A double-blind placebo-controlled study to evaluate the safety and efficacy of L-2-oxothiazolidine-4-carboxylic acid in the treatment of patients with acute respiratory distress syndrome*

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Objective: Acute respiratory distress syndrome is an abrupt inflammatory illness that involves damage from reactive oxygen species. We examined the efficacy and safety of oxothiazolidine-4-carboxylic acid (OTZ), a free radical scavenger, in treating acute respiratory distress syndrome.

Design: Double-blind, placebo-controlled trial.

Setting: Multicentered study.

Patients: Patients with a $Pa_{O_2}/F_{IO_2} \leq 200$ and bilateral infiltrates on chest radiograph, and requiring mechanical ventilation.

Interventions: We randomized 215 patients to receive OTZ, 210 mg/kg per day every 8 hrs for 14 days or placebo.

Measurements and Main Results: Ventilator-free days (the number of days alive and free from ventilator requirement) during the first 30 days of study were 8.3 vs. 13.5 days for the OTZ and placebo groups, respectively ($p < .001$). Mortality was 30/101 (29.7%) in the OTZ group and 18/114 (15.8%) in the placebo group during the 30-day study period ($p = .014$). This study was terminated prematurely for safety reasons after 215 of the planned 352 patients were enrolled.

Conclusions: OTZ does not improve survival or reduce ventilator time in patients with acute respiratory distress syndrome and may worsen outcome, although mortality in the OTZ group was similar or lower than most similar trials. Alternatively, our results may be best explained by the unusually excellent outcome in the placebo group. (Crit Care Med 2008; 36:782–788)

KEY WORDS: oxothiazolidine-4-carboxylic acid; glutathione; acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a life-threatening inflammatory process. The incidence of ARDS has been variously estimated at up to 150,000 patients (1) in the United States affected annually. In these patients, ARDS develops as a result of injury, either direct (e.g., trauma, bacterial or viral pneumonia, pulmonary trauma) or indirect (e.g., sepsis, multiple trauma, pancreatitis, multiple transfusions, thermal burns) (2). Although there have been significant advances in elucidating the inflammatory mechanisms, the overall 28-day mortality rate for ARDS remains high at 25% to 40% (1). There are remarkably few pharmacologic interventions that have been shown to improve outcome. Current medical management essentially attempts to preserve and restore organ function and to prevent additional organ failure.

Reactive oxygen species may play an important role in the pathogenesis of ARDS, especially those derived from activated neutrophils (3). Superoxides (ions from neutrophils) can be metabolized to hydroxyl radicals, hydrogen peroxide, and hypochlorous acid under appropriate conditions. The resultant injury may be due in part to an overwhelmed antioxidant defense system. Decreases in both lung and whole blood glutathione have been suggested as factors in the elaboration of lung injury (4–10).

Glutathione (L–glutamyl-L-cysteinyl-glycine) is a tripeptide composed of L-glutamate, L-cysteine, and glycine that neutralizes reactive oxygen species and may play an important role in protecting the lung from oxidant injury (11–14). Glutathione synthesis often is limited by the supply of intracellular cysteine, such that providing cysteine in a bioavailable, nontoxic form could have therapeutic value in ARDS. L-2-oxothiazolidine-4-carboxylic acid (OTZ) is a cysteine pro-drug, metabolized to cysteine intracellularly, where glutathione synthesis occurs. Preclinical research demonstrated that OTZ increased glutathione levels in animal models of oxidative stress or chemical means (15; unpublished, Metabolism of [14C]-OTC administered IV to rats. Baxter Report PO067490066, 1991). Dr. Bernard and colleagues (15) reported ARDS patients receiving OTZ demonstrated an increase in red blood cell glu-

tathione on days 3, 7, and 10, as well as shorter intensive care time and trends toward improved survival compared with placebo.

The current study was designed to compare the effectiveness and safety of 14-day therapy with intravenous OTZ, 210 mg/kg per day, to placebo in the treatment of patients with ARDS.

MATERIALS AND METHODS

In this double-blind, randomized, placebo-controlled, multicentered study, patients diagnosed with ARDS were assigned to receive OTZ or placebo. This trial was prospectively approved by the institutional review boards of the participating institutions. Entry criteria for ARDS included a Pao_2/Fio_2 ≤200 mm Hg, infiltrates on chest radiograph involving a minimum of three quadrants, requirement for mechanical ventilation, absence of evidence of left heart failure, and presence of a known ARDS risk factor. Patients must have been enrolled in the study (i.e., randomized) within 24 hrs of meeting the chest radiograph criterion and within 48 hrs of first meeting the Pao_2/Fio_2 criterion. The first dose of study drug must have been administered within 4 hrs of enrollment. See Appendix for inclusion and exclusion criteria.

Because this study was conducted in critically ill patients on mechanical ventilation and typically receiving sedation and/or anesthesia, a family member or other person with legal responsibility for the patient granted informed consent.

Patients received intravenous OTZ at a dose based on two prior Phase II studies (15; unpublished, Determination of the biologically effective or maximally tolerated dose of procysteine injection for the prevention of multiple organ dysfunction in subjects with sepsis syndrome. Procysteine Investigator Brochure. Boeringer Ingelhelm internal report, 1997), administered as 70 mg/kg every 8 hrs for 14 days, or a placebo (5% dextrose) identical in appearance. Patients weighing >100 kg were dosed at a maximum of 100 kg. By protocol, the study drug was discontinued 48 hrs following cessation of mechanical ventilation. In human patients, OTZ was readily eliminated from the plasma after intravenous administration; OTZ is metabolized to cysteine intracellularly (unpublished).

Statistical Methods

Sample Size. The estimated sample size for this study was based on the expected difference in average number of days alive and off ventilator (ventilator-free days, or VFDs) between the OTZ and placebo groups. It was planned that 352 patients would be recruited into this trial.

Primary End Point. The primary end point for the study was VFDs during the first 30 days after study enrollment. Secondary efficacy end points were: mortality, new onset of organ dysfunction, and days in intensive care and hospital. Patients were enrolled from May 1997 until March 1998. For the intent-to-treat analysis, the primary efficacy variable, VFDs were compared between the two treatment groups using a two-way analysis of variance, with main effects for treatment and etiology of ARDS risk factor (pneumonia, sepsis non-pneumonia, and all other factors). For the subgroup of intent-to-treat patients with ARDS risk factor of pneumonia, sepsis non-pneumonia, and all other factors, the treatment comparisons were performed using a one-way analysis of variance with treatment as the main effect. The mean changes from baseline in each of the organ function variables at treatment end point and study end point were assessed by a two-way analysis of variance model, which included main effect terms for treatment and ARDS for the intent-to-treat patients. The mean change within each treatment group was further analyzed by a paired Student's *t*-test. Both statistical and medical criteria were applied to determine the safety of OTZ. Adverse experiences, classified using the Coding Symbols for Thesaurus of Adverse Reaction Terms dictionary, were summarized for the two treatment groups by body system and by the number and percentage of patients reporting at least one occurrence. Differences between the two treatment groups in the incidence of adverse experiences were assessed using Fisher's exact test.

Early Termination. Two interim analyses were planned in the study protocol. No formal stopping rules were specified. After the first planned safety analysis, the Safety Monitoring Board recommended continuation of the study; however, the Food and Drug Administration requested additional information on the number of patients enrolled and number of deaths by treatment group. Then a second, unplanned interim analysis was completed on 213 patients. This analysis revealed a significantly higher mortality rate among patients treated with OZT and the Safety Monitoring Board recommended that the study be placed on hold pending assessment of baseline risk and mechanisms of death. The sponsor and Food and Drug Administration concurred. The final assessment of baseline data and mechanisms of death did not provide evidence that could fully explain the observed treatment difference in mortality.

We were not prospectively identified as the writing team for this trial. Following a protracted interval after cessation of the trial, we were made aware by the second sponsor (Boehringer-Ingleheim) of its willingness to provide the study report but not the study's propriety electronic database nor access to the sponsor's biostatistics team. As a reflection of our commitment to see these data released to the public, this report was prepared with ac-cess only to the sponsor's final written study report, which was prepared by the independent, contract research organization associated with the study. Access to the electronic database may have enabled many other analyses, particularly to determine whether a difference in tidal volume existed between groups. (Although tidal volume size likely was well balanced between study groups given that this was a blinded, randomized trial.) As well, because the study was terminated early and considered negative, the sponsor did not pursue analyses of banked study specimens, namely the cytokine and antioxidant levels of blood and bronchoalveolar lavage samples obtained at baseline and throughout the study. As with the electronic database, we were not granted access to these specimens. Therefore, we made a decision to forgo any possible further analyses that the electronic database may have permitted, and to make the public aware of this study based upon the limited but still interpretable and very important data.

RESULTS

Patient Disease Characteristics at Baseline. A total of 52 investigators randomized a total of 125 men (58.4%) and 89 women ranging in age from 17 to 88 yrs (mean, 50; SD, 18 yrs). Of these, 100 patients received ≥1 dose of study medication; 114 placebo patients received ≥1 dose of study medication. One patient died in the treatment arm before receiving any study medication. Therefore, the number of patients who were randomized and received study medication was 100 OTZ patients and 114 placebo patients. After 215 of the planned 352 patients were enrolled, the study was terminated early in light of safety concerns.

Subgroups of ARDS were categorized as pneumonia, sepsis (nonpneumonia), and nonsepsis-nonpneumonia. As shown in Table 1, among the OTZ patients, 20 had pneumonia, 34 patients had an ARDS risk factor of sepsis, and 46 had a risk factor other than sepsis or pneumonia.

Table 1. Subgroups of acute respiratory distress syndrome (ARDS) risk factors

	OTZ	Placebo
All patients, no.	100	114
Mortality, no. (%)	29 (29)	18 (15.8)
ARDS-sepsis, no.	34	40
Mortality, no. (%)	11 (32)	7 (17.5)
ARDS-pneumonia, no.	20	19
Mortality, no. (%)	8 (40)	4 (21)
ARDS-other, no.	46	55
Mortality, no. (%)	10 (22)	7 (13)

OTZ, L-2-oxothiazolidine-4-carboxylic acid.

Among the placebo patients, 19 patients had pneumonia, 40 patients had an ARDS risk factor of sepsis, and 55 patients had an ARDS risk factor other than sepsis or pneumonia.

Extent of Exposure to Study Medication. Patients treated with OTZ received a mean of 31.3 doses of a possible 42 doses of OTZ during the treatment period. Patients in the placebo group received a mean of 27.4 doses ($p = .018$). Patients who received OTZ had a statistically significant longer period of days on study medication (OTZ, 11.3 days vs. placebo, 10.0 days; $p = .020$). Deviations from the maximum possible dose in each treatment group resulted primarily from deaths and withdrawals and not from lack of compliance with the study protocol.

Among the subgroup of intent-to-treat patients with ARDS risk factor of sepsis, a greater proportion of patients in the OTZ group (73.5%) had a positive culture than in the placebo group (47.5%) ($p = .017$). Among the subgroup of intent-to-treat patients with an ARDS risk factor of pneumonia, patients in the OTZ group had a mean white blood cell count of 12.6 × 10^3/uL compared with 17.4 × 10^3/uL in the placebo group, and this difference was statistically significantly different ($p = .049$). Although not statistically different, the OTZ group was older, 51.1 vs. 48.9 yrs. Similarly, at study entry, the OTZ group had a higher mean serum creatinine (1.4 vs. 1.2 mg/dL) and total Acute Physiology and Chronic Health Evaluation III score (53.3 vs. 50.6) (Table 2). No other significant differences were noted between treatment groups at baseline.

Ventilator-Free Days. The primary outcome variable was VFDs. The mean VFDs were 8.3 days (SD, 9.8; confidence interval [CI], 6.4–10.2; median, 2.0; range, 0.0–29.0) for the OTZ group and 13.5 days (SD, 10.6; CI, 11.6–15.5; median, 16.0; range, 0.0–29.0) for the placebo group. The difference was significant, favoring the placebo group ($p < .001$). This finding of more VFDs in the placebo arm also was evident in the risk factor subgroups: in ARDS-sepsis, mean VFDs were 7.4 vs. 13.9 days, ($p = .007$); in ARDS-pneumonia, mean VFDs were 6.7 vs. 13.9 days ($p = .043$); and in ARDS from other risk factors, mean VFDs were 9.6 vs. 13.2 days ($p = .088$). Among the 70 OTZ patients and 96 placebo patients who remained alive during the study, the placebo group stayed on the ventilator for a significantly shorter time (13.9 days) compared with the OTZ group (18.3 days, $p = .005$).

Mortality. There were 215 patients randomized to receive OTZ, 210 mg/kg per day every 8 hrs for 14 days, or placebo. Mortality was 30/101 (29.7%) in the OTZ group and 18/114 (15.8%) in the placebo group during the 30-day study period ($p = .014$). One patient was randomized to OTZ but died before receiving study medication. This patient was excluded from subsequent analyses in the trial's statistical report. An additional three patients in the OTZ group died during the follow-up period, on days 31, 32, and 91. Two additional patients in the placebo group died during the follow-up period, on days 38 and 43. During the 30-day study period, the mean survival times were 25 days and 27 days, respectively, for the OTZ and placebo groups.

Distribution of Deaths. As shown in Figure 1, the survival curves of both treatment groups have a similar pattern during the first 10 days of the study, while patients were still receiving study medication. During days 12 to 19, the

Table 2. Selected baseline disease characteristics in randomized patients who received at least one dose of study drug

Characteristics	OTZ (n = 100)	Placebo (n = 114)	p Value	Total (n = 214)
PaO₂/FIO₂, mm Hg				
No.	100	114		214
Mean (SD)	114.6 (43.5)	117.5 (44.9)	.712	116.2 (44.2)
Range	45.4–197.5	39.0–200.0		39.0–200.0
Creatinine, mg/dL				
No.	97	113		210
Mean (SD)	1.4 (1.1)	1.2 (1.1)	.271	1.3 (1.1)
Range	0.3–6.6	0.3–8.9		0.3–8.9
Platelets, ×10³/uL				
No.	99	113		212
Mean (SD)	152.2 (101.3)	162 (108.1)	.347	157.5 (104.9)
Range	15.0–572.0	36.0–637.0		15.0–637.0
Glasgow Coma Score				
No.	100	114		214
Mean (SD)	13.2 (2.5)	13.4 (2.5)	.725	13.3 (2.5)
Range	3.0–15.0	3.0–15.0		3.0–15.0
Total APACHE III score				
No.	100	114		214
Mean (SD)	53.5 (20.6)	50.4 (18.9)	.263	51.8 (19.7)
Range	3.0–120.0	12.0–122.0		3.0–122.0

OTZ, L-2-oxothiazolidine-4-carboxylic acid; APACHE, Acute Physiology and Chronic Health Evaluation.
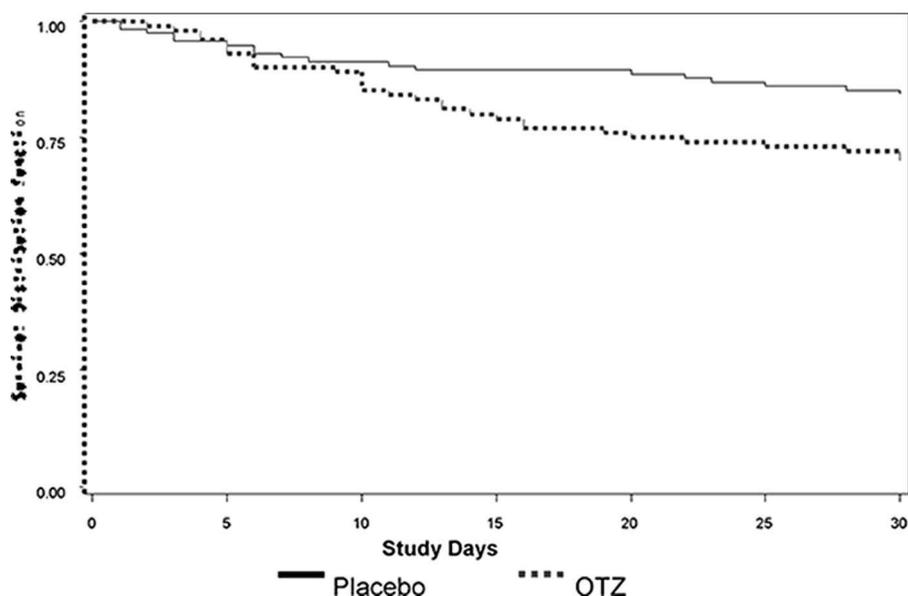

Figure 1. Survival during the 30-day study period of intent-to-treat-patients. The *solid line* represents the placebo group and the *dashed line* the group treated with L-2-oxothiazolidine-4-carboxylic acid (*OTZ*).
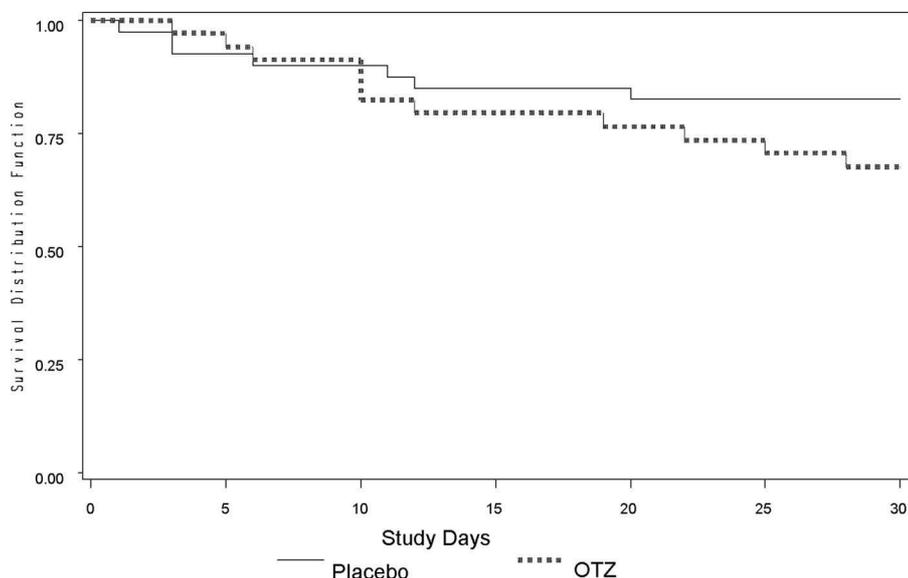
Figure 2. Survival during the 30-day study period of patients with acute respiratory distress syndrome related to sepsis. The *solid line* represents the placebo group and the *dashed line* the group treated with L-2-oxothiazolidine-4-carboxylic acid (*OTZ*).
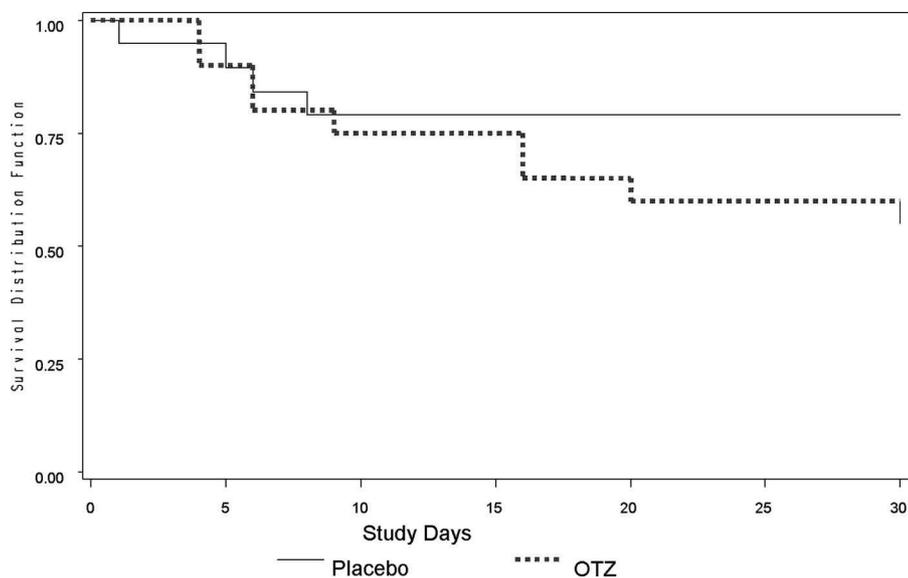

Figure 3. Survival during the 30-day study period of patients with acute respiratory distress syndrome related to pneumonia. The *solid line* represents the placebo group and the *dashed line* the group treated with L-2-oxothiazolidine-4-carboxylic acid (*OTZ*).

survival rate for the placebo group remained relatively steady, while the OTZ group continued to decline. After day 19, both groups declined in a similar manner. To help demonstrate that there was no particular mortality signal among the subgroups of ARDS etiologies, results also are shown for the subgroups of intent-to-treat patients with ARDS risk factors of sepsis-nonpneumonia (Fig. 2), pneumonia (Fig. 3), and without sepsis or pneumonia (Fig. 4).

Clinically Important New Organ Dysfunction. There was at least one occurrence of a clinically important new organ dysfunction in the cardiovascular, central nervous, coagulation, renal, or hepatic systems in 74 patients in each treatment group (74% on OTZ vs. 65% on placebo; $p = .145$). In each specific organ system, the proportion of patients with a new organ dysfunction was similar between the two treatment groups, although a trend for increased renal failure in the OTZ group was noted (Table 3).

Summary of Adverse Events. The proportion of patients who experienced at least one occurrence of an adverse experience during the study was the same (93.0%) in the OTZ and placebo groups. Serious adverse experiences were reported for 46 (46.0%) OTZ patients and 33 (28.9%) placebo patients. Of those, nine (9.0%) OTZ patients and eight (7.0%) placebo patients had serious adverse experiences considered to be possibly, probably, or definitely related to the study drug. In both the OTZ and placebo groups, five patients (5.0% and 4.4%, respectively) were withdrawn because of adverse experiences. No differences were noted in adverse experiences when based on gender or age. The most frequently reported serious adverse experiences were death, bacterial infection, anemia, hypotension, fever, and sepsis. Adverse experiences considered possibly, probably, or definitely related to the study drug were reported for 18 (18.0%) patients in the OTZ group and 21 (18.4%) in the placebo group. Pneumothorax occurred more often in the OTZ group at 9% than in the placebo group at 2.6% and approached statistical significance ($p = .071$). The sodium content of the OTZ formulation was approximately 2.4 g per day for a 70-kg patient receiving a 15 g per day dose of OTZ. There was a higher incidence of hypernatremia in the OTZ group compared with placebo (Table 4).

DISCUSSION

The results of this study demonstrated an increased overall mortality, and a reduced number of VFDs with OTZ treatment. These findings were unexpected in view of the clinical and preclinical data available at the start of the study. Specifically, ARDS has been shown to be associated with the sequestration of neutrophils in the lungs, and the release of toxic oxygen metabolites that may lead to further lung tissue damage. Glutathione, a major endogenous antioxidant, is depleted in the blood and alveolar lining fluid in patients with ARDS. Hence, a beneficial effect of OTZ in patients with ARDS was expected in this study.

Multiple organ failure was seen in a similar number of patients in both groups during the 30-day study period. It is difficult to assess any specific adverse event in isolation because of the multiple etiologic factors present in critically ill patients. The differential incidence of death raises the possibility of some adverse effect of OTZ on pulmonary function in patients with ARDS. However, from the preclinical information available
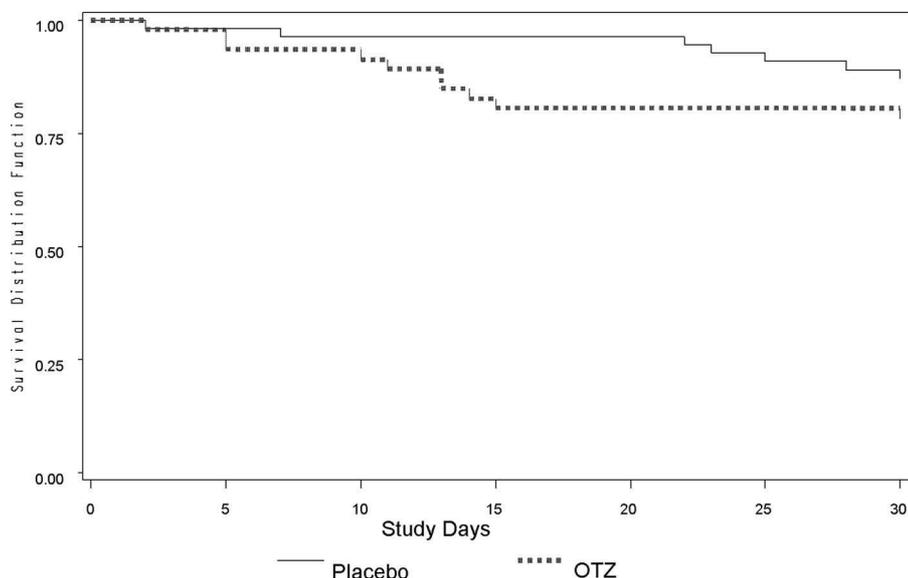
Figure 4. Survival during the 30-day study period of patients with acute respiratory distress syndrome not related to risk factors of sepsis or pneumonia. The *solid line* represents the placebo group and the *dashed line* the group treated with L-2-oxothiazolidine-4-carboxylic acid (*OTZ*).

Table 3. Summary of patients with clinically important new organ dysfunction through day 30

New Organ Dysfunction	OTZ (n = 100)	Placebo (n = 114)	p Value[a]
No. (%) of patients with ≥1 new organ dysfunction	74 (74)	74 (65)	.145
Cardiovascular system	52 (52)	68 (60)	.304
Central nervous system	29 (29)	26 (23)	.287
Coagulation system	15 (15)	14 (12)	.541
Renal system	17 (17)	10 (9)	.076
Hepatic system	16 (16)	18 (16)	.888

OTZ, L-2-oxothiazolidine-4-carboxylic acid.

[a]Treatment *p* value obtained using Cochran-Mantel-Haenszel test, stratified by etiology of acute respiratory distress syndrome.

Table 4. Adverse events

	OTZ	Placebo	p Value
Generalized edema, %	11	1	.002
Hypernatremia, %	11	3.5	.057
Central and peripheral nervous system disorders, %	18	10.5	.166
Acidosis, %	7	1.8	.086
Pneumothorax, %	9	2.6	.071
Skin ulceration, %	14	7	.116
QT interval at treatment end point, msecs	20.6	3.3	.031

OTZ, L-2-oxothiazolidine-4-carboxylic acid.

damage to the lungs by bacterial pathogens. A greater mortality was observed in all three subsets of ARDS etiologies (pneumonia, sepsis nonpneumonia, and nonsepsis-nonpneumonia), suggesting that excess mortality in the OTZ cohort was not augmented exclusively in patients with infectious ARDS etiologies. A better understanding of these associations would be highly desirable, but it seems highly unlikely that additional clinical trials using OTZ will be undertaken in patients with ARDS.

Baseline imbalances sometimes can explain unexpected study results, and indeed there were some differences between the two groups at baseline. The OTZ group had a greater age, Acute Physiology and Chronic Health Evaluation III score, and creatinine concentration, as well as a lower Pao_2/Fio_2 ratio, than the placebo group. Although none of these differences reached statistical significance, these non–treatment-related factors may have contributed to the higher mortality in the OTZ patients. Given the severity of illness in the two groups of patients studied here, a relatively low mortality was observed in the placebo group, but mortality also was slightly lower than expected in the OTZ group. In recent ARDS clinical trial studies, 28-day mortality has ranged from 24% to 39% for various treatment groups even though the milder oxygenation requirements of acute lung injury were used (15, 18–29). A prior study of ARDS patients reported a 40% mortality rate in the placebo (15) as compared with the 15.8% placebo mortality rate evident in this study. A study by Dr. Dellinger and colleagues (25) examining the effects of inhaled nitric oxide on patients with ARDS excluded patients in shock and had a reported placebo mortality of 30%. In a phase III study of surfactant administration to ARDS patients, the placebo mortality was 40% (27). The apparent differences between OTZ and placebo groups in this trial is perhaps better explained by the unexpectedly low mortality in the placebo group rather than by a high mortality in the treated group.

While advances in the knowledge base regarding best management of ARDS have been made over the last 10 yrs, it is important to point out that at the time of this study, management standardization for ventilator tidal volume, fluid administration, or sedation was uncommon. Interpreting this study's results is limited

on the drug, and the related compound N-acetylcysteine, it is difficult to envision the mechanism responsible for worsened pulmonary function nor has this phenomenon been observed in previous trials of N-acetylcysteine and OTZ (15). Rather,

OTZ previously had been associated with an improvement in pulmonary function as manifested by a reduced number of days on mechanical ventilation (15).

Prior preclinical and clinical studies have supported the hypothesis that OTZ increases glutathione while exhibiting low toxicity. Our findings of a significantly lower placebo mortality rate in the presence of treatment-associated mortality rates within the expected range, as compared with other studies conducted during this period, may have led to premature study cessation. A possible mechanism by which progressive pulmonary failure can occur is by progressive infection (e.g., pneumonia). It is known that the physiologic function of free radicals generated by neutrophils is to enhance the killing of bacteria. By providing abundant reducing capacity in the form of glutathione, this killing effect on bacteria could be impeded, resulting in greater

by the lack of these now more common standardizations.

There were relatively few adverse events attributable to OTZ. The sodium content of the OTZ formulation may be related to the observation that hypernatremia was more common in the OTZ group compared with placebo. This also may have resulted in more fluid retention with the potential for worsening pulmonary edema under conditions of increased microvascular permeability. The recent findings of the ARDS Clinical Trials Network study of fluid management in acute lung injury provides evidence that a fluid restrictive strategy provides for improved pulmonary function and shortened time on mechanical ventilation (28). The increased rate of acidosis in the OTZ group may be related to a greater occurrence of progressive respiratory failure in the OTZ group or to the drug itself. As noted in Table 4, the QT interval at treatment end point increased to a larger degree in patients receiving placebo. This may have been related to the greater reduction in mean heart rate in the placebo group (-12.0 beats/min) vs. the OTZ group (-4.5 beats/min) at treatment end point. Pneumothorax occurred more often in the OTZ group, 9%, than in the placebo group, 2.6%, and approached statistical significance ($p = .071$). Although pneumothorax could be related to OTZ, pneumothorax also can be a complication of needle puncture of lung during central venous catheter placement, or a result of hyperinflation of the lungs and high airway pressure needed to ventilate patients with progressive ARDS. Thus, this differential incidence could be due to the OTZ patients having a more severe illness and longer time on ventilator.

This clinical trial of OTZ in ARDS was stopped early because of an emerging difference in mortality between OTZ and placebo groups in favor of placebo. The intent to treat groups were reasonably well matched at baseline with only minor differences in important variables. No specific adverse event or pattern of organ dysfunction emerged to suggest organ toxicity of OTZ. These results are not consistent with prior studies of OTZ and other cysteine replacement trials. Finally, the 30-day mortality in the placebo group of only 15.8% is lower than that which has been documented in any other major clinical trial in ARDS, casting some doubt on the meaning of the mortality differences observed in this trial. It is unfortunate that one of the first large, well-designed trials of antioxidant therapy in ARDS failed to produce results sufficient to move this previously promising treatment forward.

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APPENDIX

Time Window. Patients must have been enrolled in the study (i.e., randomized) within 24 hrs of meeting the chest radiograph criterion and within 48 hrs of first meeting the PaO_2/FIO_2 criterion. The first dose of study drug must have been administered within 4 hrs of enrollment.

Inclusion Criteria

A. Have given informed consent either directly or through a legal representative or family member and,
B. Meet the criteria for a diagnosis of ARDS, manifested by all of the following:

1. $PaO_2/FIO_2 \leq 200$ mm Hg, regardless of positive end-expiratory pressure.
2. Chest radiograph revealing bilateral infiltrates consistent with pulmonary edema involving a minimum of three quadrants and not explained by atelectasis, pleural effusion, or lung mass.
3. Requirement for mechanical ventilation. Mechanical ventilation is defined as all methods of artificial ventilation that restore or initiate breathing by forcing air into and/or out of the lungs to establish a rhythm of inspiration and expiration. Such methods include, but are not limited to: iron lung, turtle shell, bilevel positive airway pressure, oscillators, high frequency ventilators, jet ventilators, volume controlled ventilators, and pressure cycled ventilators. This definition does not require that an artificial airway be present. Mechanical ventilation does not include continuous positive airway pressure if it is applied without any other mode of mechanical ventilation (regardless of the method of application).
4. A known ARDS risk factor: sepsis, severe traumatic injury, hemorrhage requiring ≥ 7 units of whole blood or packed red blood cells, smoke inhalation, extensive thermal burns ($\geq 40\%$ body surface area), pancreatitis, aspiration of stomach contents, pulmonary contusion, viral or bacterial pneumonia, or near drowning.

Exclusion Criteria

1. Pregnant or lactating females.
2. Age <17 yrs in the United States and Canada, or age <18 yrs in other countries.
3. Documented severe chronic lung disease: chronic obstructive pulmonary disease; forced expiratory volume at 1 sec or forced vital capacity <50% predicted; pulmonary fibrosis, on the basis of known prior reduced total lung capacity <50% predicted or static compliance <70% predicted; or a previous chest radiograph showing bilateral interstitial infiltrates.
4. Pulmonary edema due to congestive heart failure (a pulmonary capillary wedge pressure of >18 mm Hg lasting >1 hr during the 12 hrs before study entry. Patients with a known history of cardiogenic pulmonary edema, or risk factors for cardiac failure such as cardiomegaly on standing posterior-anterior chest radiograph or echocardiography may not be entered unless they have a pulmonary capillary wedge pressure <18.
5. Ventilator failure because of neurologic disease (e.g., amyotrophic lateral sclerosis, Guillain-Barre syndrome).
6. Presence of an acute myocardial infarction in the past 6 wks.
7. Severe hepatic dysfunction (e.g., bilirubin >3 times the upper limit of normal, prothrombin time >1.5 times normal, cirrhosis, ascites, or a history of esophageal variceal bleeding).
8. Severe head trauma or stroke with focal neurologic deficits, or Glasgow Coma Score <9. (Patients without evidence of head trauma or focal neurologic deficits who are receiving sedation and/or neuromuscular blockers should have such agents withheld to allow an accurate assessment of neurologic status. If this is not possible, an assessment of Glasgow Coma Score before institution of sedation and/or neuromuscular blocking agents may be used to assess Glasgow Coma Score relative to study entry.)
9. Patient moribund (not expected to live 24 hrs).
10. Physician, family, or patient not committed to full medical support. (Exception: A patient will not be excluded if he/she is to receive all life support except attempts at resuscitation if cardiac arrest occurs.)
11. Renal failure requiring dialysis.
12. Neutrophil count <1000 attributed to cancer chemotherapy.
13. Leukemia, lymphoma, or other hematologic malignancy not in remission.
14. Use of prednisone or other glucocorticoid in doses exceeding prednisone 0.5 mg/kg per day for >2 wks.
15. Primary immune deficiency diseases.
16. Known human immunodeficiency virus positive.
17. Metastatic or inoperable solid malignancy.
18. Bone marrow transplantation within past 6 months.
19. Use of another investigational drug within 30 days of enrollment. An exception is a patient who received nitric oxide by inhalation. These patients may be enrolled in this study within 6 hrs of last receiving NO by inhalation.
20. Receipt of N-acetylcysteine within 12 hrs of study entry.
21. Known hypersensitivity to OTZ, or derivative thereof.
22. Enrollment time window has been exceeded.