A pilot open-label study of aldose reductase inhibition with AT-001 in patients hospitalized for COVID-19 infection: Results from a registry-based matched-control analysis

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Introduction

- Cardiometabolic disease may confer increased risk of severe disease in COVID-19 by upregulation of the nucleotide-binding oligomerization domain (NOD), leucine-rich repeat–containing receptor (NLR) family pyrin domain-containing 3 (NLRP3) inflammasome pathway and induction of trained innate immunity with increased risk of hyperinflammatory response to COVID-19.[1]
- Aldose Reductase, the rate-limiting step of the polyol pathway, plays a critical role in mediation of oxidative tissue damage in setting of inflammation induced by infection or ischemia and may contribute to NLRP3 inflammasome activation in diabetic patients with COVID-19 . In addition to its critical role in cardiac dysfunction and ischemic injury, increased aldose reductase activity exacerbates lung inflammation in an experimental model of sepsis.[2-7]
- We hypothesized that aldose reductase inhibition with AT-001 (caficrestat) might represent a novel therapeutic approach to reduce risk of adverse outcomes in diabetic patients with COVID-19 disease.

Methods

Subject Selection

- Adults with diabetes mellitus, and history of hypertension, coronary artery disease, or heart failure, and COVID-19 infection requiring hospitalization at New York University Langone Health (NYULH) Hospitals were eligible for enrollment in this prospective open-label clinical trial.
- Diabetes mellitus was defined as history of diabetes mellitus documented in the medical record or blood glucose level >126 mg/dl at the time of hospitalization.
- COVID-19 infection was confirmed by laboratory RT-PCR testing.

Methods cont'd

Study Design

- The study was designed as a prospective open-label clinical trial to assess safety, tolerability and efficacy of AT-001 (caficrestat) in hospitalized patients with COVID-19.
- AT-001 (caficrestat) 1500 mg twice daily was administered by mouth or nasogastric tube for up to 14 days. For patients discharged home before completion of 14 days of AT-001 (caficrestat) treatment, the study drug regimen was completed at home with remote adverse event monitoring conducted by telephone interview.
- The World Health Organization COVID-19 ordinal scale for clinical improvement status was assessed at day 30 from the last dose of study drug.

Data Analysis

- To provide observational control data, matched controls from a contemporaneous de-identified registry of hospitalized patients with clinical COVID-19 diagnosis at the same institution were selected according to two matching strategies based on ICD-10 billing codes and clinical characteristics.
- The first matching approach selected all subjects in the registry with diabetes mellitus ~~and~~ hypertension, and available data to match participants who received AT-001 (caficrestat) for gender, age group, weight, and C-reactive protein (CRP) value at the time of hospital admission.
- The second matching approach selected all subjects in the registry with diabetes mellitus and available data to match participants who received AT-001 (caficrestat) for gender, age group (in bins of 5 years), and weight ±0.5 Kg interval.

Results

Clinical Outcomes

- Of the 10 participants treated with AT-001 (caficrestat) in the prospective clinical trial, eight survived, and were discharged from the hospital, with median hospital length of stay of 5 days (range 3-35 days), and two died during the index hospitalization due to COVID-19 complications (progressive hypoxic respiratory failure).
- The in-hospital mortality observed in the AT-001 (caficrestat) group was 20% vs. 31% in matched control-1 and 27% in matched control-2.
- Length of hospital stay observed in the AT-001 (caficrestat) group was numerically less than length of hospital stay in the two matched control groups

Table 1-Patient Demographics*

	AT-001 (N=10)	Control Group 1 (N=16)	Control Group 2 (N=55)
Age (years)	66.4 ± 6.6	65±7.7	64.5±5.3
Male sex (%)	80	87.5	80
Weight (kg)	86.8±16.2	93.3±9.5	88.3±12.7
C-Reactive Protein (mg/dL)	52.5 (7.7; 176.5)	79.2 (8.3; 183)	60.7 (7.9; 110.5)

*data are presented as percentage, mean ± standard deviation, and median (interquartile range)

Table 2 – Summary of hospital length of stay (LOS) data*

	All Subjects			Surviving Subjects		
	AT-001 (N=10)	Control Group 1 (N=16)	Control Group 2 (N=55)	AT-001 (N=8)	Control Group 1 (N=11)	Control Group 2 (N=40)
Median LOS	5 (4,29)	10 (5,20)	25 (16,36)	5 (4,35)	6 (4,85)	17 (7,39)
Estimated difference in median LOS		1.5 (-2, 12)	14 (1,36)		1 (-2, 19)	11 (1,49)

*data are presented as 95% CI and interquartile range

Results

- Previous observational studies have reported that patients with hypertension, heart failure, diabetes mellitus, and obesity are at greater risk of severe disease complications and death due to COVID-19.
- In this pilot study of COVID-19 patients with these comorbid conditions, treatment with the selective, potent aldose reductase inhibitor AT-001 (caficrestat) was associated with numerically shorter length of hospital stay and decreased mortality when compared with contemporary matched control subjects treated for COVID-19 at the same institution. AT-001 (caficrestat) was well tolerated, consistently with a favorable tolerability profile observed in prior studies of non-COVID-19 patients with diabetic cardiomyopathy.

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