More patients with acute ischemic stroke who received ancrod had good functional status at 3 months

Sherman DG, Atkinson RP, Chippendale T, et al., for the STAT Participants. **Intravenous ancrod for treatment of acute ischemic stroke. The STAT study: a randomized controlled trial.** JAMA. 2000 May 10;283:2395-403.

QUESTIONS

In patients with acute ischemic stroke, is the defibrinogenating agent ancrod safe, and does it improve functional status?

DESIGN

Randomized (allocation concealed*), blinded (patients, clinicians, and outcome assessors),* placebo-controlled trial with 3-month follow-up (Stroke Treatment with Ancrod Trial [STAT]).

SETTING

48 centers in the United States and Canada.

PATIENTS

2613 patients were screened, and 500 (mean age 73 y, 51% men) were included. Inclusion criteria were acute or progressing ischemic neurologic deficit in any vascular territory and treatment start between 30 minutes and 3 hours of symptom onset, although the 3-hour limit was sometimes relaxed. 80% completed their allocated therapy, and follow-up was 99%.

INTERVENTION

Patients received ancrod (n = 248) or placebo (n = 252) as a continuous 72-hour infusion with additional 1-hour infusions at approximately 96 and 120 hours after initial treatment. Ancrod infusion rates were 0.167, 0.125, and 0.082 IU/kg of body weight/h on the basis of initial fibrinogen levels (> 13.23, 10.29 to 13.20, and 2.94 to 10.26 µmol/L, respectively). Fibrinogen levels were monitored. Aspirin, anticoagulants, thrombolytic agents, dextran, or other drugs that might affect the fibrinolytic system were not allowed during treatment. At the end of treatment, standard prophylactic therapy was allowed.

MAIN OUTCOME MEASURES

Favorable functional status defined as survival at 90 days with a Barthel Index ≥ 95 (need for little or no help with activities of daily living). Secondary outcomes were mortality and adverse effects at 3 months.

MAIN RESULTS

Logistic regression, intention-to-treat analyses were done with adjustment for treatment group, study center, age, and pretreatment stroke scale scores. More patients in the ancrod group had favorable functional status at 3 months than did patients in the placebo group (42.2% vs 34.4%, P = 0.04). The groups did not differ for mortality (25% in the ancrod group vs 23% in the placebo group, P = 0.6) or adverse effects (98% vs 99%). The patients in the ancrod group had more asymptomatic intracranial hemorrhage (19% vs 11%, P = 0.01) but fewer venous thromboembolic events (5% vs 10%, P = 0.05). Symptomatic intracranial hemorrhage occurred in 5.2% of the ancrod group and 2% of the placebo group (P = 0.06).

CONCLUSION

More patients with acute ischemic stroke who received ancrod had good functional status (Barthel Index ≥ 95) at 3 months.

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*See Glossary.

COMMENTARY

Ancrod may be effective for acute stroke. Because of borderline statistical significance, the STAT results should be validated, although a positive effect on stroke outcome is consistent with a previous safety and efficacy trial (1).

Comparison of the results of STAT with the U.S. National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (t-PA) study (2) (Table) helps in understanding its relative importance and potential. STAT appeared to have about half the favorable outcome effect of the NINDS study, but this finding could be because patient entry was later on average in STAT, with only 5% of patients enrolled in < 2 hours after stroke onset. The earlier t-PA is given, the more effective it is; greater benefit with ancrod may have been achieved if more patients had been given the drug earlier.

Ancrod may have a better safety profile than t-PA. With t-PA, the hemorrhage rate increases if it is given after 3 hours (3). Despite 16% of patients in STAT being enrolled after 3 hours, the study showed a lower hemorrhage ratio when comparing active drug with placebo than that in the NINDS study or in recent thrombolytic trials. Ancrod, however, is still potentially risky. The European counterpart of STAT, which enrolled patients up to 6 hours after stroke, was stopped early because a planned interim analysis showed that benefit was highly unlikely. Early changes of ischemia on computed tomography (CT) increase the risk for hemorrhage with t-PA, and their detection needs a trained eye. The low rates of hemorrhage in STAT were achieved without screening for early CT ischemic changes. Physicians without CT training could give ancrod; thus, ancrod may be attractive for smaller community hospitals if additional studies establish its efficacy.

Comparison of STAT and NINDS trials

Characteristic	STAT	NINDS
Patients enrolled within 2 hrs	5%	>48%
Patients enrolled after 3 hrs	16%	0%
Barthel Index ≥ 95 (absolute difference)	6%	12%
Barthel Index ≥ 95 (relative difference)	16%	32%
Hemorrhage ratio of active drug vs placebo	2.6	10

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