Intravenous *N*-Acetylcysteine Improves Transplant-Free Survival in Early Stage Non-Acetaminophen Acute Liver Failure

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See related article, Kitzberger R et al, on page 1000 in *CGH*; see CME quiz on page 1162.

BACKGROUND & AIMS: *N*-acetylcysteine (NAC), an antidote for acetaminophen poisoning, might benefit patients with non–acetaminophen-related acute liver failure. **METHODS:** In a prospective, double-blind trial, acute liver failure patients without clinical or historical evidence of acetaminophen overdose were stratified by site and coma grade and assigned randomly to groups that were given NAC or placebo (dextrose) infusion for 72 hours. The primary outcome was overall survival at 3 weeks. Secondary outcomes included transplant-free survival and rate of transplantation. **RESULTS:** A total of 173 patients received NAC (n = 81) or placebo (n = 92). Overall survival at 3 weeks was 70% for patients given NAC and 66% for patients given placebo (1-sided P = .283). Transplant-free survival was significantly better for NAC patients (40%) than for those given placebo (27%; 1-sided P = .043). The benefits of transplant-free survival were confined to the 114 patients with coma grades I–II who received NAC (52% compared with 30% for placebo; 1-sided P = .010); transplant-free survival for the 59 patients with coma grades III–IV was 9% in those given NAC and 22% in those given placebo (1-sided P = .912). The transplantation rate was lower in the NAC group but was not significantly different between groups (32% vs 45%; P = .093). Intravenous NAC generally was well tolerated; only nausea and vomiting occurred significantly more frequently in the NAC group (14% vs 4%; P = .031). **CONCLUSIONS: Intravenous NAC improves transplant-free survival in patients with early stage non–acetaminophen-related acute liver failure. Patients with advanced coma grades do not benefit from NAC and typically require emergency liver transplantation.**

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Acute liver failure is a relatively rare syndrome associated with a high mortality rate and frequent need for liver transplantation. Since the 1950s, trials of therapies to limit further damage or improve hepatic regeneration have failed to show evidence of benefit.[1–6] In recent years, acetaminophen poisoning, either intentional or unintentional, has become the most common etiology of acute liver failure identified both in Europe and in the United States.[7] When given within the first 24 hours after ingestion, *N*-acetylcysteine (NAC) effectively can prevent or minimize liver damage caused by acetaminophen, even after massive overdoses.[8–10]

Treatment with NAC may benefit patients with other forms of acute liver failure,[11] either by improving systemic hemodynamics, tissue oxygen delivery,[12–16] or via other favorable effects on the acutely injured liver.[17,18] No clinical trials using NAC for patients with non-acetaminophen acute liver failure have been performed.[19] In 1998, the Acute Liver Failure Study Group, funded by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, began a registry at 24 participating sites around the United States to better characterize and understand mechanisms of acute liver failure. A prospective, randomized, double-blind, placebo-controlled trial of NAC for patients of acute liver failure not caused by acetaminophen was initiated in late 1998, ending in 2006. This article summarizes the outcomes of this trial.

Abbreviations used in this paper: CI, confidence interval; DILI, drug-induced liver injury; NAC, *N*-acetylcysteine.

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Methods

Objective

The primary outcome measure for this trial was the overall number of patients surviving at 3 weeks after study admission; our research hypothesis was that patients receiving NAC would have a significantly higher overall survival rate than those receiving the placebo. The secondary outcome measures were the number of patients surviving without transplantation and the number of patients undergoing transplantation at 3 weeks after study admission. Our research hypothesis for transplant-free survival was that patients receiving NAC would show higher rates of transplant-free survival. The research hypothesis for transplantation was a 2-tailed test. Because of the extensive experience with NAC for acetaminophen-related liver failure, our original protocol specified the use of 1-sided tests for overall survival and transplant-free survival because it seemed very unlikely that NAC would harm patients in this setting.

Study Population

Detailed prospective data as well as serum, tissue, and DNA were collected on all patients of acute liver failure meeting study criteria beginning in January 1998. Eligibility for the registry included age 18 years and older and evidence of acute liver failure (any degree of encephalopathy and coagulopathy: international normalized ratio $\geq$ 1.5) caused by an illness of less than 24 weeks' duration. Medical histories and clinical and laboratory findings were recorded on case report forms through death, transplantation, or 3 weeks after study admission and at long-term follow-up visits 1 and 2 years after study entry.

Eligibility requirements were the same for both the NAC trial and registry with the following exceptions. Patients were excluded from the NAC trial for known or suspected acetaminophen overdose if they previously had received NAC or if they were determined to have hepatic ischemia (shock liver), liver failure caused by pregnancy, or cancer. Patients with refractory hypotension, septic shock, and those expected to undergo transplantation imminently (ie, in $<$8 h), or those older than age 70 also were excluded. Because all participants were, by definition, encephalopathic, informed consent was obtained from next of kin. The study was approved by the institutional review boards at all participating centers.

Study Design

Randomization was stratified by the standard hepatic encephalopathy (coma) categories (I–II vs III–IV),[20] and by site with a blocking factor of 4. The site pharmacist received the randomization list prepared by the biostatistician (J.S.R.); all study personnel (except the 2 biostatisticians: L.S.H. and J.S.R.) remained blinded throughout the study. After consent was obtained, patients were weighed and coma grade was determined so that the site pharmacist could randomize the patient and prepare the medication.

Response to treatment was recorded carefully, including vital signs, progression of coma grade, and the use of other supportive measures such as mannitol, need for intubation, increase in intracranial pressure in patients with an intracranial monitor inserted, and assessment of adverse events. All other aspects of care conformed to the standard of care at each study site, all of which were liver transplant centers during the study except for one site, which had ready transplantation access nearby.

Study Medication

After randomization, infusion of either 5% dextrose (placebo) or 5% dextrose with *N*-acetylcysteine (Acetadote; Cumberland Pharmaceuticals, Nashville, TN) was begun, with an initial loading dose of 150 mg/kg/h of NAC over 1 hour, followed by 12.5 mg/kg/h for 4 hours, then continuous infusions of 6.25 mg/kg NAC for the remaining 67 hours.

Study Outcomes

The primary outcome of the trial was overall survival at 3 weeks after randomization. To obtain long-term outcomes, we used information gathered by the sites, in addition to the original study data set, censored 365 days after study admission. Secondary outcomes specified in the protocol were transplant-free survival and transplant rate. Two additional secondary outcomes also listed in the original protocol were length of hospital stay and a composite of the number of organ systems failing, using specific definitions for hepatic encephalopathy, evidence for cerebral edema, use of vasopressor or ventilatory support, serum creatinine level ($\geq$300 μmol/L) or bacteremia. Data were reviewed twice yearly by a Data and Safety Monitoring Board and 3 interim analyses were performed, after 57, 113, and 170 patients had been enrolled.

Sample Size

Based on our own prestudy data, overall survival for non–acetaminophen-related acute liver failure in the United States at the start of the trial was estimated at 57%.[1] Assuming overall survival (combining transplant-free plus transplanted and alive) of 57% (25% + 32%) in the placebo arm and a predicted improvement in overall survival to 75% in the treated arm (45% + 30%), 170 patients were targeted for enrollment to achieve 80% power (likelihood of rejecting the hypothesis of equal response rates) with a 1-sided test of proportions at the 0.05 significance level.

Statistical analyses were based on the intention-to-treat principle and involved all randomized patients except for 9 who represented protocol violations (see later).

Statistical Analysis

Univariate analyses were performed for patient demographic and illness characteristics at baseline for

descriptive purposes and to determine their possible influences on the primary and secondary outcomes using the chi-squared or the Fisher exact test, and independent group Student *t* test or Mann–Whitney *U* test as indicated. Additional analyses were performed on the baseline measures to separately compare the entire consented group, the placebo group, and the group of eligible patients who were not consented.

The primary outcome, patients who survived (with or without transplant) vs those who died, and 2 of the secondary outcomes, (1) patients who survived without transplantation vs those dead or transplanted and (2) patients transplanted vs not transplanted, were compared for the 2 treatment groups using chi-squared analysis, Breslow–Day homogeneity of odds ratio test, and the Mantel–Haenszel Common Odds Ratio tests. Results are presented using percentages and two-sided 95% confidence intervals (95% CIs). As stated in the protocol, both overall survival and transplant-free survival were 1-sided tests with the research hypothesis that the NAC group was expected to have higher or equal proportions of survival and transplant-free survival than the placebo group.

Three separate Kaplan–Meier models were developed for the primary/secondary measures censored at 1-year testing for group differences using the log-rank test. A single measure was defined to combine treatment group and coma category into one variable: NAC I–II, NAC III–IV, placebo I–II, and placebo III–IV.

The statistical packages used to analyze the data were SPSS V16 (SPSS Inc, Chicago, IL) and SAS V 9.1 (SAS Software, Cary, NC). Assumptions of all statistical tests were examined (normality, homogeneity of variance, and so forth) because most variables were distributed nonnormally, nonparametric analyses were used to analyze the data. Unless otherwise noted, all statistical tests were 2-sided and a *P* value of less than .05 was considered significant. No corrections to the *P* values were made for multiple comparisons.

Results

Study Population

Among 820 eligible patients at sites with institutional review board approval, 558 (68%) met exclusion criteria (Supplementary Figure 1). Of the remaining 262 patients, 89 were excluded either because consent was refused (46 patients), was unobtainable (34 patients), or, after randomization, because of protocol violations (9 patients). The 9 protocol violations included inadvertent enrollment of 2 prisoners who were removed from consideration once their status was recognized, 1 patient for whom all hospital records were lost, 4 patients who met exclusion criteria but mistakenly were offered participation in the study, 1 patient who underwent transplantation before the first dose of NAC was administered, and 1 patient who was withdrawn because the trial solution turned pink in the intravenous bottle. This harmless dye reaction was considered by the site investigator at the time as evidence of possible bacterial contamination; the patient was withdrawn from the study and given open-label medication. Data on the first 3 protocol violations were not available. For the latter group, 2 of the 6 patients were slated to, or did, receive NAC.

Thus, 173 patients comprised the final study group (Table 1), 92 patients were randomized to receive placebo and 81 patients were randomized to receive NAC. The imbalance in size of the study groups was related to the randomization process whereby patients were stratified by site and coma grade (I–II vs III–IV); not all sites

Table 1. Baseline Characteristics at Enrollment by Treatment Group

	Placebo		NAC		
Categorical variables	% of n = 92	95% CI	% of n = 81	95% CI	χ^2 *P* value
Sex, female	68%	58%–79%	47%	35%–58%	.004
Race, Caucasian	55%	45%–66%	56%	44%–67%	.987
Coma grade I–II on admission	62%	51%–72%	73%	63%–83%	.129

Continuous variables	N	Median	Range	N	Median	Range	Mann–Whitney *P* value
Age, *y*	92	40.5	18–71	81	42	17–69	.682
Weight, *kg*	92	74.4	45–138	81	81	38–178	.066
Symptom to coma, days	91	17	0–69	80	15	0–117	.346
Jaundice to coma, days	86	12	0–65	75	7	0–153	.026
Bilirubin level, *mg/dL*	92	20.3	0.7–62.4	81	22.3	0.7–51.5	.645
Creatinine level, *mg/dL*	92	1.0	0.5–9.5	81	1.3	0.2–6.6	.341
International normalized ratio	92	2.9	1.1–14	81	2.4	1.4–20.1	.258
ALT level, *IU/L*	90	756.5	31–13,100	79	999	13–10,153	.304
MELD	92	33	19–49	81	32	12–57	.673

No differences were observed between the 2 groups except in the time from jaundice to coma and in sex.
MELD, Model for End-stage Liver Disease.

Table 2. Overall Survival and Transplant-Free Survival for Treatment Groups Stratified by Coma Category at Randomization at 21 Days of Follow-Up Evaluation

Outcome	Coma category at randomization	Treatment group		Treatment group by outcome for each coma category, 1-sided *P* value	Overall treatment group by outcome, 1-sided *P* value	Breslow–Day	
		Placebo	NAC			1-sided *P* value	Odds ratio (NAC/Placebo)
Overall survival							
21 days	I–II	75%, n = 56 63%–87%	79%, n = 58 68%–91%	.292	.283	.262	1.28 0.53–3.07
	III–IV	53%, n = 36 35%–70%	48%, n = 23 25%–70%	.645			0.82 0.29–2.34
	Total	66%, n = 92 56%–77%	70%, n = 81 60%–81%				
Transplant-free survival							
21 days	I–II	30%, n = 56 17%–43%	52%, n = 58 38%–65%	.010	.043	.012	2.46 1.14–5.30
	III–IV	22%, n = 36 7%–37%	9%, n = 23 0%–22%	.912			0.33 0.06–1.74
	Total	27%, n = 92 18%–37%	40%, n = 81 28%–51%				

NOTE. Percentage, n, and 95% CIs are shown.

reached a balance point on the randomization lists. During the course of the trial, the project biostatisticians verified the accurate use of the randomization scheme with the site pharmacist before each Data and Safety Monitoring Board meeting. The majority of patients enrolled comprised 4 etiologies: drug-induced liver injury (DILI; n = 45), autoimmune hepatitis (n = 26), hepatitis B virus (HBV; n = 37), and indeterminate cause (n = 41). Patient numbers were reasonably well balanced between the placebo and treatment groups within each etiology. The characteristics of the patients in the 2 groups were similar at enrollment (Table 1), except that the placebo group had a longer median duration between jaundice and encephalopathy than the treated group (12 vs 7 days; $P = .026$) and a higher percentage of females ($P = .004$). The 80 unconsented patients did not differ from the enrolled group (n = 173) or the placebo group (n = 92), except for lower median alanine aminotransferase (ALT) values than either comparison group (both $P < .001$, results not shown). Patients were enrolled at 22 sites over the period of the study, with 12 sites enrolling 8 or more patients (range, 1–19 patients). Five sites enrolled 3 or fewer patients.

Overall, 58 (63%) patients in the placebo arm and 48 (59%) patients in the NAC arm completed 72 hours of therapy (Supplementary Figure 1), and the majority (138 of 173; 80%) of patients received at least 24 hours of treatment. Reasons for early discontinuation included death or withdrawal of support (n = 17), transplantation (n = 36), or side effects possibly caused by the drug (5 total, 4 thought to be caused by NAC).

Study Outcomes

Overall survival at 3 weeks was 70% (95% CI, 60%–81%; n = 81) for NAC and 66% (95% CI, 56%–77%; n = 92) for placebo (1-sided $P = .283$; Table 2). However, transplant-free survival was significantly higher at 40% (95% CI, 28%–51%; n = 81) in the treatment group as compared with 27% for the placebo group (95% CI, 18%–37%; n = 92; 1-sided $P = .043$). When examining transplant-free survival by coma category at randomization (I–II vs III–IV), the largest difference was observed in patients with coma grades I–II: 52% (95% CI, 38%–65%; n = 58) survived in the NAC group as compared with 30% (95% CI, 17%–43%; n = 56) in the placebo group (1-sided $P = .010$). This was not the case for coma III–IV patients, in whom transplant-free survival was only 9% (95% CI, 0%–22%; n = 23) with NAC vs 22% (95% CI, 7%–37%; n = 36) with placebo (1-sided $P = .912$). The odds ratios comparing the treatment groups for transplant-free survival were 2.46 (95% CI, 1.14–5.30) for coma category I–II and 0.33 (95% CI, 0.06–1.74) for coma category III–IV; that is, patients in coma category I–II receiving NAC were 2.46 times more likely to survive than those in the placebo group, whereas those with advanced coma (III–IV) receiving NAC were only 0.33 (95% CI, 0.06–1.74) times as likely to survive as those in the placebo group (Breslow–Day χ^2 [1] = 5.11; $P = .012$). Overall transplantation rates were 32% (95% CI, 21%–43%; n = 81) for NAC vs 45% (95% CI, 34%–55%; n = 92) for placebo ($P = .093$; Table 3).

Survival Analysis

Treatment group/coma category was found to have significantly different survival times using the log-rank test ($P = .007$; Figure 1). Patients in the NAC I–II group were found to have significantly longer survival than the placebo III–IV ($P = .012$) and NAC III–IV ($P = .002$) groups, but not the placebo I–II group ($P = .350$). For the secondary outcome of survival without trans-

Table 3. Transplantation Rate for Treatment Groups Stratified by Coma Category at Randomization at 21 Days of Follow-Up Evaluation

Coma category at randomization	Treatment group		Treatment group by outcome for each coma category, *P* value	Overall treatment group by outcome, *P* value	Breslow–Day	
	Placebo	NAC			*P* value	Odds ratio (NAC/Placebo)
I–II	46%, n = 56 32%–60%	28%, n = 58 15%–40%	.037	.093	.180	0.44 0.20–0.96
III–IV	42%, n = 36 24%–59%	43%, n = 23 21%–66%	.891			1.08 0.37–3.10
Total	45%, n = 92 34%–55%	32%, n = 81 21%–43%				

NOTE. Percentage, n, and 95% CIs are shown.

plant, treatment group/coma category was significantly different ($P = .001$; Figure 2). Patients in the NAC coma category I–II group were found to have significantly longer transplant-free survival time than the other 3 groups (largest $P = .017$). For the other secondary outcome, transplantation, the treatment group/coma category was found to be significant ($P = .025$). Patients in the NAC coma category I–II group were found to have a significantly longer time to transplantation than the other 3 groups (largest $P = .032$; Figure 3). In a subanalysis of the primary and secondary outcomes for patients receiving 4 or more hours or 24 or more hours of infusion, the results were similar to those reported (results not shown).

When overall and transplant-free survival were considered within each of the 4 largest etiologic groups, patients with DILI or HBV showed improved outcomes compared with those with autoimmune hepatitis or indeterminate etiologies (Table 4). For example, transplant-free survival for DILI patients was 58% (95% CI, 33%–83%) for those receiving NAC compared with 27% (95% CI, 8%–46%) for those receiving placebo, and was 40% (95% CI, 19%–61%) for NAC vs 17% (95% CI, 0%–42%) for placebo for HBV patients. Because the numbers in each group were small, we did not draw conclusions or calculate significance based on these analyses.

Use of Acetaminophen

To determine if unrecognized acetaminophen toxicity might have caused some of the indeterminate patients illnesses, sera from 113 patients (those with available samples) were analyzed after the conclusion of the trial using a highly sensitive and specific assay for acetaminophen adducts in serum.[21,22] Three patients in each treatment group had adduct levels strongly implicating high-dose acetaminophen ingestions. A re-analysis ex-

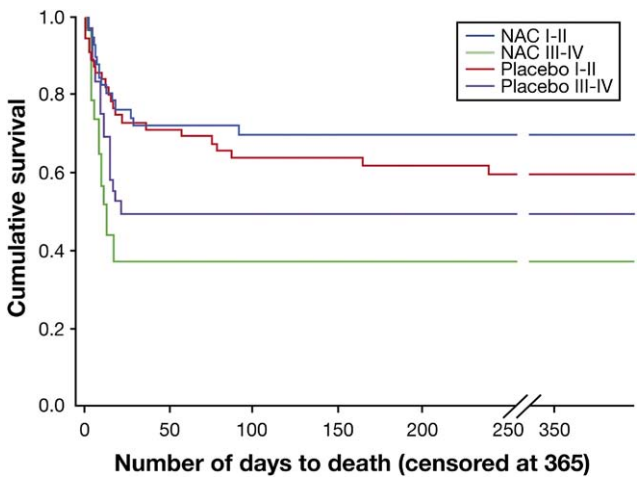

Figure 1. Kaplan–Meier curve for each group (treatment by coma category) was used to show overall survival to 365 days. In separate analyses, patients in the NAC I–II group showed significantly higher survival rates than either placebo III–IV ($P = .012$) or NAC III–IV ($P = .002$) groups. Number of patients with censored data before 365 days: 14 in the NAC I–II, 5 in the NAC III–IV, 12 in the placebo I–II, and 7 in the placebo III–IV groups.

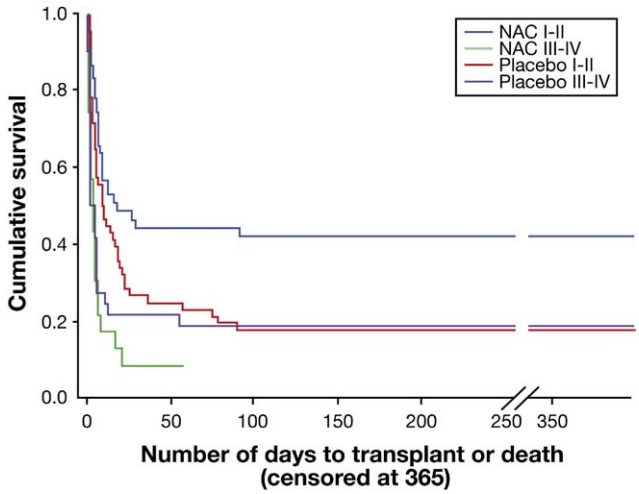

Figure 2. Kaplan–Meier curves for each group (treatment by coma category) showing transplant-free survival to 365 days. Patients in the NAC I–II group showed significantly higher transplant-free survival rates than the other 3 groups (largest $P = .017$). Number of patients with censored data before 365 days: 10 in the NAC I–II, 2 in the NAC III–IV, 5 in the placebo I–II, and 2 in the placebo III–IV groups. Note that 2 patients in the NAC III–IV group were censored, 1 patient at day 34 and the other patient at day 58.

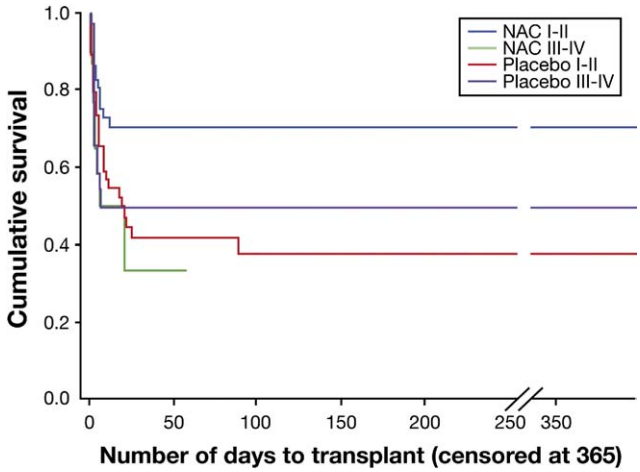

Figure 3. Kaplan–Meier curves for each group (treatment by coma category) showing number of days to transplantation to 365 days. Patients in the NAC I–II group showed significantly longer time to transplantation than the other 3 groups (largest $P = .032$). Number of patients with censored data before 365 days: 10 in the NAC I–II, 2 in the NAC III–IV, 5 in the placebo I–II, and 3 in the placebo III–IV groups. Note that 2 patients in the NAC III–IV group were censored, 1 patient at day 34 and the other patient at day 58.

cluding these 6 patients showed no difference in outcomes or percentage survival for the 2 treatment groups.

Length of Hospital Stay, Number of Organ Systems Failing

In comparing the length of hospital stay among survivors, a trend was observed for NAC-treated patients to have shorter hospital stays (median, 9 vs 13 days; $P = .056$). Comparison of organ system failure(s) between the 2 treatment groups failed to show individual (or total group) significant differences (Supplementary Table 1). This appears to relate to the small number of defined organ failure events occurring during the immediate study period. Progression or regression of encephalopathy between the 2 treatment groups appeared to be similar.

Adverse Events

Adverse events were equal between the groups (Supplementary Table 2); side effects were minimal with no differences in incidence except for nausea and vomiting, present in 14% (95% CI, 6%–22%; n = 81) of NAC-treated patients and 4% (95% CI, 0%–9%; n = 92) of placebo-treated patients ($P = .031$). Although bronchospasm has been reported with NAC, only 1 patient in each treatment group experienced this symptom.

Discussion

There is no established treatment for non-acetaminophen acute liver failure other than liver transplantation. Our study suggests that transplant-free survival was improved by NAC. However, this improvement in survival was observed primarily in those with early stage hepatic encephalopathy: among those with coma grades I–II at admission, 52% receiving NAC survived without transplantation vs 30% survival for those who received placebo. This finding was supported by the survival analyses (Figures 1 and 2).

Advanced coma grade patients showed no benefit from NAC but represented a smaller patient group, half the size of the early coma grade group. Within the advanced coma group, 10% died or were withdrawn from care while still on study medication, 50% died or underwent transplantation by 4 days, and nearly 90% achieved these outcomes by 3 weeks. Among the 100 study patients of all grades listed for transplantation, 67 received a graft, 30 (45%) within 48 hours of study initiation. Twenty-one of 59 advanced coma grade patients (36% overall, 57% of those listed) received a transplant by day 4, compared with 23 of 114 (20% overall, 37% of those listed) with early coma grades, confirming that coma grade at admission determines outcome, and, more specifically, whether a transplant will be obtained and used in rapid fashion. Only 4 additional patients in the advanced coma group were transplanted after day 4, vs 19 additional grafts for those with early grade encephalopathy. The majority of patients recovered after transplantation, although short-

Table 4. Overall and Transplant-Free Survival According to Etiology

	Overall survival		Transplant-free survival	
Etiology	Placebo	NAC	Placebo	NAC
DILI	65%, n = 26	79%, n = 19	27%, n = 26	58%, n = 19
N = 45	45%–86%	58%–100%	8%–46%	33%–83%
Autoimmune hepatitis	67%, n = 15	64%, n = 11	27%, n = 15	9%, n = 11
N = 26	34%–94%	31%–97%	1%–52%	0%–31%
HBV	50%, n = 12	76%, n = 25	17%, n = 12	40%, n = 25
N = 37	18%–83%	57%–95%	0%–42%	19%–61%
Indeterminate	69%, n = 26	60%, n = 15	23%, n = 26	40%, n = 15
N = 41	50%–89%	32%–88%	5%–41%	12%–68%

NOTE. Percentage, n, and 95% CIs are shown. Patients with DILI or HBV appeared to have improved overall and transplant-free survival when compared with those with AIH or indeterminate acute liver failure.

term survival was decreased slightly when compared with patients with chronic liver disease.[23] Thus, high early mortality, rapid transplantation, and excellent early post-transplant survival rates appeared more likely than any possible medical therapy to affect overall survival for those with advanced coma grades. By contrast, patients with early hepatic encephalopathy only reached the 50% outcome point by 10 days. There appeared to be additional benefit beyond 3 weeks in that the differences between the treatment/coma categories observed during the initial 21 days were more significantly different at 365 days. The apparent benefit for those with early encephalopathy suggests that NAC treatment, to affect outcome, must be instituted early in the course of disease.

The overall survival of 66% for the placebo group was 9% higher than the 57% we had predicted. Although the overall registry includes equal numbers of patients in coma grades I–II vs III–IV, and we had predicted equal enrollment of early and late coma grade patients, as noted earlier, twice as many patients with early coma grades were enrolled in the study (66% [114 patients] with coma grades I–II vs 35% [59 patients] with coma grades III–IV). We did not specifically target the early coma grades for enrollment; however, we excluded those considered preterminal or about to undergo liver transplantation. Although the apparent improved overall survival for placebo subjects in all coma grades likely is related to the overrepresentation of early coma grades, improvement in overall survival during the trial period for other reasons, such as improved intensive care, also might play a role.

Establishing prognosis in non-acetaminophen acute liver failure has proven difficult and is confounded by transplantation because this rescue intervention, which affected 40% of our patients, does not allow the true outcome (death or recovery) to occur. We predicted that NAC therapy might benefit patients undergoing transplantation but could not show this. Because short-term outcomes of transplantation hinge on many other factors, such as organ quality and availability, it seems unlikely, in retrospect, that a short-term pretransplant medical therapy would make much difference. The main prognostic factors in 3-week survival for the overall group using multivariate analyses were coma grade and international normalized ratio at admission to the study; these important variables have been noted previously and used by others.[24]

The study groups were well balanced in terms of age, sex, weight, and etiology. Although the placebo patients had a longer apparent duration of illness, the groups were well matched in all other parameters including Model for End-stage Liver Disease scores.[25–27] The imbalance in numbers enrolled in the 2 groups reflected the randomization scheme, which took into account site as well as coma grade using a blocking factor of 4, and did not appear to affect the balance in each group.

Of note, there were relatively similar numbers of patients (range, 26–45) among the 4 main etiologies: DILI, autoimmune hepatitis, HBV, and indeterminate cause. There was a trend for improved overall and transplant-free outcomes among the DILI and HBV patients and for less favorable overall outcomes among those with autoimmune hepatitis or indeterminate cause.

The study occurred over nearly 8 years despite the large number of study sites because of the difficulties encountered with enrollment for this already rare condition: it was necessary to choose only the subgroup that was unrelated to acetaminophen, which represents less than half of all patients with acute liver failure in the United States,[7] then to identify next of kin in a timely fashion and to help them understand both the data registry and the nature of the trial so that informed consent could be obtained. The urgent nature of the study setting and the simultaneous consideration of transplantation often distracted attention from the study. In the early years, competing trials of liver-assist devices and, later, availability of intravenous NAC (Acetadote; Food and Drug Administration approved for acetaminophen poisoning in 2003) also confounded enrollment. Among our registry, 58 non-acetaminophen patients received NAC before consideration for study enrollment despite the lack of evidence regarding its efficacy.

Examining the evolution to secondary end points disclosed a trend toward shorter hospital stays but no other differences between the 2 treatment groups, possibly reflecting that few of our specified outcomes (such as the use of mannitol and intubation) were reached during treatment. There were no changes in mean arterial pressure or urine output during NAC infusion; however, pulmonary artery catheters or other hemodynamic measurements were not mandated by the study and rarely were used. A recent retrospective study using historical controls in pediatric acute liver failure not caused by acetaminophen showed improved transplant-free survival and shorter hospital stays with NAC.[28]

Nausea and vomiting were the only symptoms more frequent during treatment with NAC than in the placebo group. Along with its excellent safety profile, NAC is easy to administer, does not require intensive care, and can be given in community hospitals.

In summary, a significantly improved transplant-free survival at 3 weeks and at 1 year was observed with the use of NAC for the treatment of non–acetaminophen-related acute liver failure, the benefit being confined to those with early hepatic encephalopathy. Extrapolating NAC efficacy to patients with less severe liver injury (eg, coagulopathy without encephalopathy) cannot be made from our study because all study patients were required to show some degree of encephalopathy at enrollment. The use of NAC should not be a substitute for early referral to a transplant center for any patient showing evidence of coagulopathy (prolonged international nor-

malized ratio), regardless of whether encephalopathy is present, because referral ensures that these critically ill patients can undergo urgent transplantation, should it be needed. Based on the present study and its generally favorable safety profile, intravenous NAC should be considered for patients with early stage non-acetaminophen acute liver failure. Additional studies are needed to determine the optimal dose and duration of NAC therapy, predictors of response, and the physiologic basis for these improved outcomes.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2009.06.006.

Appendix

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The authors dedicate this article to the memory of Andres T. Blei, our friend and colleague. Andy was a passionate contributor to the work of the Acute Liver Failure Study Group for nearly 12 years.

Conflict of interest

The authors disclose no conflicts. The statistical analysis of the entire data sets pertaining to efficacy (specifically primary and major secondary efficacy end points) and safety (specifically, serious adverse events as defined in federal guidelines) have been confirmed independently by a biostatistician who is not employed by the corporate entity. The corresponding author had full access to all of the data and takes full responsibility for the veracity of the data and analysis. This was a randomized clinical trial (ClinicalTrials.gov number NCT00004467).

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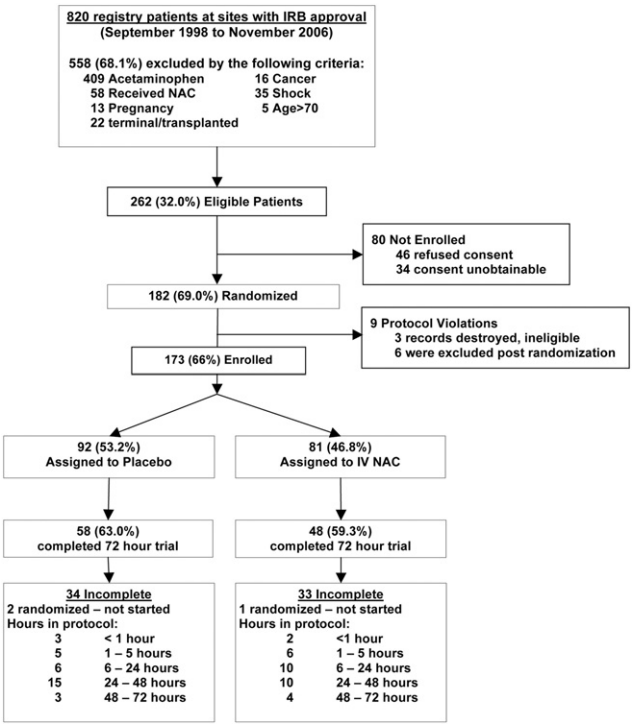

Supplementary Figure 1. Study design. A total of 820 patients were screened, leading to 173 patients enrolled in the final study. IRB, institutional review board; IV, intravenous.