UK-279,276, a Neutrophil Inhibitory Glycoprotein, in Acute Stroke

Tolerability and Pharmacokinetics

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Background and Purpose—UK-279,276, a recombinant glycoprotein, binds selectively to the CD11b/CD18 integrin on neutrophils and has the potential to modulate the neuroinflammation associated with acute stroke. After preclinical evidence of neuroprotection, UK-279,276 has entered clinical development. The purposes of this study were to evaluate the safety and tolerability of UK-279,276 and to examine its pharmacokinetics and pharmacodynamics (binding to neutrophil CD11b) in patients with acute stroke.

Methods—This was a multicenter, double-blind, dose-escalation study in 176 patients randomized to a single intravenous dose of UK-279,276 (6 cohorts: 0.06, 0.1, 0.2, 0.5, 1.0, 1.5 mg/kg) or placebo (3:1 randomization within each cohort) within 12 hours of stroke onset.

Results—Age and stroke severity were well balanced across groups, with a mean age of 70 years (range, 39 to 92 years) and moderate baseline stroke severity (mean Scandinavian Stroke Scale score, 36.5 to 43.2; mean National Institutes of Health Stroke Scale score, 6.3 to 8.5). UK-279,276 was well tolerated at doses up to 1.5 mg/kg. There was no evidence of a relationship between dose of UK-279,276 and adverse events or clinical chemistry or hematology laboratory tests, or of an increased incidence of infection-related adverse events with the study drug. A dose-dependent UK-279,276-specific IgG antibody response was observed in patients treated with the 1.0- and 1.5-mg/kg doses. UK-279,276 displayed nonlinear pharmacokinetics across the dose range investigated. The duration of CD11b saturation was dose dependent, with >80% saturation achieved for at least 7 days after treatment with UK-279,276 1.0 and 1.5 mg/kg.

Conclusions—UK-279,276 was well tolerated in acute stroke patients at single doses up to 1.5 mg/kg. Further clinical investigation of UK-279,276 is ongoing. (Stroke. 2003;34:□□□-□□□.)

Key Words: antigens □ neuroprotection □ neutrophils □ stroke, acute □ treatment outcome

Various approaches have been explored to counteract neurotoxicity after cerebral ischemia. However, despite positive preclinical and early clinical results, neuroprotectants such as N-methyl-D-aspartate antagonists and free radical scavengers have so far failed to demonstrate consistent benefits on clinical outcome without deleterious adverse event profiles in clinical trials.1–3

The importance of inflammatory mechanisms in the pathogenesis of neuronal injury occurring after acute stroke is increasingly recognized. The inflammatory response, characterized by local expression of inflammatory cytokines and resulting in chemotactic cytokine release and leukocyte adhesion molecule upregulation, promotes the recruitment and migration of macrophages and neutrophils into the area of ischemic injury.6,7 Polymorphonuclear leukocytes accumulate progressively for at least 24 hours after acute stroke, and these cells remain elevated for ~1 week.8 This accumulation correlates with the severity of the brain tissue damage and poor neurological outcome.8

In a clinical trial, blockage of neutrophil adhesion to endothelium by monoclonal antibodies (Enlimomab) in acute ischemic stroke has been associated with worse functional outcome and an unacceptable number of adverse reactions, mainly fever and infections.9 This is possibly explained by activation of host antibodies by the protein, resulting in activation of circulating neutrophils and complement.10

UK-279,276 blocks neutrophil adhesion by a different mode of action. It is a recombinant glycoprotein, known as neutrophil inhibitory factor, that binds selectively to the CD11b integrin of MAC-1 (CD11b/CD18) predominantly expressed on neutrophils.11 As a result, neutrophil adhesion to endothelial cells is inhibited by UK-279,276,12 preventing...
subsequent migration of the neutrophils into the cerebral parenchyma. In transient (2-hour) focal ischemic models of middle cerebral artery occlusion in rats, UK-279,276 reduced neutrophil infiltration and infarct volume, with a therapeutic time window of 4 to 6 hours after onset of ischemia.\textsuperscript{13,14} Subsequent clinical studies in normal volunteers have demonstrated that UK-279,276 is well tolerated in doses up to 1.5 mg/kg when administered as a single intravenous infusion over 15 minutes; nonlinearity in both the mean maximum observed plasma concentration (C\textsubscript{max}) and area under the concentration-time curve (AUC\textsubscript{t}) was observed, with higher doses associated with disproportionately high C\textsubscript{max} and AUC.

The objectives of this study were to assess the safety and tolerability of UK-279,276 at doses up to 1.5 mg/kg administered within 12 hours to patients with acute stroke and to describe the pharmacokinetic and pharmacodynamic (neutrophil CD11b binding) profiles of the drug in this population.

**Materials and Methods**

**Study Design**

This was a multicenter, double-blind, placebo-controlled, dose-escalation study with central, interactive voice-response randomization to study medication. The study received approval from independent ethics committees and was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from patients or their next of kin before study entry.

**Patients**

Previously independent (modified Rankin Scale score, 0 to 2) male and postmenopausal female patients with acute ischemic or hemorrhagic stroke (within 12 hours of stroke onset) were eligible for entry into the study. Symptoms were required to have been present for at least 1 hour without rapid improvement, and the diagnosis of stroke was confirmed by CT or MRI scan within 7 days of symptom onset. Exclusion criteria were the following: pathology other than cerebral infarction on CT or MRI scan (if imaging preceded enrollment), reduced level of consciousness (Scandinavian Stroke Scale [SSS] score <4), seizure since stroke onset, hypoglycemia or hyperglycemia requiring new intervention (excluding type II diabetes who were temporarily switched from oral hypoglycemic drugs to insulin), signs or symptoms of concurrent infection (eg, urinary, pulmonary), preexisting neurological damage from nonstroke illness, serious allergy or previous toxic response to drugs, other significant concomitant disease likely to affect the safety or tolerability of UK-279,276 (including hepatic or renal impairment), and other significant life-threatening conditions. Patients were also excluded if they had been treated with thrombolytic agents such as tissue plasminogen activator since admission or had participated in any trial of an investigational drug within the previous 3 months.

**Study Treatments**

Study treatment was administered as a 15-minute intravenous infusion prepared by dilution of a sterile aqueous solution of 2.5 mg/mL UK-279,276 with 0.9% sodium chloride to 100 mL before administration. The randomization allocated patients to receive either UK-279,276 (6 cohorts at escalating doses of 0.06, 0.1, 0.2, 0.5, 1.0, and 1.5 mg/kg) or matching saline placebo in a 3:1 ratio within each cohort. A Data Safety Monitoring Committee, comprising 2 investigators, an independent member, and sponsor representatives, reviewed all available data in a blinded fashion after each cohort was filled and approved escalation to the next dose level.

**Outcome Measures**

Patients were hospitalized for at least 7 days after stroke onset, during which time a CT or MRI brain scan was performed to confirm the diagnosis. Vital signs were recorded on admission and at intervals throughout the dosing period. A 12-lead ECG was performed before 1 hour and 1, 3, and 7 days after dosing. Blood samples for hematology and clinical chemistry were collected on admission and 1, 3, 7, 21, and 90 days after dosing. All adverse events (free reporting) were recorded until 30 days after dosing. In addition, blood samples for serum antibody responses to UK-279,276 were collected on admission and 7, 21, and 90 days after dosing. IgG, IgM, A, D, E, and complements 3 (C3) and 4 (C4) were assayed for antibody responses and neutralizing response with enzyme-linked immunosorbent assay and flow cytometry assay.

Neurological status was assessed using the National Institutes of Health Stroke Scale (NIHSS)\textsuperscript{15} and SSS\textsuperscript{16} on admission and 7, 21, and 90 days after dosing by NIHSS-certified investigators. Additionally, at 7, 21, and 90 days after dosing, functional status and disability were assessed with the Barthel Index\textsuperscript{17} and modified Rankin Scale,\textsuperscript{18,19} respectively. Patients who died before day 90 were excluded from analyses. The study was neither designed nor powered to detect differences in efficacy, and no adjustments were made for multiple testing; these assessments were collected for descriptive purposes only.

Blood samples were collected for analysis of UK-279,276 concentrations and CD11b saturation analysis on 9 to 10 occasions up to 21 days after dosing; the specific times depended on the dose of UK-279,276 received. Study site personnel were trained in the initial processing; some sites used a qualified technician to perform the sample handling. Plasma concentrations of UK-279,276 were determined centrally with a dissociation enhanced lanthanide fluorescence immunoassay with a lower limit of quantification of 5 ng/mL. A time profile of CD11b saturation on neutrophils was determined by Cytometry Associates Incorporated using a flow cytometry immunoassay method. Observed reportable parameters were mean CD11b expression and percent CD11b saturation on neutrophils.

**Results**

The study was conducted between March 16, 1999, and January 20, 2000, and included 41 active centers in Australia, Denmark, Finland, France, Germany, Norway, Sweden, and the United Kingdom. One hundred seventy-six patients were enrolled (Figure 1). Two patients did not receive study treatment (1 did not meet entry criteria, and 1 experienced aspiration and developed ventricular fibrillation before drug administration), leaving 174 who received study treatment with either UK-279,276 (n = 131) or placebo (n = 43). All 174 patients were analyzed for safety and tolerability, pharmacodynamics, and efficacy, and plasma samples of all 131 patients receiving UK-279,276 were analyzed for pharmacokinetics. Three patients receiving placebo and 7 patients...
receiving UK-279,276 did not complete follow-up visits; 9 patients died within the 90-day study period; and 1 patient withdrew consent for study procedures 5 days after receiving UK-279,276 1.0 mg/kg for reasons unrelated to the study drug.

Patient demographics were similar in all groups (Table 1). The mean age of the study population was 70 years (range, 39 to 92 years); 105 (60.3%) were male; and all subjects were white. One hundred fifty patients (86%) had ischemic stroke: 34 of the CT/MRI scans were interpreted as normal, and hemorrhagic stroke was confirmed in 13 scans, and infarction was confirmed in 116 of the 173 scans collected. Overall, only 5 patients (2.9%) were treated within 4 hours of the onset of stroke symptoms; 42 patients (24.1%) were treated within 6 hours. Centers involved in this trial had to exclude patients who were treated with thrombolysis and thrombectomy or clinical chemistry laboratory tests related to any dose of study drug. In particular, UK-279,276 administration was not associated with greater likelihood of decreased white blood cell counts (6.1% [6 of 99] versus 11.1% [3 of 27]) or increased C-reactive protein levels (36.8% [42 of 114] versus 32.4% [11 of 34]). Compared with placebo, the incidence of increased blood urea nitrogen was higher in patients receiving

**TABLE 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 43)</th>
<th>UK-279,276, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (range), y</strong></td>
<td>72 (47–87)</td>
<td>65 (41–85)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>23 (53)</td>
<td>11 (55)</td>
</tr>
<tr>
<td><strong>Mean time to treatment (range), h</strong></td>
<td>7.8 (3.4–12.0)</td>
<td>8.7 (4.1–14.4)</td>
</tr>
<tr>
<td><strong>Patients treated &lt;6 h, n (%)</strong></td>
<td>13 (30)</td>
<td>4 (20)</td>
</tr>
<tr>
<td><strong>Stroke type, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>7 (16)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>30 (70)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>4 (9)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>Mean baseline SSS score (range)</strong></td>
<td>40.3 (10–58)</td>
<td>37.2 (11–49)</td>
</tr>
<tr>
<td><strong>Mean baseline NIHSS score (range)</strong></td>
<td>7.5 (1–20)</td>
<td>7.8 (3–17)</td>
</tr>
<tr>
<td><strong>Preexisting disease, n (%)</strong></td>
<td>20 (47)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (14)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>7 (16)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>7 (16)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (14)</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>

There was no consistent clinically relevant trend in hematology or clinical chemistry laboratory tests related to any dose of study drug. In particular, UK-279,276 administration was not associated with greater likelihood of decreased white blood cell counts (6.1% [6 of 99] versus 11.1% [3 of 27]) or increased C-reactive protein levels (36.8% [42 of 114] versus 32.4% [11 of 34]). Compared with placebo, the incidence of increased blood urea nitrogen was higher in patients receiving
UK-279,276 (10.9% [13 of 119] versus 2.6% [1 of 39]). However, there was no clinically relevant effect on the median and 95% confidence intervals for this parameter over time. There was also no evidence of an effect of UK-279,276 on blood pressure, heart rate, or ECG parameters (QRS, PR, QT, or QTc intervals).

Nine patients died within the 90-day study period, and another died on day 92 (mortality rates, 4.6% and 9.3% with UK-279,276 and placebo, respectively). Thirteen patients in the placebo group (30.2%) and 23 randomized to UK-279,276 (17.6%) had at least 1 serious adverse event. Five of the serious adverse events were considered to be related to UK-279,276 (severe hemiplegia 1 hour after dose [0.2 mg/kg], progression of stroke 19 hours after dosing [1.5 mg/kg], severe headache 49 hours after dosing [0.5 mg/kg], hematoma of the right arm/chest wall 5 days after dosing [0.1 mg/kg], and severe bacterial infection 11 days after dosing [1.5 mg/kg]); according to investigator reports, these 5 all resolved with treatment (hemiplegia after 1 month, stroke progression after 9 days).

**Pharmacokinetics and Pharmacodynamics**

The pharmacokinetics of UK-279,276 were clearly nonlinear (Figure 2). C<sub>max</sub> and AUC<sub>1-24h</sub> increased 36- and 168-fold over the 25-fold dose range. Plasma levels >1000 ng/mL were maintained beyond day 7 after the UK-279,276 1.0- and 1.5-mg/kg doses.

After intravenous dosing of UK-279,276, there was rapid onset of binding to CD11b at all doses (Figure 3), achieving levels >80% within 1 hour. The duration of binding to CD11b was dose related: saturation of CD11b >80% was achieved for at least 7 days at UK-279,276 dose levels of 1.0 and 1.5 mg/kg.

**Clinical Outcome**

Patients receiving UK-279,276 had a higher mean change from baseline SSS score on day 90 compared with those who received placebo (Figure 4). With baseline SSS included as a covariate, the adjusted mean change from baseline achieved statistical significance (P < 0.05) only for the UK-279,276 1.0-mg/kg dose. The NIHSS results showed a similar trend.

### Table 2. Incidence of Adverse Events (All Cause) Occurring in >10% in at Least 1 Subgroup

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n=43)</th>
<th>Total (n=131)</th>
<th>0.06 (n=20)</th>
<th>0.1 (n=22)</th>
<th>0.2 (n=25)</th>
<th>0.5 (n=22)</th>
<th>1.0 (n=22)</th>
<th>1.5 (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7 (16)</td>
<td>33 (25)</td>
<td>7 (35)</td>
<td>3 (15)</td>
<td>4 (18)</td>
<td>6 (24)</td>
<td>8 (36)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Fever</td>
<td>10 (23)</td>
<td>25 (19)</td>
<td>9 (45)</td>
<td>4 (20)</td>
<td>3 (14)</td>
<td>3 (12)</td>
<td>2 (9)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (7)</td>
<td>18 (14)</td>
<td>4 (20)</td>
<td>2 (10)</td>
<td>2 (9)</td>
<td>3 (12)</td>
<td>5 (23)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8 (19)</td>
<td>16 (12)</td>
<td>4 (20)</td>
<td>0 (0)</td>
<td>4 (18)</td>
<td>5 (20)</td>
<td>1 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (7)</td>
<td>15 (12)</td>
<td>3 (15)</td>
<td>1 (5)</td>
<td>3 (14)</td>
<td>3 (12)</td>
<td>3 (14)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (7)</td>
<td>10 (8)</td>
<td>4 (20)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (14)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>3 (7)</td>
<td>10 (8)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>2 (8)</td>
<td>4 (18)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (5)</td>
<td>10 (8)</td>
<td>5 (25)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (9)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (5)</td>
<td>9 (7)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>3 (12)</td>
<td>3 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (9)</td>
<td>8 (6)</td>
<td>0 (0)</td>
<td>3 (15)</td>
<td>0 (0)</td>
<td>2 (8)</td>
<td>3 (14)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (7)</td>
<td>7 (5)</td>
<td>3 (15)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>1 (5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1 (2)</td>
<td>7 (5)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (8)</td>
<td>3 (14)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2 (5)</td>
<td>7 (5)</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (8)</td>
<td>3 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (14)</td>
<td>6 (5)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>1 (2)</td>
<td>5 (4)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>3 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pain</td>
<td>0 (0)</td>
<td>5 (4)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Confusion</td>
<td>2 (5)</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>3 (15)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (5)</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>3 (15)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Raised gamma-glutamyl-transf.</td>
<td>1 (2)</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (14)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are numbers (percent).

**Figure 2.** Mean plasma concentrations of UK-279,276 after single doses.
There was no evidence of a trend toward improvement with increasing dose for either the Barthel Index or modified Rankin Scale. Patients receiving UK-279,276 achieved better scores than placebo-treated patients on the Barthel Index and modified Rankin Scale, with the exception of 0.2 mg/kg for the Barthel Index and 0.1 mg/kg for the modified Rankin Scale. The effect was greatest for the 1.0-mg/kg dose.

**Discussion**

The primary objective of this study was to establish the safety and tolerability of a single 15-minute intravenous infusion of UK-279,276 in patients with acute stroke. Overall, UK-279,276 was well tolerated at doses up to 1.5 mg/kg with no dose-dependent increase in any of the adverse events or laboratory tests.

It is conceivable that binding of UK-279,276 to CD11b receptors on polymorphonuclear leukocytes and monocytes may interfere with the ability to mount an immune response to infection. In this study, fever was a frequent adverse event; however, the incidence was similar to that expected in a stroke population20 and was slightly lower in patients treated with UK-279,276 than those randomized to placebo (19.1% versus 23.3%). In addition, there was no increase in the occurrence of infection-related adverse events such as pneumonia, urinary tract infection, or sepsis in patients receiving UK-279,276. These data are particularly important given the results of recent studies with other investigational stroke compounds targeting leukocytes that have shown a significantly higher rate of adverse events, primarily infections and fever, with such agents compared with placebo.9

R6.5 (Enlimomab) and Hu23F2G (LeukArrest) both inhibit leukocyte adhesion to the endothelial cell wall and subsequent transmigration21,22 and have undergone clinical investigation for stroke; however, after disappointing phase III results, the clinical development of these agents has been halted. R6.5 (a murine antibody against endothelial intercellular adhesion molecule 1 [ICAM-1]), Hu23F2G (a humanized anti-CD11/CD18 monoclonal antibody), and UK-279,276 (a recombinant protein that binds selectively to the CD11b integrin) all inhibit neutrophil adhesion via different mechanisms. The increased selectivity of UK-279,276 for neutrophils over other white blood cells in contrast to the alternative approaches may provide a possible explanation for the observed differences in adverse event profiles. This study provides indirect evidence that safety concerns encountered with the anti-ICAM antibody Enlimomab in acute stroke may have been an agent-specific rather than a class effect.

The dose-dependent development of a weak to moderate specific IgG antibody response to UK-279,276 by day 21 requires further investigation. This study showed that by day 90, neutralizing antibodies were detectable in approximately one third of patients randomized to 1.0 mg/kg and one half of those randomized to 1.5 mg/kg. The development of such antibodies in UK-279,276-naive patients should not interfere with its potentially beneficial effect, but reexposure of patients with existing antibodies to subsequent doses of UK-279,276 may increase the risk of allergic reaction and/or result in reduced levels of circulating UK-279,276.

UK-279,276 has been shown in vitro to bind to active neutrophils and block a range of functions mediated by CD11b/CD18.12 In animal stroke models in vivo, continuous infusion of UK-279,276 immediately after transient (2-hour) focal cerebral ischemia significantly inhibited the infiltration of neutrophils into ischemic tissue and reduced infarction volume.13 However, UK-279,276 was not neuroprotective in animal models of permanent middle cerebral artery occlusion4; the present study specifically excluded patients treated with thrombolytic therapy in whom reperfusion is most likely to occur. UK-279,276 was neuroprotective when treatment was delayed until 4 hours but not 6 hours after initiation of occlusion of the middle cerebral artery.14 In this clinical study, UK-279,276 was administered within 12 hours of the onset of stroke symptoms: <5% of patients received study treatment within 4 hours, 25% within 6 hours, 50% within 8 hours, and 75% within 11 hours.

After UK-279,276 administration to animals for 48 hours after ischemia, no neuroprotection was apparent after 7 days, although the same dosing regimen was effective when infarct volume was determined immediately after UK-279,276 cessation.14 This preclinical evidence highlights the importance of blood levels sufficient to block neutrophil function continuously throughout the time course of neutrophil activation. The minimum effective concentration of UK-279,276 has been estimated to be 500 ng/mL on the basis of inhibition of human neutrophils in vitro.12 In the present study, the 2 highest doses of UK-279,276 maintained plasma levels
≥1000 ng/mL for at least 7 days, coinciding with sustained >80% CD11b saturation over the same time period. Modeling of the pharmacokinetic and pharmacodynamic parameters showed that there was no difference between the weight-adjusted dose and the calculated absolute dose in the variability of either plasma concentrations or CD11b binding.

Overall, stroke severity in the population studied was generally mild, with baseline mean NIHSS scores of 6.5 to 8.5 (range, 1 to 23) and SSS scores of 36.5 to 43.2 (range, 8 to 58) across the groups. This was associated with a relatively low mortality rate of 5.7%. The effect of UK-279,276 on outcome measures described here follows a survivor-only analysis, but the study was neither designed nor powered to detect differences in efficacy between the groups, and results on outcome parameters should be interpreted with extreme caution.

In conclusion, UK-279,276 was well tolerated in patients with acute stroke at single intravenous doses of up to 1.5 mg/kg, with no apparent tolerability or safety issues resulting from treatment, despite the theoretical risk of increasing the rate of infection. The pharmacokinetic and pharmacodynamic evaluation showed that UK-279,276 doses up to 1.5 mg/kg achieved plasma levels above the minimum effective dose estimated from human neutrophil inhibition in vitro, sustained for at least 7 days after dosing, in association with persistent >80% saturation of the CD11b integrin. Studies in patients describing the natural history of neutrophil accumulation after acute stroke suggest therefore that at the higher doses, UK-279,276 has the ability to modulate neutrophil accumulation in a sustained fashion over the most critical initial poststroke period.

A dose-ranging phase IIB study of UK-279,276, using an adaptive design and incorporating real-time allocation to doses to determine the effect on neurological function in acute stroke patients, has now been undertaken.

Acknowledgments

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References

UK-279,276, a Neutrophil Inhibitory Glycoprotein, in Acute Stroke. Tolerability and Pharmacokinetics
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