JACC: CASE REPORTS
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION.

VOL. 2, NO. 9, 2020

HEART FAILURE AND IMAGING

INTERMEDIATE

CASE REPORT: CLINICAL CASE

A Recovered Case of COVID-19 Myocarditis and ARDS Treated With Corticosteroids, Tocilizumab, and Experimental AT-001

Justin Coyle, DO,[a] Efehi Igbinomwanhia, MD, MPH,[b] Alejandro Sanchez-Nadales, MD,[b] Sorin Danciu, MD, MS,[a] Chae Chu, MD,[c] Nishit Shah, MD[a]

ABSTRACT

We describes a case of a critically ill patient with myocarditis and severe acute respiratory distress syndrome related to coronavirus disease-2019. This case highlights management strategies, including the use of corticosteroids, an interleukin-6 inhibitor, and an aldose reductase inhibitor, resulting in complete clinical recovery. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:1331-6) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 57-year-old man presented to the emergency department with shortness of breath, fevers, cough, myalgias, decreased appetite, nausea, and diarrhea for 1 week. The patient tested positive for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), subsequently complicated by severe acute respiratory distress syndrome (ARDS) and acute cardiac injury.

LEARNING OBJECTIVES

- Prevalence and prognostic implications of cardiac injury (defined as troponin elevation >99th percentile upper reference limit) in COVID-19.
- Considerations for differentiating causes of cardiac injury in COVID-19.
- Management strategies for myocarditis and severe ARDS in COVID-19.

PAST MEDICAL HISTORY

He had a history of hypertension and was taking lisinopril.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included SARS-CoV-2 causing severe ARDS and acute cardiac injury from direct viral toxicity (i.e., myocarditis), acute coronary syndrome (ACS), demand ischemia, and stress cardiomyopathy.

From the [a]Department of Cardiovascular Medicine, Advocate Illinois Masonic Medical Center, Chicago, Illinois; [b]Department of Medicine, Advocate Illinois Masonic Medical Center, Chicago, Illinois; and the [c]Department of Pulmonology and Critical Care Medicine, Advocate Illinois Masonic Medical Center, Chicago, Illinois. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received April 15, 2020; accepted April 20, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.04.025

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ARDS = acute respiratory distress syndrome

ARI = aldose reductase inhibitor

CMR = cardiac magnetic resonance

COVID-19 = coronavirus disease-2019

CT = computed tomography

ECG = electrocardiogram

Fio_2 = fraction of inspired oxygen

LGE = late gadolinium enhancement

SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

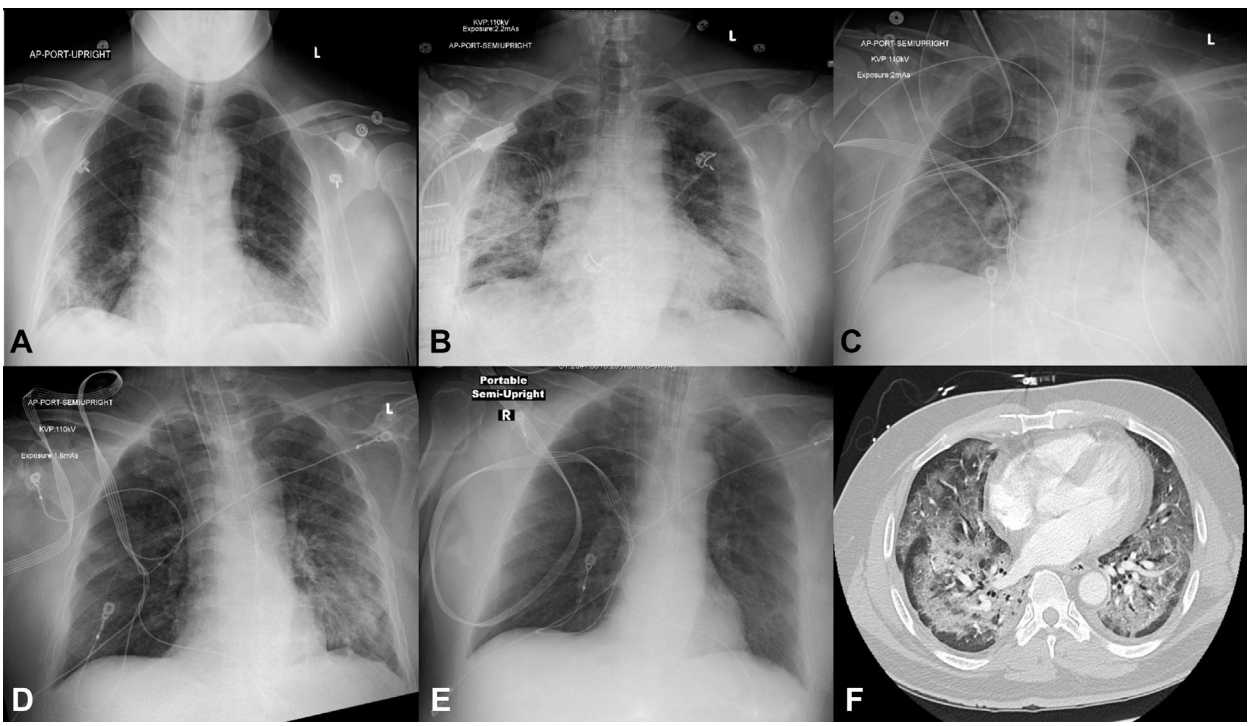
INVESTIGATIONS

Initial evaluation revealed a positive SARS-CoV-2 test result, with extensive viral, bacterial, and fungal panels returning negative results. Sequential chest radiographs and computed tomography of the chest showed progressive bilateral patchy interstitial opacities (Figures 1A to 1F) correlating with the patient's severe hypoxia. Laboratory results were most notable for lymphopenia, elevated inflammatory markers, a rapid rise in troponin I, and elevated N-terminal pro-B-type natriuretic peptide (Table 1). Serial electrocardiograms (ECGs) demonstrated sinus tachycardia without ST-T wave changes (Figure 2). A transthoracic echocardiogram on the third day of admission revealed moderate diffuse hypokinesis with relative apical sparing and a left ventricular ejection fraction of 35% to 40%. Notably, there was no ventricular dilation or pericardial effusion. On hospital day 18, cardiac magnetic resonance (CMR) demonstrated a recovery of ejection fraction to 82% and diffuse biventricular and biatrial edema with a small area of late gadolinium enhancement (LGE), as shown in Figures 3A and 3B.

MANAGEMENT

Initial management consisted of hydroxychloroquine, azithromycin, and ceftriaxone for SARS-CoV-2 pneumonia and possible concomitant bacterial infection. On hospital day 3, ARDS developed, and the patient required elective endotracheal intubation and mechanical ventilation. The patient was also treated for presumed myocarditis with the following: methylprednisolone, 500 mg intravenously daily for 4 days, with subsequent prednisone taper; colchicine, 0.6 mg every 12 h; and hemodynamic monitoring with the FloTrac system (Edwards Lifesciences, Irvine, California) through existing arterial and central venous

FIGURE 1 Serial Chest Radiographs and CT Scan



(A) Initial chest radiograph with bibasilar patchy interstitial opacities. **(B)** Chest radiograph on day 3 with worsening bilateral opacities. **(C)** Chest radiograph on day 5 following intubation. **(D)** Chest radiograph on day 6 with marked improvement in aeration. **(E)** Chest radiograph on day 8 showing normal lung parenchyma. **(F)** Computed tomography (CT) of the chest on day 3 revealed extensive diffuse bilateral airspace consolidations and ground-glass opacities most pronounced in the right upper lobe and bilateral lower lobes, with areas of subpleural sparing. Trace bilateral pleural effusions and minimal coronary artery calcification were noted.
AP = anteroposterior; L = left; R = right.

catheters. The next day, a milrinone infusion was started for cardiogenic shock as evidenced by hypotension, a cardiac index of 1.4 l/min/m^2, and systemic vascular resistance of 3,000 dynes/s/cm^{-5}. On hospital day 5, the ratio of the arterial partial pressure of oxygen to the fraction of inspired oxygen (Fio_2) (P/F ratio) worsened to 75, thus meeting criteria for severe ARDS. Changes in management for his ARDS included increasing positive end-expiratory pressure from 10 to 17 cm H_2O, Fio_2 up to 90%, increasing the inspiratory-to-expiratory ratio, and neuromuscular blockade with continuous rocuronium infusion. Hemodynamically, the patient required a 3-fold increase in milrinone infusion and initiation of norepinephrine to support blood pressure with diuresis. Finally, the interleukin-6 inhibitor tocilizumab, at 4 mg/kg (400 mg), was administered as a single infusion. Within 24 h the patient's oxygenation and hemodynamics improved, as evidenced by a P/F ratio of 246, cessation of norepinephrine, and reduction in milrinone. On hospital day 7, an aldose reductase inhibitor (ARI) currently known as AT-001 was initiated at a dose of 1,500 mg every 12 h for a 14-day course. Over the next 3 days the patient was weaned from neuromuscular blockade, milrinone, and mechanical ventilatory support until extubation on hospital day 10 (total of 7 days of mechanical ventilation), and he was eventually discharged on hospital day 19.

TABLE 1 Laboratory Test Results

Laboratory Tests	Reference Values	Arrival	Hospital Day 3	Hospital Day 5	Hospital Day 6
Fio_2 (%)		21	40	80-90	50
Pao_2 (mm Hg)	83-108	–	59*	60†	123‡
Pao_2/Fio_2 ratio	300-500	~310	148	75	246
pH	7.35-7.45	–	7.55	7.43	7.38
$Paco_2$ (mm Hg)	35-48	–	28	37	43
Troponin I (ng/ml)	<0.05	–	0.02-7.33§	0.54	0.30
NT-proBNP (pg/ml)	<126	–	859	1,300	520
Interleukin-6 (pg/ml)	0.0-5.0	–	18	–	–
C-reactive protein (mg/dl)	<1.0	8.1	12.9	20.7	5.1
Ferritin (ng/ml)	26-388	2,106	–	2,280	1,678
Lactate dehydrogenase (U/l)	86-234	347	487	559	367
White blood cells ($\times 10^9$/l)	4.2-11	4.7	–	–	–
Absolute lymphocytes ($\times 10^3$)	1.0-4.0	0.5	–	–	–
Procalcitonin (ng/ml)	<0.10	0.18	–	–	–
AST (U/l)	1.0-35	113	–	–	–
ALT (U/l)	1.0-45	106	–	–	–

*Venturi mask with Fio_2 40%. †Assist control volume control 18 respirations/min, 400 ml, FiO_2 80%, 10 cm H_2O then increased to 18 respirations/min, 400 ml, FiO_2 90%, 17 cm H_2O. ‡Assist control volume control 20 respirations/min, 400 ml, FiO_2 50%, 15 cm H_2O. §3 h later.

ALT = alanine aminotransferase; AST = aspartate transaminase; Fio_2 = fraction of inspired oxygen; NT-proBNP = N-terminal pro-B-type natriuretic peptide; $Paco_2$ = arterial partial pressure of carbon dioxide; Pao_2 = arterial partial pressure of oxygen.

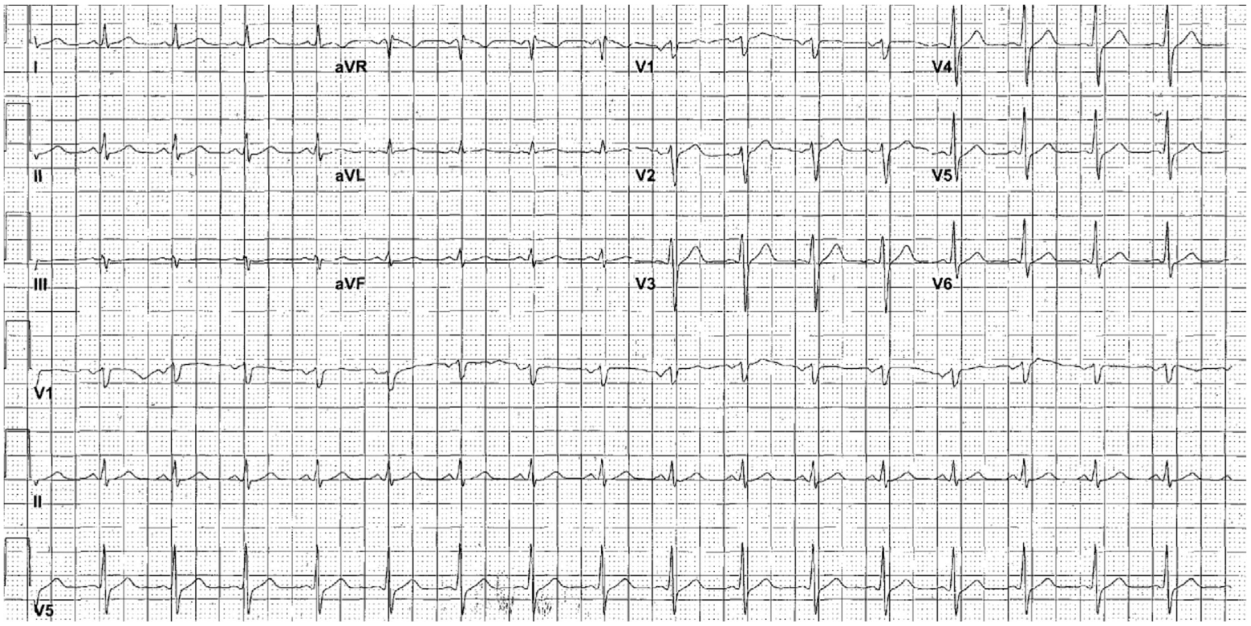
DISCUSSION

The COVID-19 pandemic has caused tremendous morbidity and mortality, claiming 120,000 lives at an observed case-mortality rate of at least 4% since the first reported death in China on January 11, 2020. The virus has infected more than 2 million people across at least 180 countries in just over 3 months (1,2). The virus invades cells by binding and crossing the cellular membrane through angiotensin-converting enzyme 2. This protein is found in high concentration in pneumocytes and myocytes, thus explaining 2 of the principal organs involved in the disease process. Following initial viremia, the infection transitions into a cytokine-release phase that can lead to development of ARDS and acute myocardial inflammation (3). If treatment is delayed or absent, the resulting myocarditis may progress to long-term heart failure with irreversible dilatation and tissue fibrosis.

Our understanding of this virus and corresponding treatment strategies continues to expand, but it remains in an early investigative period. Multiple institutions have released guidelines to assist in management. The majority of the guidance focuses on the associated respiratory dysfunction, which is derived from abundant existing data on ARDS management. However, less guidance exists on cardiac complications of the virus despite its prevalence and poor prognostication related to the disease. A study from China revealed that patients hospitalized for COVID-19 infection developed cardiac injury in roughly 20% of cases thus leading to >50% mortality (4). A retrospective analysis of cause of death in Chinese patients infected with COVID-19 revealed that 40% of patients died at least in part because of myocardial injury and circulatory collapse (5). These organ systems do not operate independently and often compound complications. For instance, patients with cardiac injury are more than 5-fold more likely to require mechanical ventilation (4).

We describe a case of COVID-19 resulting in critical illness in the form of severe ARDS and suspected myocarditis with ensuing cardiogenic shock. Similar to reported averages, our patient exhibited rapid respiratory failure on hospital day 3 and 10 days after symptom onset. Concomitantly, the patient had a significant rapid rise in troponin without ischemic changes on ECG, as well as global hypokinesis with relative apical sparing on the echocardiogram suggestive of myocarditis. Eventually, CMR showed diffuse biventricular and biatrial edema with mild LGE, thereby making myocarditis the most likely cause of the acute cardiac injury in this context. Other

FIGURE 2 Electrocardiogram With Sinus Tachycardia



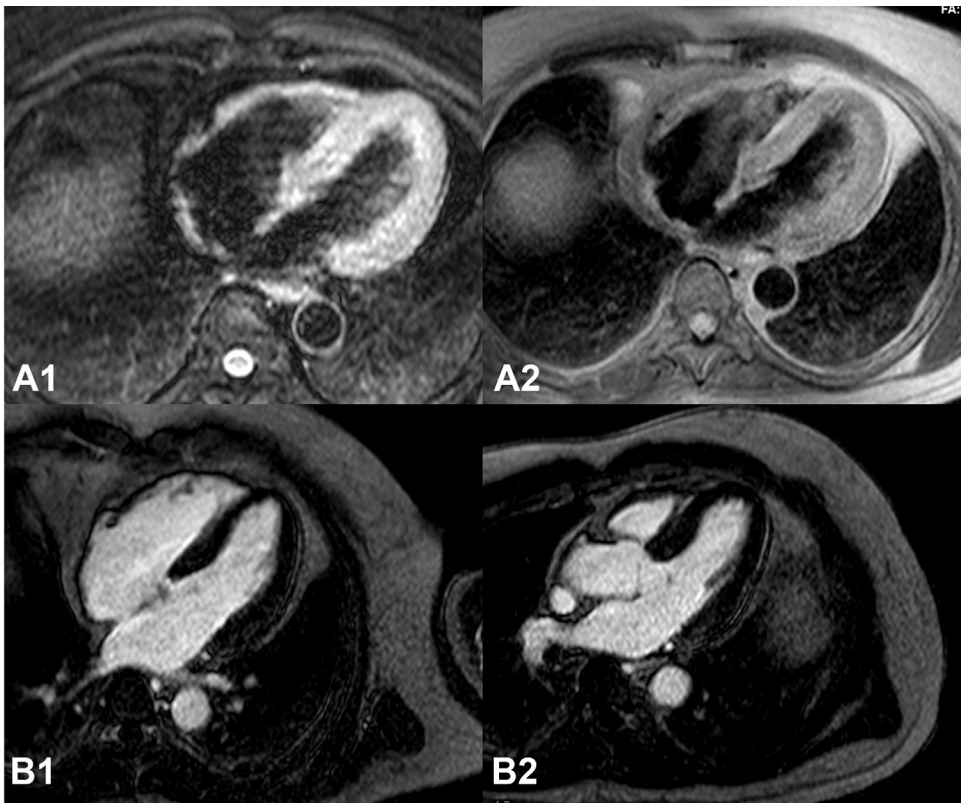
reasonable but less likely causes include stress cardiomyopathy (inverted variant or reverse takotsubo cardiomyopathy, given apical sparing), ACS, or demand ischemia. In stress cardiomyopathy, more than 95% of cases exhibit ECG changes, and CMR shows edema without LGE in the areas of regional wall motion abnormalities. Additionally, reverse takotsubo cardiomyopathy makes up <5% of cases, thus further decreasing its likelihood (6). Given the absence of ECG changes, minimal coronary artery calcification on chest computed tomography, and regional wall motion abnormalities outside of coronary distributions, ACS was also improbable. Further investigation with endomyocardial biopsy to confirm the histological diagnosis of myocarditis was deferred, given the risk of the procedure, the critical state of the patient, and the goal to minimize viral exposure to health care personnel. Angiograms to evaluate coronary disease or Swan-Ganz catheters to assess hemodynamics were avoided for similar reasons. These limitations will pose ongoing diagnostic and therapeutic uncertainty in COVID-19 patients with cardiac injury. Reliance on clinical acumen and noninvasive techniques will be required to guide management.

Treatment of our patient's myocarditis with high-dose intravenous corticosteroids was guided by treatment of other forms of fulminant myocarditis (7). Additionally, some studies indicate a mortality benefit and reduced duration of mechanical intubation in ARDS, including observational data from China (8,9). When the patient's respiratory and hemodynamic status worsened in the setting of persistently elevated inflammatory markers, an interleukin-6 inhibitor tocilizumab was infused. Tocilizumab has Food and Drug Administration approval for treating inflammatory conditions such as rheumatoid arthritis and giant cell arteritis. It also carries an off-label use for treating cytokine-release syndrome, which may help attenuate this phase of COVID-19 infection. A Chinese study reported positive outcomes with tocilizumab use for treating COVID-19 pneumonia, and phase III clinical trials are currently under way in the United States (10). Subsequently, an ARI currently known as AT-001 was initiated and was aimed at further mitigating pulmonary and cardiac inflammatory sequelae. In the setting of endotoxins, ARIs have shown reduced inflammatory markers, recovery of cardiac function, and mortality benefit in animal models (11). Improved airway inflammation has also been observed in animals treated with ARIs (12).

CONCLUSIONS

SARS-CoV-2 principally invades pneumocytes and myocytes, thereby generating a significant inflammatory cascade that can render critical illness in the

FIGURE 3 **CMR Images**



(A1 and A2) Cardiac magnetic resonance (CMR) T_2-weighted images showing diffusely increased signal uptake, higher than skeletal muscle, involving both ventricles and atria. **(B1 and B2)** Cardiac magnetic resonance T1-weighted images with small, patchy late gadolinium enhancement of the midwall of the basal inferolateral segments.

form of ARDS and cardiac injury associated with high mortality. The differential diagnosis of cardiac injury in COVID-19 mainly includes myocarditis, ACS, demand ischemia, and stress cardiomyopathy. Our case highlights the use of noninvasive methods for early detection and differentiation of cardiac injury. Early aggressive treatment of suspected myocarditis with intravenous corticosteroids followed by tocilizumab and AT-001 likely contributed to our patient's full recovery.

ADDRESS FOR CORRESPONDENCE: Dr. Alejandro Sanchez-Nadales, Department of Internal Medicine, Advocate Illinois Masonic Medical Center, 856 West Nelson Street, Chicago, Illinois 60657. E-mail: alejandro.sanchez2@advocatehealth.com.

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020 Feb 24 [E-pub ahead of print].

2. Johns Hopkins University Coronavirus Resource Center. COVID-19 map. Available at: coronavirus.jhu.edu/map.html. Accessed May 1, 2020.

3. Yi Y, Lagniton PNP, Ye S, Li E, Xu RH. COVID-19: what has been learned and to be learned about the novel coronavirus disease. Int J Biol Sci 2020;16:1753–66.

4. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020:e200950.

5. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan. Intensive Care Med 2020;46:846–8.

6. Lyon AR, Bossone E, Schneider B, et al. Current state of knowledge on takotsubo syndrome: a position statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2016;18:8–27.

7. Maisch B. Cardio-immunology of myocarditis: focus on immune mechanisms and treatment options. Front Cardiovasc Med 2019;6:48.

8. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the

management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med 2020;48:e440–69.

9. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020:e200994.

10. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A 2020;117:10970–5.

11. Ramana KV, Willis MS, White MD, et al. Endotoxin-induced cardiomyopathy and systemic inflammation in mice is prevented by aldose reductase inhibition. Circulation 2006;114:1838–46.

12. Yadav UC, Ramana KV, Aguilera-Aguirre L, Boldogh I, Boulares HA, Srivastava SK. Inhibition of aldose reductase prevents experimental allergic airway inflammation in mice. PLoS One 2009;4:e6535.

KEY WORDS aldose reductase inhibitor, ARDS, cardiac magnetic resonance, cardiogenic shock, corticosteroids, COVID-19, myocarditis, SARS-CoV-2, tocilizumab, 2019-nCoV