Original Contributions

Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN)
An Adaptive Dose-Response Study of UK-279,276 in Acute Ischemic Stroke

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Background and Purpose—UK-279,276 (neutrophil inhibitory factor) reduced infarct volume in a rat middle cerebral artery occlusion reperfusion model. ASTIN (Acute Stroke Therapy by Inhibition of Neutrophils) was an adaptive phase 2 dose-response–finding, proof-of-concept study to establish whether UK-279,276 improves recovery in acute ischemic stroke. The prime objective was to determine the dose that gave a clinically relevant effect in patients.

Methods—A Bayesian sequential design with real-time efficacy data capture and continuous reassessment of the dose response allowed double-blind, randomized, adaptive allocation to 1 of 15 doses (dose range, 10 to 120 mg) or placebo and early termination for efficacy or futility. The primary end point was change from baseline to day 90 on the Scandinavian Stroke Scale (ΔSSS), adjusted for baseline SSS, aiming for a 3-point additional mean recovery above placebo.

Results—Nine hundred sixty-six acute stroke patients (887 ischemic, 204 cotreated with intravenous tissue plasminogen activator; mean baseline SSS score, 28; range, 10 to 40) were treated within 6 hours of symptom onset. Mean ΔSSS was approximately +17 points of improvement on SSS for the overall evaluable population. There was no treatment effect for UK-279,276 (posterior probability of futility, 0.89). The trial was stopped early for futility. Post hoc analysis indicated a mean 1.6-point additional improvement on ΔSSS in the tissue plasminogen activator–treated subset (credible interval=0.5, 2.6). UK-279,276 was generally well tolerated, with no increased incidence of infections.

Conclusions—UK-279,276 did not improve recovery in acute ischemic stroke patients but was devoid of serious side effects. The adaptive design facilitated early termination for futility. (Stroke. 2003;34:2543-2548.)

Key Words: dose-response relationship, drug ■ neuroprotection ■ neutrophils ■ research design

In experimental stroke models, inflammation contributes to cerebral ischemic injury.1 This begs the question of whether modulating inflammatory response may improve functional recovery in stroke patients.2 A number of molecules altering leukocyte infiltration into the ischemic region reduce infarct size in transient middle cerebral artery occlusion (MCAO) rat stroke models.3 Two inhibitors of leukocyte adhesion to the endothelial wall, R6.5 (Enlimomab) and Hu23F2G (LeukArrest), have previously been studied in stroke patients. Safety concerns led to discontinuation of the clinical development programs in both cases.4,5

UK-279,276 (neutrophil inhibitory factor), a recombinant glycoprotein with selective binding to the CD11b integrin of MAC-1 (CD11b/CD18), reduced neutrophil infiltration and infarct volume in transient (2-hour) rat MCAO models when administered within 4 hours after onset of ischemia.6 In a thromboembolic rat stroke model, UK-279,276 reduced infarct size only in combination with tissue plasminogen activator (tPA) while prolonging the efficacy “time window” for tPA from 2 to 4 hours.7 In a phase 2a safety study, UK-279,276, when administered to acute stroke patients, was well tolerated over a wide dose range.8 In particular, there was no increased incidence of infections, which is a theoretical concern of neutrophil inhibition. UK-279,276 showed a nonlinear pharmacokinetic profile. The duration of >90% CD11b/CD18 saturation was dose dependent and varied from 1 to 15 days. We hypothesized that acute ischemic stroke patients treated with UK-279,276 would show improved neurological recovery through inhibition of neutrophil migration. The prime objective of ASTIN (Acute Stroke Therapy by Inhibition of Neutrophils) was to explore the dose response of UK-279,276 in acute ischemic stroke patients and to determine the correct dose to be taken in future confirmatory efficacy studies. A Bayesian design with sequential adaptive treatment allocation and an early termination rule was used, allowing termination of the trial at the earliest time point at which either futility or efficacy was established.9

Received April 2, 2003; final revision received May 9, 2003; accepted June 24, 2003.

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A list of the members of the ASTIN Study Investigators appears in the Appendix.

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Stroke is available at http://www.strokeaha.org DOI: 10.1161/01.STR.0000092527.33910.89
Subjects and Methods

Study Design
This was a multicenter, double-blind, dose-response study with randomized adaptive allocation to 1 of 15 doses of UK-279,276 (dose range, 10 to 120 mg) or placebo. An automated fax system provided real-time data input/output, receiving Scandinavian Stroke Scale (SSS) scores for each patient at baseline and follow-up visits (days 7, 21, 90) and faxing back dosing instructions within minutes after receiving baseline information. Treatment allocation occurred centrally, with a computer algorithm determining the “optimal” dose for minimizing the expected variance of the response at the ED$_{50}$ (minimal dose achieving near maximal efficacy). In a sequential setup, patients were randomized either to placebo (at least 15% of patients over the course of the trial) or the optimal dose, given the latest information about the dose response. A termination rule based on bounds of posterior probability was used to recommend cessation of recruitment after either futility or efficacy was established. The protocol required data from a minimum of 500 evaluable patients before a recommendation of termination for futility could be endorsed by the Independent Data Monitoring Committee (IDMC) or from a minimum of 250 evaluable patients before a recommendation of termination for efficacy could be endorsed. The maximum sample size was set at 1300 patients. Simulations characterized the behavior of this design for different dose-response curves and conditions. Simulating flat dose responses, the median sample size before cessation was 661, with a <5% false-positive rate. For sigmoid dose-response curves with 3-point additional benefit on SSS, 85% of simulations correctly stopped for efficacy (median sample size, 595); with 4 points the power was 97% (median sample size, 320). The study received approval from independent ethics committees and was conducted in accordance with guidelines for good clinical practice and the Declaration of Helsinki.

Patients
Patients had to be previously independent, aged >50 years, and present within 6 hours after onset of symptoms of an acute stroke with baseline SSS score of 10 to 40. Concomitant tPA treatment was allowed if administered in accordance with local regulatory and ethics committee regulations. Exclusion criteria were as follows: impaired consciousness, premenopausal status in women, fixed-eye deviation with hemiplegia, seizure since onset of stroke, temperature >38°C, concurrent infection, and any condition or treatment at baseline confounding efficacy or safety assessments. Patients previously treated with UK-279,276 were excluded. The “evaluable population” was defined as the set of patients with ischemic stroke (CT verified) who were alive at day 90.

Study Treatment
To obtain equidistant increments of duration over which >90% saturation of CD11b was achieved and an absolute range from 0 to 11 days, the following doses of UK-279,276 were used: 10, 16, 22, 27, 33, 38, 45, 52, 59, 67, 76, 84, 96, 108, and 120 mg. Twenty-milliliter vials contained 0, 1, or 3 mg/mL of UK-279,276. Active drug and placebo were identical in appearance. Two vials were allocated to each patient. A dose instruction fax specified volumes between 10 and 20 mL to be transferred from each vial into a 50-mL syringe. The syringe was topped up with 0.9% saline to 50 mL. Through this procedure, investigators and pharmacy were blinded to the dose they prepared. Study drug was administered as a single intravenous infusion over 15 minutes. All centers administered standard care in accordance with European Stroke Initiative guidelines.

Trial Committees
Independent Data Monitoring Committee
Three stroke clinicians and a statistician received efficacy and safety data, including weekly updates of the probability of the trial warranting termination for futility or efficacy. The IDMC could remove doses with an unacceptable safety profile and could stop the study with endorsement by the Steering Committee if there was evidence of substantial harm, efficacy, or futility.

Steering Committee
An executive steering committee monitored the conduct of the study and reviewed center performance, in particular door-to-needle time for ASTIN study drug (recommended goal, <90 minutes).

Outcome Measures
The primary efficacy end point was change from baseline to day 90 ($\Delta$) on SSS, adjusted for baseline SSS score in surviving patients. Patients who died before 90 days were excluded from the primary analysis because of difficulty in deciding on an imputed meaningful day 90 SSS score in this group. Secondary efficacy end points included change on the National Institutes of Health Stroke Scale (NIHSS) and day 90 Barthel Index and modified Rankin Scale in all patients. Videotapes and training sessions on outcome measures (SSS, modified Rankin Scale) before and during the trial were intended to reduce interrater variability. Center selection criteria included extensive prior experience in acute stroke trials and NIHSS certification. Safety parameters included routine hematology and clinical chemistry examinations and measurement of C-reactive protein, immunoglobulins, and complements C$_{3}$ and C$_{4}$. Serum antibody responses to UK-279,276 were collected on day 90.

Statistical Analysis
Primary Efficacy End Point
During the trial a computer algorithm continuously reassessed the dose-response curve. A normal dynamic linear model (NDLM) was applied to all $\Delta$SSS data of evaluable patients to estimate the dose-response relationship. Patients who died were not included in this model. The NDLM fitted a normal linear regression at each dose, allowing only small changes in the regression parameters between neighboring doses, thereby ensuring smoothness. During the course of the study the computer algorithm corrected only for baseline SSS. In the final analyses the following prespecified covariates were added: age, tPA therapy, and onset-to-treatment time. Copenhagen Stroke Study data suggested that placebo subjects on average improve by 10 points on the SSS, with SD of 12. The study was sized to detect an additional mean treatment effect of 3 points on $\Delta$SSS. Analyses using the NDLM were to present posterior estimates and 95% posterior credible intervals (CrI) of the dose-response curve, the minimal dose that yields near maximal efficacy (ED$_{95}$), and the effect over placebo at the ED$_{95}$.

Longitudinal Model
To allow the dose allocation system to be updated before a patient’s day 90 scores became available, a longitudinal model was used, built from the Copenhagen Stroke Study database, to estimate preliminary day 90 scores for eligible patients. Once available, true scores would be substituted for the estimates. After sufficient trial data were available, the longitudinal model was continuously updated through SSS data collected from within the study.

Termination Rule
A sequential stopping rule operated such that each time the posterior estimate of the dose-response curve was calculated, the estimate of the effect over placebo at the ED$_{95}$ was also evaluated. A lower 80% CrI boundary (1 sided) of >2 points on $\Delta$SSS or an upper boundary (1 sided) of <1 point on $\Delta$SSS would indicate that the study should be stopped for efficacy or futility, respectively. During the course of the study, primary end point data were captured in real time. The dose-response relationship and termination rule were continuously reassessed with the use of specifically written C+ software run by Tessella plc.

After an early termination, all outstanding follow-ups were to be collected and used in the final analysis to produce a dose-effect curve on $\Delta$SSS data and to assess the probability for showing the predefined efficacy threshold of futility or efficacy.
Secondary Efficacy Analyses
The NDLM was also applied to NIHSS data. The modeling approach using the NDLM on stroke scale data was complemented by traditional analyses comparing pooled dose groups (10 to 33, 38 to 67, and 76 to 120 mg) against placebo. Modified Rankin Scale and Barthel Index data, split into the categories dead or poor outcome (<55), moderate outcome (60 to 90), and good outcome (≥95) at day 90, were analyzed with the use of ordinal logistic regression techniques, with baseline SSS as a covariate.

Mortality
Logistic regression analyses and a Cox proportional hazards model were used to estimate the overall dose effect on mortality by fitting dose as continuous and categorical effects.

Results
Nine hundred sixty-six patients were randomized and treated between November 2000 and November 2001, of whom 887 had an ischemic stroke (92%), and 204 were cotreated with tPA (21%). Figure 1 outlines the trial profile. There were 746 evaluable patients. Figure 2 summarizes patient allocation to treatment arms.

Demographics and baseline characteristics, including risk factors, were similar between groups: mean age was 72 years (range, 36 to 96 years), 43% were female, and 97% were white. Mean stroke severity at baseline was 28 points on the SSS (range, 10 to 40) or 13 points on the NIHSS (range, 4 to 29). Median onset-to-treatment time was 248 minutes (interquartile range, 96 minutes); median door-to-needle time was 140 minutes (interquartile range, 88 minutes).

Clinical Outcome
Mean improvement of the overall evaluable population (placebo and treated) was 17 points on SSS (−7 on NIHSS) from baseline to day 90. UK-279,276 did not produce any statistically significant effect on any of the efficacy variables at any dose or dose category for any of the analyzed populations. The dose-effect curve in Figure 3A (ΔSSS effect over placebo, 95% CrI), as calculated from the evaluable population, is consistent with a flat dose response, as is the point estimate for the ED95 (54 mg; 95% CrI, 2 to +142 mg). The posterior probability of futility was 0.89. Significant covariates of interest were as follows (estimated effect on ΔSSS and 95% CrI in evaluable population): baseline stroke severity (−0.3; 95% CrI, −0.4, −0.2 for each point of increase in baseline SSS), use of tPA (+1.6; 95% CrI, 0.5, 2.6), and age (−0.1; 95% CrI, −0.2, 0 for each year increase in age).

The study was not designed or powered to establish whether there was an interaction between UK-279,276 and tPA. In a post hoc analysis, the dose responses of UK-279,276 for tPA-treated and non–tPA-treated patients were not significantly different (Figure 3B and 3C). When we corrected for the aberrant response of a single patient in the placebo group, the “apparent” tPA interaction disappeared almost completely.

Figure 4 shows the course of the continuously updated probability of futility or demonstration of an efficacy signal of >2 points on ΔSSS over time. The algorithm allowed a conclusion of futility at week 40. As soon as data from 500 evaluable patients were available, the IDMC, in accordance with the protocol, recommended discontinuation of recruitment. The steering committee endorsed and the sponsor acted on this recommendation with minimal delay.

Application of the NDLM to the NIHSS mirrored the aforementioned SSS results: UK-279,276 did not produce any statistically significant effect in any of the NIHSS analyses conducted.

The effect of dose of UK-279,276 was not statistically significant in the ordinal logistic regression analyses on the modified Rankin Scale or the Barthel Index.

**Figure 1.** Enrollment diagram. ITT indicates intention to treat.
Tolerability and Safety
All treatment arms had similar mortality rates: placebo, 15%; 10 to 33 mg, 17%; 38 to 67 mg, 15%; and 76 to 120 mg, 18%. Dose of UK-279,276 was not statistically significant in the logistic regression analyses on mortality. The most common causes of death were pneumonia, cerebral hemorrhage, cardiac failure, and cerebral edema. Sepsis was reported in 1% of patients treated with UK-279,276 and in 1.6% of patients treated with placebo; pneumonia was reported in 12% and 11%, respectively; and urinary tract infections were reported in 17% of patients in both groups.

UK-279,276 was well tolerated at all dose levels. The pattern of deaths, serious adverse events, adverse events, and laboratory test abnormalities was consistent with that expected from a population with acute ischemic or hemorrhagic stroke. There was no dose-dependent increase of adverse events, with the exception of headache (17% in placebo group, 23% in high-dose group).

There was a dose-dependent specific antibody response at day 90 (Figure 5) but no nonspecific antibody response on IgG, IgM, C3, or C4.

Discussion
There are 3 main findings from this study: first, UK-279,276 did not improve outcome in acute ischemic stroke patients on any of the clinical efficacy parameters. Second, UK-279,276 was well tolerated in the population studied and was not associated with increased clinical complications of infection or inflammation. Third, computer-assisted real-time learning about the dose response has been successfully deployed for the first time in a large international stroke study.

The preclinical testing of UK-279,276 had shown a reduction of infarct volume in transient MCAO models but not in animals with permanent occlusion.6 Perfusion status was not
assessed in ASTIN, and a subset of patients with complete vessel occlusions is likely to have been included. Future trials may benefit from imaging technology (eg, perfusion CT, M-mode transcranial Doppler) to assess perfusion over time, either as an entry criterion or as covariate of interest. More recently, UK-279,276 was shown to work in a thromboembolic stroke model, but only in combination with tPA, indicating an enhanced tPA effect at 2 hours and the potential for widening the time window for tPA. While a fifth of patients were cotreated with tPA, ASTIN was neither designed nor powered to establish whether the therapeutic effect or time window of tPA could be extended by modulating neuroinflammation with UK-279,276. In a post hoc analysis, the dose responses of UK-279,276 for tPA-treated and non-tPA-treated patients were not significantly different.

The expectation of this trial was to find a mean increase in SSS improvement of ≥3 points in treated patients. Post hoc analyses indicate that after correction for baseline severity and age, there was a 1.6-point additional improvement in tPA-treated patients. It may be argued that the expectation of finding an effect twice as strong as the actually observed tPA treatment effect might have been overly ambitious.

Has the hypothesis of improving functional recovery in acute ischemic stroke through modulation of inflammatory response been disproved? The absence of evidence is not evidence of absence; the effect size aimed for may have been greater than the effect size achievable with this type of therapy, and the primary measure may not have been sufficiently sensitive to a small drug effect.

Why was the expected average recovery in ASTIN greater than that predicted by the Copenhagen Stroke Study? ASTIN entry criteria may have selected a less severely affected set of stroke patients than the unselected cohort observed in the Copenhagen Stroke Study. ASTIN patients may have been assessed earlier after symptom onset than in the Copenhagen Stroke Study and documented early neurological improvement more effectively. ASTIN data were collected nearly a decade later than the Copenhagen Stroke Study, reflecting changes in stroke management. ASTIN patients were recruited exclusively from acute stroke units and were treated according to European Stroke Initiative guidelines, and the study population contained a considerable subset of tPA-treated patients.

Before a patient’s day 90 score became available, a longitudinal model was used to impute the final SSS score from earlier data. At the start of the study, imputation was based on a longitudinal model estimated solely from the Copenhagen Stroke Study data. There is evidence that the imputed values were positively biased by approximately 5 points (to be discussed more extensively elsewhere). However, after 27 weeks the longitudinal model was updated with data from ASTIN itself. By week 35 the imputed values were no longer biased. It is unlikely that this early bias will have negatively affected the adaptive treatment allocation since bias applied equally to all groups.

Concentrating on survivors for the efficacy analysis, while sensitive, is controversial, but secondary analyses and IDMC procedures considered all patients.

Running a trial with 16 different treatment arms was challenging, both conceptually and logistically. The dose-dependent development of specific UK-279,276 antibodies (Figure 5) is indirect evidence for successful administration of the drug across a wide dose range.

Striving for high data quality was a key priority in designing and implementing ASTIN. Good interactions between individual stroke centers, steering committee, and sponsor, video training on outcome measures, regular feedback on individual onset-to-treatment time performance, and repeated assessments of rater performance on neurological stroke scales helped to achieve this. Future trials may benefit from implementing similar procedures, particularly to reduce interrater variability on clinical end points.

Raters participating in ASTIN were asked to assess videotaped stroke patients on the SSS and NIHSS: the SD was 3.9 for SSS and 1.5 for NIHSS (to be reported more extensively elsewhere). While it is reassuring that ASTIN was able to demonstrate a tPA treatment effect, more stringent efforts to contain interrater variability would have increased the sensitivity to a potential treatment effect and would have decreased the sample size required to make an early termination decision.

A traditional phase 2 design comparing placebo with 3 active doses would have required a total of 1080 evaluable patients to have a power of 80% to detect a 3-point ΔSSS. By deploying a traditional design, the information value would have been reduced from learning about 15 doses and the dose response to exploring only 3 doses.

ASTIN for the first time used real-time learning in a large international stroke trial. The adaptive design efficiently examined the dose response and recommended early discontinuation. With slower recruitment and without the protocol requirement to accumulate day 90 data from 500 evaluable patients before termination for futility, the trial would have stopped even earlier. This methodology has great potential in the design of future phase 2 dose-response–finding studies of neuroprotection and thrombolysis therapies.

Appendix

ASTIN Study Investigators

Independent Data Monitoring Committee

K.R. Lees, Glasgow, UK (chair); K. Asplund, Umea, Sweden; J.M. Orgogozo, Bordeaux, France; D. Spiegelhalter, Cambridge, UK. J. Kirkpatrick, Cambridge, UK, prepared IDMC reports.
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Stroke. 2003;34:2543-2548; originally published online October 16, 2003; doi: 10.1161/01.STR.0000092527.33910.89
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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