Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 102328

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

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

Juan Gaztanaga [b], Ravichandran Ramasamy [a], Ann Marie Schmidt [a], Glenn Fishman [a], Shoshana Schendelman [c], Karthinathan Thangavelu [c], Riccardo Perfetti [c,*], Stuart D. Katz [a]

[a] From the New York University Grossman School of Medicine, Department of Medicine, New York, NY, USA
[b] Division of Internal Medicine, Department of Cardiology, NYU Winthrop Hospital, Mineola, NY, USA
[c] Applied Therapeutics, New York, NY, USA

ARTICLE INFO

Article history:
Received 27 September 2021
Received in revised form
23 October 2021
Accepted 25 October 2021

Keywords:
AT-001
Caficrestat
Diabetes mellitus
Type II Diabetes
COVID-19
Diabetic cardiomyopathy

ABSTRACT

Background and aims: Cardiometabolic disease may confer increased risk of adverse outcomes in COVID-19 patients by activation of the aldose reductase pathway. We hypothesized that aldose reductase inhibition with AT-001 might reduce viral inflammation and risk of adverse outcomes in diabetic patients with COVID-19.

Methods: We conducted an open-label prospective phase 2 clinical trial to assess safety, tolerability and efficacy of AT-001 in patients hospitalized with COVID-19 infection, history of diabetes mellitus and chronic heart disease. Eligible participants were prospectively enrolled and treated with AT-001 1500 mg BID for up to 14 days. Safety, tolerability, survival and length of hospital stay (LOS) were collected from the electronic medical record and compared with data from two matched control groups (MC1 and MC2) selected from a deidentified registry of COVID-19 patients at the same institution.

Results: AT-001 was safe and well tolerated in the 10 participants who received the study drug. In-hospital mortality observed in the AT-001 group was 20% vs. 31% in MC1 and 27% in MC2. Mean LOS observed in the AT-001 group was 5 days vs. 10 days in MC1 and 25 days in MC2.

Conclusions: In hospitalized patients with COVID-19 and co-morbid diabetes mellitus and heart disease, treatment with AT-001 was safe and well tolerated. Exposure to AT-001 was associated with a trend of reduced mortality and shortened LOS. While the observed trend did not reach statistical significance, the present study provides the rationale for investigating potential benefit of AT-001 in COVID 19 affected patients in future studies.

© 2021 Published by Elsevier Ltd on behalf of Diabetes India.

1. Introduction

An outbreak of viral pneumonia in Hubei province China in December 2019 led to the identification of a novel coronavirus (SARS-CoV-2, subsequently renamed as COVID-19) as the etiologic agent [1–4]. By the end of 2020, over 100 million COVID-19 cases and 4 million deaths have been reported worldwide. Severe manifestations of COVID-19 infection occur more frequently in patients with co-morbid obesity, diabetes, hypertension and heart failure. 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.

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 [5–10]. In addition to its mediatory role in cardiac dysfunction and ischemic injury, increased aldose reductase activity exacerbates lung inflammation in an experimental model of sepsis [11]. Taken together these studies provide strong rationale for testing the beneficial effects of aldose reductase inhibitors in

* Corresponding author. Applied Therapeutics, 545 Fifth Avenue, Suite 1400, New York, NY, 10017, USA.
E-mail address: rperfetti@appliedtherapeutics.com (R. Perfetti).

https://doi.org/10.1016/j.dsx.2021.102328
1871-4021/© 2021 Published by Elsevier Ltd on behalf of Diabetes India.

COVID19 patients. AT-001 (caficrestat) is a selective inhibitor of aldose reductase enzymatic activity that decreases biomarkers of myocardial stress and is currently being studied in a Phase 3 global registrational study in patients with diabetic cardiomyopathy (ARISE-HF) [12–14]. 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.

In order to assess the therapeutic potential of aldose reductase inhibition with AT-001 (caficrestat) in COVID-19, we conducted an open-label prospective phase 2 clinical trial to assess safety and tolerability of AT-001 (caficrestat) treatment in patients hospitalized with COVID-19 infection and history of diabetes mellitus and heart disease. The study design prospectively included selection of matched controls from a contemporaneous registry of COVID-19 patients hospitalized at the same institution.

2. 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 the 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 during the index hospitalization. COVID-19 infection was confirmed by laboratory RT-PCR testing. Key exclusion criteria included inability to take study drug by mouth or nasogastric tube, participation in another FDA-regulated investigational drug placebo-controlled clinical trial within previous 30 days, and women of childbearing potential. The study protocol was approved by the institutional review board of New York University Grossman School of Medicine. All participants provided written informed consent prior to initiation of study procedures. The study was registered as a clinical trial on the clinicaltrials.gov website (Identifier NCT04365699) prior to the start of enrollment.

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. To minimize risk to participants and study personnel during the COVID-19 pandemic, study procedures were conducted remotely. Subject eligibility was determined by review of the electronic medical record. After informed consent was obtained, AT-001 (caficrestat) 1500 mg twice daily was administered by mouth or nasogastric tube for up to 14 days. The electronic medical record was used to extract information on demographics, co-morbid medical conditions, COVID-19 complications, adverse events, hospital discharge and transfer information. 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 determined at 30 days after the last dose of study drug. The study design prospectively planned analysis of matched control subjects of patients hospitalized with COVID-19 infections at the study enrollment sites. Clinical data related to an index hospitalization for COVID-19 infection for matched control subjects were extracted from a deidentified data registry.

Study drug administration. AT-001 (caficrestat) 500 mg capsules were provided by the Sponsor (Applied Therapeutics Inc., New York NY), and stored and distributed by the NYULH Investigational Pharmacy. After confirmation of written informed consent and participant eligibility, an electronic order was placed by the site Principal Investigator (SDK and JG). The Investigational Pharmacy dispensed a 14-day supply of AT-001 (caficrestat) 500 mg capsules to the inpatient hospital unit. A dose of AT-001 (caficrestat) 1500 mg (3 capsules) were administered by mouth twice daily for up to 14 days per discretion of the investigators and treatment team. If hospital discharge occurred prior to completion of treatment, the remaining supply of AT-001 (caficrestat) capsules were given to the participant at the time of discharge with instructions for self-administration post-discharge. Study drug administration was tracked in the electronic medical record prior to discharge, and by daily telephone contact post-discharge.

Data Analysis. To provide observational control data in hospitalized COVID-19 patients not treated with AT-001 (caficrestat), 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. As of February 15, 2020, the NYULH registry database had captured data on approximately 43,000 patients with COVID-19 diagnosis hospitalized in the NYULH Tisch and NYULH Long Island Hospitals (11,563 patients with at least one inpatient encounter diagnosis for diabetes mellitus, and 3608 patients with at least one inpatient encounter diagnosis for hypertension). There were 1931 patients with history of diabetes mellitus, 559 patients with history of hypertension, and 190 patients with history of both diabetes mellitus and hypertension who also had available data to match participants who received AT-001 (caficrestat). 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 (in bins of 5 years), 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 kgs interval. Each participant in the prospective AT-001 (caficrestat) study had more than one matching control group patient. There was no specific hierarchy of selection for the matches, as the variables were considered as independent of each other. Descriptive statistics are reported for the participant prospectively collected data and retrospective data from the matched cohorts. The median length of stay with its 95% confidence interval for participants who receive AT-001 (caficrestat) and matched control subjects and the between group difference in median of length of stay with its 95% confidence interval (using the Hodges-Lehmann estimate of location shift) for the AT-001 (caficrestat) and the control groups are reported.

3. Results

Study cohort. Between April 2020 and December 2020, 10 patients hospitalized at NYULH Tisch and NYULH Long Island hospitals for COVID19 infection were enrolled in the prospective trial and received open-label treatment with AT-001 (caficrestat). All participants in the prospective study had history of diabetes mellitus and hypertension, and were treated with supplemental oxygen. Based on the two sets of matching criteria described in the methods, 16 and 55 patients were identified for matching control groups 1 and 2, respectively. Table 1 summarizes demographic and clinical characteristics of the prospective clinical trial participants and two control groups.

Study drug safety and tolerability. Five of the 10 participants in the prospective clinical trial completed >80% of scheduled 28 doses of AT-001 (caficrestat), with overall mean of 15 completed doses. AT-001 (caficrestat) treatment was discontinued early due to adverse events not related to study drug in two participants, due to mild-moderate grade adverse events possibly linked to study drug in three participants (nausea/GI upset (n = 2) and localized skin

Table 1
Summary of demographics and clinical characteristics of participants in the prospective clinical trial, and two matched control groups. Data are presented as percentage, mean ± standard deviation, or median (interquartile range).

	All patients		
	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)[a]	52.5 (7.7; 176.5)	79.2 (8.3; 183)	60.7 (7.9; 110.5)

[a] For patients with available C-Reactive Protein value available at hospital admission.

Table 2
Summary of hospital length of stay (LOS) data in participants enrolled in the prospective clinical trial of AT-001 and two groups of matched control subjects. LOS and estimated differences in LOS data are shown as median (95% Confidence Intervals) and are presented in number of days.

	All Subjects			Surviving Subjects		
	AT-001	**Match 1**	**Match 2**	**AT-001**	**Match 1**	**Match 2**
N	10	16	55	8	11	40
Median LOS (95% CI)	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)

rash (n = 1)), and due to patient preference in three participants. Safety laboratory monitoring during hospitalization did not demonstrate any treatment-related abnormal findings.

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 percent mortality observed in the AT-001 (caficrestat) group (20%) was numerically lower than that observed in both matched controls groups (first matched control group 5 out of 16 subjects (31.3%) and second matched control group 15 out of 55 subjects (27.3%)). 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 2).

4. Discussion

This single-center, prospective, open-label pilot study was performed to assess the safety, tolerability and efficacy of aldose reductase inhibition with AT-001 (caficrestat) in 10 hospitalized patients with COVID-19 and co-morbid diabetes mellitus and hypertension. AT-001 (caficrestat) was generally safe and well tolerated. Analysis of mortality and length of hospital stay showed numerical trends in favor of AT-001 (caficrestat).

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. The underlying causal pathways linking cardiometabolic diseases to adverse outcomes in COVID-19 remain uncharacterized, but may be in part be attributable to upregulation of the NLRP3 inflammasome pathway and induction of trained innate immunity in these populations. 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. In contrast to other therapies currently employed for treatment of COVID-19, such as remdesivir, monoclonal antibodies and convalescent plasma, AT-001 (caficrestat) is dosed orally and can be administered in an outpatient setting.

Despite important advances in prevention and treatment, the COVID-19 pandemic continues to be a major global health crisis, and strategies to mitigate risk of acute disease complications and death are urgently needed. COVID-19 is associated with increased risk of adverse outcomes in patients with diabetes mellitus, and also may lead to acute and chronic alterations in glycemic control. Although strategies for disease eradication through vaccination have been at the forefront of public health strategies, management of the acute and long-term complications of the disease in affected individuals remains an important consideration that may persist beyond the duration of current pandemic. Note this is a pilot study and further studies are needed to better understand the role of aldose reductase inhibition and AT-001 (caficrestat) in patients with COVID-19. Further study of inhibition of the aldose reductase pathway might lead to novel treatment strategies in COVID-19 patients with CV complications and other acute and chronic inflammatory diseases.

Declaration of competing interest

Shoshana Shendelman, PhD and Riccardo Perfetti, MD, PhD are both employees and shareholders of Applied Therapeutics.All other authors have no conflicts of interest to disclose.

Acknowledgements

The present study was funded by Applied Therapeutics Inc.

References

[1] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in wuhan, China. J Am Med Assoc 2020;323(11):1061–9.
[2] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62.
[3] Zhou P, Yang X, Wang X, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3.
[4] Giacco F, Brownlee. Oxidative stress and diabetic complications. *M.Circ Res.* 2010;107(9):1058–70.
[5] Son NH, Ananthakrishnan R, Yu S, Khan RS, Jiang H, Ji R, et al. Cardiomyocyte aldose reductase causes heart failure and impairs recovery from ischemia.

PLoS One 2012;7:e46549.
[6] Ruef J, Liu SQ, Bode C, Tocchi M, Srivastava S, Runge MS, et al. Involvement of aldose reductase in vascular smooth muscle cell growth and lesion formation after arterial injury. Arterioscler Thromb Vasc Biol 2000;20:1745–52.
[7] Pal PB, Sonowal H, Shukla K, Srivastava SK, Ramana KV. Aldose reductase mediates NLRP3 inflammasome-initiated innate immune response in hyperglycemia-induced Thp1 monocytes and male mice. Endocrinology 2017;158(10):3661–75.
[8] Vedantham S, Thiagarajan D, Ananthakrishnan R, Wang L, Rosario R, Zou YS, et al. Aldose reductase drives hyperacetylation of Egr-1 in hyperglycemia and consequent upregulation of proinflammatory and prothrombotic signals. Diabetes 2014;63(2):761–74.
[9] Hwang YC, Kaneko M, Bakr S, Liao H, Lu Y, Lewis ER, et al. Central role for aldose reductase pathway in myocardial ischemic injury. Faseb J 2004;11: 1192–9.
[10] Ramasamy R, Oates PJ, Schaefer S. Aldose reductase inhibition protects diabetic and nondiabetic rat hearts from ischemic injury. Diabetes 1997;46(2): 292–300.
[11] Ravindranath TM, Mong PY, Ananthakrishnan R, Li Q, Quadri N, Schmidt AM, et al. Novel role for aldose reductase in mediating acute inflammatory responses in the lung. J Immunol 2009;183:8128–37.
[12] Perfetti P, Shendelman S. Clinical assessment of AT-001, an aldose reductase inhihibitor in development for diabetic cardiomyopathy: a 28 day proof of concept study. American Heart Association 2019;16–19. Nov.
[13] Perfetti R, Rowell P, Shendelman S, Lawson F, Ramasamy R. Preclinical and clinical Proof of Concept for Metabolic Intervention in diabetic cardiomyopathy. Heart Failure Society of America; 2019. Sep 13-16.
[14] Nasrien Ibrahim N, Januzzi JL, Perfetti R, Lawson F, Shendelman S. 2 the ARISE-HF study – Development of AT-001 for the treatment of diabetic cardiomyopathy. European Society of Cardiology-Heart Failure; 2020. May 21-23.