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Auxora for the Treatment of Patients With Acute Pancreatitis and Accompanying Systemic Inflammatory Response Syndrome

Clinical Development of a Calcium Release-Activated Calcium Channel Inhibitor

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Objectives: To assess the safety of Auxora in patients with acute pancreatitis (AP), systemic inflammatory response syndrome (SIRS), and hypoxemia, and identify efficacy endpoints to prospectively test in future studies.

Methods: This phase 2, open-label, dose-response study randomized patients with AP, accompanying SIRS, and hypoxemia (n = 21) to receive low-dose or high-dose Auxora plus standard of care (SOC) or SOC alone. All patients received pancreatic contrast-enhanced computed tomography scans at screenings, day 5/discharge, and as clinically required 90 days postrandomization; scans were blinded and centrally read to determine AP severity using computed tomography severity index. Solid food tolerance was assessed at every meal and SIRS every 12 hours.

Results: The number of patients experiencing serious adverse events was not increased with Auxora versus SOC alone. Three (36.5%) patients with moderate AP receiving low-dose Auxora improved to mild AP; no computed tomography severity index improvements were observed with SOC. By study end, patients receiving Auxora better tolerated solid foods, had less persistent SIRS, and had reduced hospitalization versus SOC.

Conclusions: The favorable safety profile and patient outcomes suggest Auxora may be an appropriate early treatment for patients with AP and SIRS. Clinical development will continue in a randomized, controlled, blinded, dose-ranging study.

Key Words: acute pancreatitis, CRAC channels, SIRS, inflammation

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Acute pancreatitis is a local and systemic inflammatory disease associated with significant morbidity and mortality because of clinical sequelae, most notably pancreatic necrosis and persistent organ failure.[1,2] Pancreatic necrosis occurs in 20% to 30% of patients with acute pancreatitis, with 30% of them subsequently developing infection of the necrotic tissue.[1,2] Persistent organ failure, defined using the Modified Marshall Scoring system and lasting for at least 48 hours, may occur in up to 25% of patients with acute pancreatitis.[1,3–5] Persistent organ failure signifies the development of severe acute pancreatitis and its presence increases the risk of mortality to as much as 50%.[1,3,5] Recent studies have shown that pancreatic necrosis and persistent organ failure often occur independently of each other.[6,7] In 1 post hoc analysis of patients with necrotizing pancreatitis (n = 639), 62% of patients did not develop organ failure and in a separate retrospective study of patients with multiple organ failure (n = 176), 54% had no evidence of pancreatic necrosis.[6,7] As such, it is critical that any treatment for acute pancreatitis targets the development of both pancreatic necrosis and organ failure.

In addition, a treatment targeting the development of both complications should be administered early in the course of the disease to ensure best possible outcomes. There are multiple scoring systems in use to identify patients at risk for developing pancreatic necrosis and/or persistent organ failure, but these scoring

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The trial protocol was approved by an institutional review board at each site and was overseen by an ISRC. The trial was conducted in accordance with the guiding principles of the Declaration of Helsinki and was approved by the local institutional review boards. Informed consent was obtained from either the patient or from the patient's legally authorized representative if the patient was unable to provide consent. This trial was registered at ClinicalTrials.gov number, NCT03401190.

The datasets generated and/or analyzed during the current study are not publicly available due to the Clinical Study Report being finalized but will be available from the corresponding author on reasonable request at a later time.

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systems largely incorporate variables collected over 24 to 48 hours of hospital admission.[1,8–10] Recently, a scoring system incorporating the presence of systemic inflammatory response syndrome (SIRS), hypoxemia, and age has been proposed as a prognostic tool in patients with acute pancreatitis for use in the emergency room at the time of presentation, and may allow for early identification of severe acute pancreatitis.[11] The presence of SIRS heralds the activation of complex inflammatory pathways that cause pancreatic necrosis and persistent organ failure, the most frequent and serious being respiratory failure.[12] In one prospective study of patients with acute pancreatitis (n = 252), all cases of pancreatic necrosis, death, and nearly all cases of persistent organ failure, developed SIRS during the first day of hospitalization.[13] The presence of hypoxemia has been noted to have a direct correlation with the development of respiratory failure and mortality in acute pancreatitis. In a prospective study of 60 patients referred to a tertiary care center, mild hypoxemia (PaO_2, 60–80 mm Hg) was observed in 29 patients and severe hypoxemia (PaO_2 <60 mm Hg) in 11 patients, the presence of either being associated with the development of acute respiratory distress syndrome and an increased risk for mortality.[14] The presence of SIRS and hypoxemia may identify patients early in the course of acute pancreatitis who would benefit from a treatment to target the development of both complications.

Recent evidence suggests that calcium influx via calcium release-activated calcium (CRAC) channels is involved in the development of both pancreatic necrosis and respiratory failure.[15–17] Overactivity of CRAC channels appears to play a proximal role in injuring pancreatic acinar cells, ductal cells, and stellate cells. In the acinar cell, the sustained influx of calcium damages mitochondria and converts trypsinogen to trypsin intracellularly, which together increase the risk of pancreatic necrosis.[4,18–22] The CRAC channels initiate the production and release of proinflammatory cytokines from T cells, contributing to the systemic inflammation and respiratory failure that occurs in acute pancreatitis.[15–17] It has also been suggested that CRAC channels directly contribute to respiratory failure by activating pulmonary endothelial cells, causing breakdown of the alveolar-capillary barrier, extravasation of fluid into the alveoli, and the development of hypoxemia.[15–17,23] Thus, inhibition of CRAC channels may be beneficial in reducing the frequency and severity of both respiratory failure and pancreatic necrosis in patients with acute pancreatitis.

Auxora is a potent and selective CRAC channel inhibitor that has multiple sites of action including the pancreas, immune system, and pulmonary endothelium.[16,24–26] Preclinical evidence has demonstrated that Auxora not only protects against pancreatic acinar cell death, but also rapidly reduces the inflammatory responses that manifest clinically as SIRS and decreases interleukin (IL)-6 levels in both the pancreas and lungs.[16,24–26] The use of Auxora also has been documented to improve respiratory outcomes in patients with COVID-19 pneumonia, providing further evidence of potential value in patients with acute pancreatitis with pulmonary complications.[27] As such, Auxora may be an effective compound in the early treatment of acute pancreatitis in patients, especially those with SIRS and hypoxemia.

MATERIALS AND METHODS

Patient Selection

This phase 2, randomized, open-label, dose-response study of Auxora in patients with acute pancreatitis and accompanying SIRS was conducted from March 2018 to April 2019 across multiple centers in the United States (ClinicalTrials.gov number, NCT03401190). Eligible patients were adults with a diagnosis of acute pancreatitis established by the presence of abdominal pain consistent with acute pancreatitis and 1 of the following 2 criteria: a serum lipase or serum amylase more than 3 times the upper limit normal or characteristic findings of acute pancreatitis on abdominal imaging. In addition, patients were required to have a diagnosis of SIRS and hypoxemia (full details in the Supplemental Digital Content, http://links.lww.com/MPA/A863). Patients were not eligible if they had evidence of pancreatic necrosis on contrast-enhanced computed tomography (CECT) performed in the 18 hours prior to consent or after consent and before day 1. Full inclusion and exclusion criteria can be found in the Supplemental Digital Content (http://links.lww.com/MPA/A863). An institutional review board at each site approved the trial protocol. Before screening, informed consent was obtained from either the patient or from the patient's legally authorized representative if the patient was unable to provide consent.

Study Design

This study was conducted in 2 phases. In the initial phase, female and male patients (cohorts 1 and 2, respectively) were to be randomized in a 3:1 ratio to receive a low-dose regimen of Auxora plus standard of care or standard of care alone to ensure an adequate assessment of the safety of Auxora. In the second phase, female and male patients (cohorts 3 and 4, respectively) were to be randomized in a 3:1 ratio to receive a high-dose regimen of Auxora plus standard of care or standard of care alone. Dose escalation would occur only if needed for efficacy reasons and if no events suggesting a safety signal would occur with higher dosing. After review of the efficacy, tolerability, and safety data from cohorts 1 and 2 by both CalciMedica, Inc. (La Jolla, Calif) and the United States Food and Drug Administration, the decision was made to continue the low-dose regimen in cohort 3 because of the improvements in the computed tomography severity index (CTSI) scores noted in cohort 1. Cohort 4 received the high-dose regimen as planned. Patients were followed for 90 days after randomization.

Based on safety, tolerability, and pharmacokinetic modeling from phase 1 studies in healthy volunteers, the low-dose regimen of Auxora was defined as 1.0 mg/kg on day 1 and 1.4 mg/kg daily on days 2, 3, and 4; the high-dose regimen of Auxora was defined as 2.08 mg/kg daily on days 1 and 2 and 1.6 mg/kg daily on days 3 and 4. The first infusion of Auxora was started within 6 to 8 hours of the patient providing informed consent and was administered as a continuous intravenous infusion over 4 hours. Subsequent infusions were to be started every 24 hours (±1 hour) from the start of the first infusion. Physicians were allowed to discharge patients before receiving all 4 doses if the clinical condition had improved so that the patient was tolerating an oral diet, had adequately controlled pain, and no evidence of infection. Recommended standard of care was consistent with the 2013 International Association of Pancreatology/American Pancreatic Association evidence-based guidelines for the management of acute pancreatitis.[28] In addition, local standard of care for the management of other medical conditions including organ failure was allowed. The presence of SIRS was evaluated every 12 hours. Patients were allowed to request food ad libitum and the amount of food consumed and the development of nausea or vomiting were assessed after each meal. Laboratory studies were drawn daily to evaluate the safety of Auxora and to obtain selected biomarker results.

All patients were to have an abdominal CECT scan at screening and day 5 or discharge. Patients could also receive unscheduled CECT scans over the 90-day period as required for patient care. All scheduled and unscheduled CECT scans were read locally and may have been used by the principal investigator or treating physician

for patient management as required. A blinded central reader also reviewed all screening, day 5 or discharge, and unscheduled CECT scans and gave a score for the severity of acute pancreatitis using the CTSI scoring system. The CTSI scores were not shared with the principal investigator or treating physician.

Objectives, Endpoints, and Statistical Analysis

The primary objective was to assess the safety and tolerability of Auxora in patients with acute pancreatitis and accompanying SIRS plus hypoxemia. These included the assessment of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and 90-day overall survival. Secondary objectives were to determine the potential efficacy endpoints for use in future studies of Auxora in patients with acute pancreatitis and accompanying SIRS. Prospectively identified endpoints that were evaluated to assess the potential efficacy of Auxora compared with standard of care included change in CTSI score from screening to day 5 (or discharge), the proportion of patients tolerating solid food at 72 hours and at discharge (defined as tolerating ≥50% of solid meal without vomiting or an increase in abdominal pain), the percentage of patients with persistent SIRS (lasting ≥48 hours), changes in IL-6 levels, and length of hospital stay.

For all cohorts, assessments were performed daily from days 1 to 10, or until discharge if occurring earlier. Safety and tolerability were assessed by monitoring the frequency, duration, and severity of TEAEs and SAEs. After day 10, and starting on day 12, SAEs were captured every 48 hours until day 30, or until discharge. Patients discharged before day 30 were contacted on day 30 to capture SAEs and any readmissions to the hospital. Patients were also contacted on day 90 to assess mortality.

The planned sample size of 24 patients was selected based on practical considerations that enabled the initial evaluation of efficacy and safety of Auxora in patients with acute pancreatitis and accompanying SIRS plus hypoxemia. This study was not powered for the analysis of study data with inferential statistics as the primary purpose of this study was to explore what endpoints would be most appropriate for future trials. For all endpoints, comparisons between Auxora and standard of care alone were performed in the intention to treat population.

RESULTS

Patient Disposition and Characteristics

In total, 21 patients were screened and randomized into the study. Mean age was 48.1 years and 54.9 years in the Auxora group (all doses) versus standard of care alone, respectively, and median body mass index was 30.3 and 34.0 kg/m^2, respectively (Table 1). Alcohol consumption was thought to contribute to acute pancreatitis in 3 (37.5%) patients in the low-dose Auxora group, 4 (66.7%) patients in the high-dose Auxora group, and 4 (57.1%) patients in the standard of care group. As the dose was not escalated in cohort 3, no female patients were enrolled in the high-dose Auxora group (Table 1). Mean time from onset of symptoms to infusion of Auxora was 23.6 hours. Five (63%) patients receiving low-dose Auxora and 4 (67%) receiving high-dose Auxora did not receive all 4 doses due to rapid clinical improvement leading to early discharge (n = 7) or study drug discontinuation (n = 2, both in the high-dose Auxora group) (Fig. 1).

TABLE 1. Baseline Demographics and Clinical Characteristics

	High-dose Auxora (n = 6)	Low-dose Auxora (n = 8)	Auxora Total (N = 14)	Standard of Care (n = 7)
Age, mean (SD), y	44.3 (7.09)	50.9 (14.7)	48.1 (12.1)	54.9 (10.7)
Sex, n (%)				
Female	0	5 (63)	5 (36)	4 (57)
Male	6 (100)	3 (38)	9 (64)	3 (43)
BMI, median (range), kg/m^2	28.9 (25–38.2)	31.6 (22–44.4)	30.3 (22–44.4)	34 (23.8–41.6)
Race, n (%)				
Asian	0	1 (13)	1 (7)	0
Black or African	2 (33)	1 (13)	3 (21)	3 (43)
White	4 (67)	6 (75)	10 (71)	4 (57)
Ethnicity, n (%)				
Hispanic or Latino	2 (33)	0	1 (7)	0
Not Hispanic or Latino	4 (67)	8 (100)	13 (93)	7 (100)
Acute pancreatitis etiology, n (%)				
Alcohol	4 (67)	3 (38)	7 (50)	4 (57)
Drug-induced	1 (17)	0	1 (7)	1 (14)
Biliary	0	1 (13)	1 (7)	0
Hypertriglyceridemia	1 (17)	0	1 (7)	0
Unknown	0	3 (38)	3 (21)	0
Other	0	1 (13)	1 (7)	2 (29)
Medical history, n (%)				
Chronic kidney disease	0	0	0	1 (14)
Acute pancreatitis	3 (50)	3 (38)	6 (43)	0
Diabetes, type 1 or type 2	2 (33)	3 (38)	5 (36)	2 (29)
Hypertension	4 (67)	4 (50)	8 (57)	6 (86)

*Other includes lithotripsy, diuretics, idiopathic.

BMI indicates body mass index; SD, standard deviation.

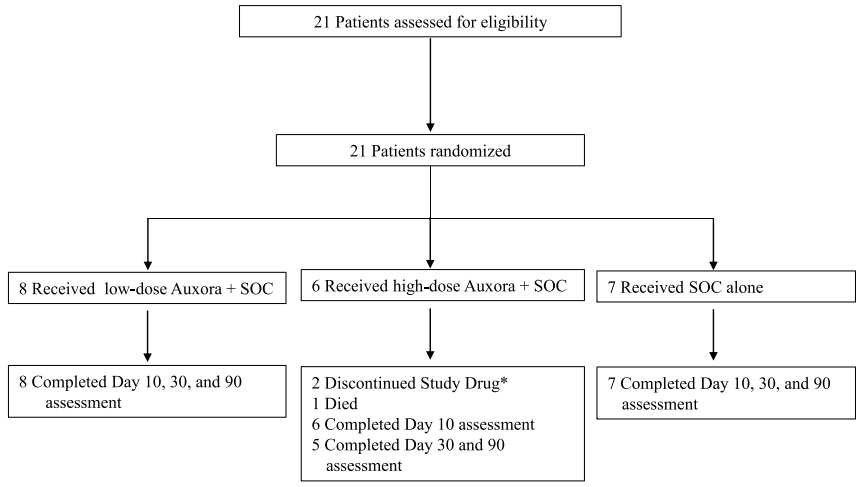

FIGURE 1. Patient enrollment and randomization. The patient in the high-dose Auxora arm who died developed multiorgan failure with acute respiratory distress syndrome and renal failure had discontinued Aurora prior to his death. The SAEs and cause of death were considered to be unrelated to study drug; survival time for this patient was 18.3 days. *The 2 patients who discontinued the study drug remained in study and were followed through the 90-day assessment or death. One patient died before the 90-day assessment. The other patient who discontinued the study drug completed the 30- and 90-day assessment. SOC, standard of care.

One patient in the high-dose Auxora group died with a survival time of 18.3 days.

Safety Assessment

Treatment-emergent AEs were reported in 5 (83%) patients receiving high-dose Auxora, 7 (88%) patients receiving low-dose Auxora, and 3 (43%) patients receiving standard of care alone (Table 2). One TEAE (chromaturia) occurring in the high-dose Auxora arm was reported as possibly treatment-related and was considered mild in severity. The majority of TEAEs in the Auxora groups were mild and were considered resolved or resolving at the end of the study. The rate of severe TEAEs was similar across treatment arms, occurring in 2 (33%) patients receiving high-dose Auxora, no patients receiving low-dose Auxora, and 2 (29%) patients receiving standard of care alone. There were 2 TEAEs in the high-dose Auxora arm leading to discontinuation of study drug, one due to the development of multiple SAEs and the other due to a mild TEAE of hypersensitivity.

Serious AEs were reported in 2 (25%) patients receiving low-dose Auxora, 1 (17%) patient receiving high-dose Auxora, and 2 (29%) patients receiving standard of care (Table 2). The majority of the SAEs had resolved or recovered other than a case of severe respiratory failure in the standard of care group. There was 1 death in the high-dose Auxora group. This patient, who had discontinued Auxora, experienced multiorgan failure (respiratory, cardiac, and renal) and abdominal compartment syndrome in association with a weight gain of approximately 10 kg secondary to aggressive volume resuscitation. The cause of his acute pancreatitis was thought to be drug-related secondary to the start of leflunomide for the treatment of underlying rheumatoid arthritis. The patient died of complications of a respiratory arrest because of acute respiratory distress syndrome. The survival time for this patient was 18.3 days.

Efficacy Endpoints

At screening, 8 patients treated with Auxora (all doses) had moderate and 5 had mild acute pancreatitis based on the CTSI score from CECT scans; no patients had severe acute pancreatitis (Fig. 2). One patient did not receive intravenous contrast and CTSI score could not be determined either at screening or at day 5. Among those with moderate acute pancreatitis, 3 (37.5%) patients, all of whom were women, received low-dose Auxora, and did not have alcohol pancreatitis, improved to mild acute pancreatitis based on the day 5/discharge CECT (Fig. 2). There were no changes to the CTSI score in the other 5 patients with moderate acute pancreatitis or in the 5 patients with mild disease.

Three patients treated with standard of care had moderate and 1 patient had severe acute pancreatitis by CTSI score at screening, but none improved at day 5/discharge. The 2 patients with mild acute pancreatitis in the standard of care group had no changes in CTSI score at day 5/discharge. One patient treated with standard of care alone did not receive a CTSI score at screening

TABLE 2. Summary of Adverse Events

	High-dose Auxora (n = 6)	Low-dose Auxora (n = 8)	Standard of Care (n = 7)
TEAE patients, n (%)	5 (83)	7 (88)	3 (43)
Severe TEAE patients, n (%)	2 (33)	0 (0)	2 (29)
SAE patients, n (%)	1 (17)	2 (25)	2 (29)
TEAEs leading to discontinuation, n (%)	2 (33)	0 (0)	0 (0)
TEAEs leading to death, n (%)*	1 (17)	0 (0)	0 (0)
Treatment-related TEAEs, n (%)†	1 (17)	0 (0)	0 (0)

*This death was due to Hypoxic-Ischemic Encephalopathy. This patient developed multiorgan failure with acute respiratory distress syndrome and renal failure. He also developed abdominal compartment syndrome in the setting of vigorous fluid resuscitation. The SAEs the patient experienced and cause of death were considered to be unrelated to study drug.

†Treatment-emergent AEs considered to be related to treatment was Chromaturia and was considered mild.

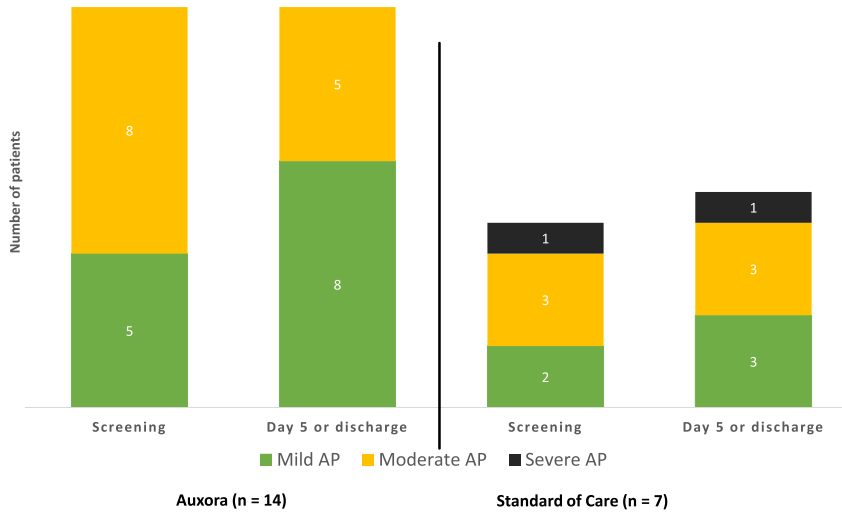

FIGURE 2. Change in acute pancreatitis from screening to day 5 or discharge based on CTSI score by CECT scans. Severity of acute pancreatitis was determined by CTSI scores according to CECT scans at screening, day 5 or discharge, or as needed over the 90-day period as required for patient care. One patient treated with high-dose Auxora did not receive a CTSI score at either screening or day 5/discharge and 1 patient treated with standard of care alone did not receive a CTSI score at screening because contrast was not given; at day 5/discharge, this patient was noted as having mild acute pancreatitis. AP, acute pancreatitis.

because contrast was not given; at day 5/discharge, this patient was noted as having mild acute pancreatitis.

All patients randomized into the study had SIRS at the time of screening. Five (35.7%) patients randomized to Auxora had persistent SIRS lasting for 48 hours or longer (all doses). Among these patients, 4 of 5 had a baseline SIRS score of 3. Of the patients randomized to the standard of care alone group, 5 (71.4%) patients had persistent SIRS, 2 of whom had a SIRS score of 3 at screening and 3 had a SIRS score of 2.

Upon admission, only 1 (7%) patient randomized to Auxora and 1 (14%) patient randomized to standard or care were able to tolerate solid food (defined as tolerating 50% or higher of solid meal without vomiting or an increase in abdominal pain). At 72 hours, 50% of patients receiving Auxora (all doses) compared with 14% of patients receiving standard of care alone were able to tolerate solid foods without vomiting or an increase in abdominal pain (Fig. 3). At day 10 or discharge, whichever came first, 93% of patients receiving Auxora versus 47% of patients receiving standard of care were able to tolerate solid food. The median time (range) to tolerating solid food for patients in the low-dose Auxora group was 57 hours (17–121 hours) and 78.5 hours (39–440 hours) for patients in the high-dose Auxora group; this measure could not be calculated in the standard of care group as more than half were sent home without tolerating solid foods.

The median hospital stay (range) was 3.7 days (1.5–18.3 days) in patients receiving Auxora (all doses) and 6.0 days (1.1–30.0 days) in patients receiving standard of care alone. In the patients with moderate or severe acute pancreatitis based on the CTSI score at screening, the median hospital stay was 4.3 days in patients receiving Auxora (all doses) and 7.3 days in patients receiving standard of

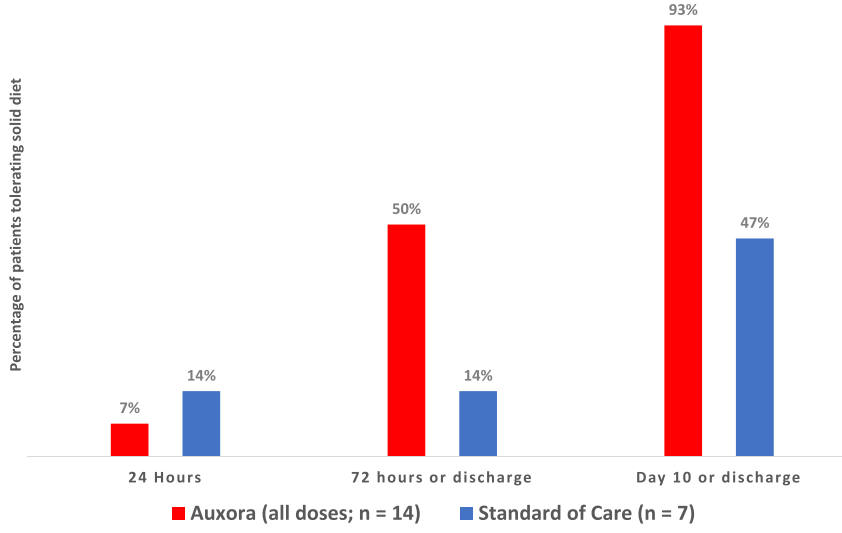

FIGURE 3. Percentage of patients tolerating a solid diet overtime. The ability to tolerate a solid diet was defined as tolerating ≥50% of solid meal without vomiting or an increase in abdominal pain.

TABLE 3. Change in IL-6 Levels From Day 1 to Day 10

	Admission IL-6 Levels		Day 10 or Discharge IL-6 Levels	
	IL-6 ≥1000 pg/mL	150 pg/mL ≤ IL-6 < 1000 pg/mL	IL-6 ≥1000 pg/mL	150 pg/mL ≤ IL-6 < 1000 pg/mL
High-dose Auxora (n = 6)	2	1	0	1
Low-dose Auxora (n = 8)	0	4	0	0
Standard of care (n = 7)	0	3	0	2

care alone. One patient randomized to standard of care alone remained hospitalized at both the day 30 and day 90 assessments. Communication from the study site confirmed that the patient was still hospitalized at the 90-day assessment.

A total of 7 patients treated with Auxora had a maximum IL-6 level of 150 pg/mL or greater in the first 24 hours, 2 of whom having IL-6 levels of 1000 pg/mL or greater. Both patients survived and neither required mechanical ventilation despite having respiratory failure at presentation. Three patients treated with standard of care had a maximum IL-6 level of 150 pg/mL or greater in the first 24 hours. Treatment with Auxora was associated with decreases of IL-6 levels to less than 150 pg/mL in 6 of 7 patients, whereas only 1 of 3 patients treated with standard of care had IL-6 levels that dropped below this threshold (Table 3). Both patients with IL-6 levels of 1000 pg/mL or greater and treated with Auxora had levels of 150 pg/mL or less after treatment.

DISCUSSION

Auxora, a novel, intravenously administered CRAC channel inhibitor, demonstrated a favorable safety profile with the majority of TEAEs being mild in severity. There was only 1 TEAE, chromaturia, which was thought to possibly be treatment related; it was considered mild in severity. There was no increase in reported SAEs compared with the standard of care.

From screening to day 5 or discharge, 3 patients receiving Auxora experienced improvements in the severity of acute pancreatitis as demonstrated by CECT scans, compared with none in the standard of care group. In addition, patients receiving Auxora experienced less persistent SIRS and more rapid restoration of gut function than patients receiving standard of care alone, allowing for better tolerability of solid foods within 72 hours of treatment, and earlier hospital discharge. This allowed for reduced median hospital stay in the Auxora treatment groups compared with those receiving standard of care, especially among patients with moderate or severe acute pancreatitis noted on Screening CECTs.

The fast-acting nature of Auxora, which was, on average, administered within 24 hours of onset of symptoms, is of particular importance as it is critical to treat the inflammatory response associated with acute pancreatitis quickly to prevent persistent organ failure and SIRS, thereby decreasing the risk of mortality.[13,25] Several studies have shown that in patients with acute pancreatitis, proinflammatory responses resulting in pancreatic inflammation, organ failure, and SIRS often occurs early in disease progression and may occur independently or together, suggesting the activation of complex inflammatory pathways.[13,29] In a prospective study of patients with acute pancreatitis, SIRS occurred in 155 (62%) patients on day 1 of hospitalization and was predictive of severe disease. In this study, all patients developing SIRS experienced at least 1 of the following: pancreatic necrosis, multisystem organ failure, or death, and 85% of persistent organ failure cases occurred in these patients.[13] In a separate study of patient with acute pancreatitis and persistent organ failure (n = 601), 370 (61.6%) had an onset of persistent organ failure less than 24 hours after hospitalization, followed by 159 (26.5%) on day 2 and 40 (6.7%) on day 3.[29]

In this trial of patients with acute pancreatitis and accompanying SIRS and hypoxemia, those receiving Auxora saw reductions in the proinflammatory cytokine, IL-6, with treatment. When elevated, IL-6 is often associated with worsening severity of acute pancreatitis.[30] These improvements in proinflammatory cytokine levels with the infusion of Auxora suggest an immediate impact on systemic inflammation in patients with acute pancreatitis, which is key to reducing the risk of severe disease and mortality. In addition, animal models have shown the ability of CRAC channel inhibitors like Auxora to attenuate cell death responses to toxic stimuli in pancreatic acinar cells, ameliorate acute pancreatitis severity, stabilize pulmonary endothelial cells, as well as block the release of proinflammatory cytokines.[17,19,20] Given the direct effects on pancreatic acinar cells, pulmonary endothelium, and immune cells associated with proinflammatory cytokine production and release, Auxora may be an appropriate therapy for the management of patients with acute pancreatitis and accompanying SIRS plus hypoxemia. Furthermore, Auxora has demonstrated rapid distribution to the pancreas and lungs, resulting in a fast onset of action (data not shown), and thereby, effective inhibition of CRAC channels in pancreatic and pulmonary tissue.

This study is limited by the open-label study design, small sample size, and by not being powered for statistical significance but rather to inform future studies. In addition, no female patients were randomized to the high-dose Auxora arm due to efficacy observed in the first phase of this trial.

The favorable safety profile and rapid improvements in patient outcomes observed with Auxora warrant further clinical development to a larger randomized, double-blind, phase 2b study. As there were signs of efficacy in both Auxora doses used in this study, a third and lower dose of Auxora will be evaluated in this upcoming clinical trial. The ability to rapidly reduce severity of disease, SIRS scores, and hospital stay while improving tolerability of solid food suggest that Auxora may be an appropriate early treatment for patients with acute pancreatitis and accompanying SIRS.

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