo arm of the factorial design in the face of an approved therapy.

Study Logistics

A well-designed protocol, poorly implemented, is a suboptimal trial. The selection of centers, facilitation of patient recruitment, and quality control are, therefore, important considerations, all of which need to be optimized for a successful outcome. A number of choices must be made in selecting study sites. First, it must be determined whether the study will be national or international. This decision may have regulatory authority implications. If an international study is planned, major international regulatory agencies should be contacted to help coordinate and unify study design. There are also significant variations in practice patterns between countries, especially related to the approach to acute stroke (eg, time to presentation, use of specialty care, availability of specific brain imaging techniques). Second, the choice of enrolling patients exclusively in academic centers versus regional or community hospitals can impact the types of patients seen.

The clinical and research experience of investigators and clinicians at participating sites must be considered. Investigators with limited experience in clinical trials may be more likely to become concerned if there is a small clustering of adverse events at their site. This can be disruptive to recruitment and lead to unwarranted concern among referring physicians. (In addition, potential bias must be considered.) Investigators not willing to randomize all patients qualifying for the study should probably not participate in the trial. Alternatively, appropriate algorithms for enrolling patients that minimize bias should be used. There is also a potential for bias in the evaluation of end points (especially if there may be clinical clues to the therapy, such as bleeding or confusion). Potential referral bias (ie, preferentially referring

or not referring patients with a particular condition even though they meet the inclusion and exclusion criteria) may be minimized. For example, those with a strong belief in the utility of anticoagulation for acute stroke may be less likely to refer someone into a trial of heparinoids, if the patient has a clear cardioembolic stroke. Not only do these types of biases cast the results of the trial into question, but they may also reduce the intended study population, which could limit the trial's power to address clinically relevant primary and secondary analyses.

There is an important interaction between the sponsor and investigators. Once a trial design has been established, direct interactions between the sponsor and the investigators at participating centers should be made optimal by determining the most efficient manner of interaction. An autonomous steering or executive committee can help in the interaction between the sponsor and individual sites for issues related to study design and execution, safety, and interim data analysis. The appropriate balance of members should be based on prior experience with trial design and execution. The steering committee should be aware of and sensitive to the concerns of the sponsor, which are most easily resolved by including appropriate individuals from the sponsor.

Assessment of outcome in a clinical trial can be only as good as the data collected. In trials, data are collected from many sources that may vary widely in both type and quality across different centers. At every stage of data collection, methods are needed to help ensure the data are accurate and secure. Examples of quality control methods include monitoring by outside reviewers, duplicate entry of data into computerized files, and consistency checking of the data to detect out-of-range values and biologically impossible combinations (eg, a left carotid territory stroke cannot produce left body weakness).

Quality control, trial performance, end point evaluation, and patient safety are concerns usually addressed by subcommittees specified in the protocol for a clinical trial. A steering committee and separate safety committee (data and safety monitoring board) are essential. Depending on the trial, other committees (eg, publications and end points) may also be required.

The steering committee should have more than a simple advisory role. A partnership should exist between the sponsor, investigators and academic members of the steering committee. All should share in their dedication to good science and the successful execution of the trial. Consultants and advisory boards should include individuals with experience in the designs and execution of clinical trials, as well as providing practical experience in the management of acute ischemic stroke protocols.

An independent safety committee must ensure that patients are not being put at excessive risk. As part of their analyses, the safety committee may have occasion to review data, which includes information about how patients were treated (ie, whether they received an active medication and the dose). The results of these analyses (and even whether they are performed) should be kept separate from the steering committee, sponsor, and investigators to avoid introducing bias into the trial.

Conclusion

The design, implementation, and conduct of clinical trials for acute ischemic stroke are challenging, time-consuming, and expensive tasks. They require close cooperation between the sponsor (typically, industry or a government agency), academic advisors, and the investigators who actually carry out the study. It is important that each part of this triumvirate be involved at every stage of the organization of the clinical drug development process and that good cooperation be established to ensure the design and performance of optimal trials with the greatest possibility to safely and fairly evaluate the drug being tested. Additionally, regulatory agencies should be consulted at various stages in the drug development process to insure that existing regulatory guidelines are met. An agreement should be reached between an industrial sponsor and the academic/investigator participants that the trial results will be presented at an appropriate public meeting and submitted for publication, even if the results are negative.

The STAIR group recognizes that the field of stroke research is evolving and there is much room for new approaches to designing and testing new therapies. The recommendations contained in this document will likely become obsolete with additional experience. However, they summarize the current thinking of the STAIR group on this topic.

Appendix

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Acknowledgments

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