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ORIGINAL RESEARCH

# Randomized Prospective Open Label Study Shows No Impact on Clinical Outcome of Adding Losartan to Hospitalized COVID-19 Patients with Mild Hypoxemia

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## ABSTRACT

***Introduction***: Despite considerable scientific debate, there have been no prospective clinical studies on the effects of angiotensin II receptor blockers (ARBs) on the course of COVID-19 infection. Losartan is the ARB that was chosen to be tested in this study.

***Methods***: Patients with COVID-19 and mild hypoxia (receipt of $\leq 3$ L/min $O_2$ by nasal cannula) admitted to three hospitals were randomized in a 1:1 ratio within 72 h of SARS-CoV-2 nucleic acid testing confirmation to prospectively receive standard of care (SOC) alone or SOC plus losartan 12.5 mg orally every 12 h for 10 days or until hospital discharge, with the option to titrate upward dependent on blood pressure tolerability. Primary composite endpoint was receipt of mechanical ventilation or death before receiving ventilation. Subjects were followed until discharge to home or until an endpoint was met in the hospital.

***Results***: Sixteen subjects received an ARB plus SOC and 15 subjects received SOC alone. The median age was 53 years for both groups. Median time from hospital admission to study enrollment was 2 days (range 1–6) for the ARB group and 2 days (range 1–4) for the SOC group. Mean Charlson comorbidity index was 2 for both groups. One subject in each group achieved the composite endpoint.

***Conclusion***: This small prospective randomized open-label study showed no clinically significant impacts of ARB therapy in mildly hypoxemic patients hospitalized with COVID-19 early in the pandemic. A larger prospective randomized placebo-controlled trial would be needed to confirm these findings or capture less pronounced effects and probably should focus on outpatients earlier in disease course.

***Trial Registration***: clinicaltrials.gov; March 27, 2020; NCT04340557.

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**Keywords:** ARB; COVID-19; Losartan; SARS-CoV-2

**Key Summary Points**

**Why carry out this study?**

Repurposing of available drugs to treat patients during the rapidly spreading COVID-19 pandemic is of great interest.

Previous studies had hinted toward possible benefit of angiotensin receptor blockers in the treatment of SARS-CoV-2-mediated respiratory disease.

This study evaluated whether the angiotensin receptor blocker therapy, losartan, could improve oxygenation and, therefore, shorten hospital stay and reduce mortality in patients with mild hypoxia due to COVID-19.

**What was learned from the study?**

Losartan did not significantly impact length of hospital stay or mortality when added to the standard of care in COVID-19 infected patients with mild hypoxia.

A larger study will be needed of COVID-19 patients with less severe disease in the outpatient setting to better understand the role of angiotensin receptor blocker therapy in COVID-19.

## DIGITAL FEATURES

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## INTRODUCTION

COVID-19 infection, as is common with many types of viral and atypical infections, is characterized by a biphasic illness [1–3]. The first relatively mild protean phase is driven by viral replication and is the foundation of the majority of asymptomatic and symptomatic disease, resolving in about a week [1–3]. SARS-CoV-2 spike protein binds to its receptor angiotensin converting enzyme II (ACE2) in order to enter the cell and begin viral replication [4]. Thus, this first phase of illness offers potential to use angiotensin receptor blocker II (ARB) to abort viral pathogenesis. The second phase, driven by the adaptive immune response to the viral infection, may lead to potentially catastrophic disease manifestations requiring hospitalization and intensive care in a minority of SARS-CoV-2-infected patients, characterized by acute respiratory distress syndrome (ARDS), vasculitis with thrombotic complications and systemic involvement [5–7]. Clinical studies are under way investigating immunomodulation of various forms to target this second phase of illness.

ARBs are currently being studied for early infected COVID-19 patients [8]. SARS-CoV and SARS-CoV-2 downregulate ACE2 by binding it via the viral spike (S1) protein, allowing for viral entry into the host cell [9]. After viral entry, the virus quickly replicates resulting in tissue injury. An ARB, like losartan, has the potential mechanism of action to inhibit viral cell entry by blocking the angiotensin II type 1 receptor (AT1R) [10]. This is the first study to prospectively evaluate the addition of an ARB to otherwise standard treatment for adults with mild to moderate hypoxemia secondary to COVID-19.

## METHODS

### Study Design

This was an open-label randomized controlled trial performed at three hospital centers: Sharp Memorial Hospital (San Diego, CA, USA), Sharp Grossmont Hospital (La Mesa, CA, USA) and Sharp Chula Vista Hospital (Chula Vista, CA, USA). The research protocol was approved by the Sharp Healthcare Institutional Review Board (IRB # 2003902) for all three sites prior to

patient enrollment and was registered on clinicaltrials.gov (March 27, 2020; NCT04340557). All participants and/or legally authorized representatives were provided complete information about the risks and benefits of participation in this study. Subjects were made aware that results of the study would potentially be published free of any subject identifiers. All participants and/or legally authorized representatives signed an the informed consent form to participate in this study, which was documented via DocuSign™. This study was performed in accordance with the Declaration of Helsinki. The study design, process of local IRB approval and adherence to the requirements obtaining an informed consent are similar to our other published studies [11, 12].

### Study Population

Adult patients $\geq$ 18 years of age presenting with COVID-19 infection confirmed by positive polymerase chain reaction testing for the SARS-CoV-2 genome in nasopharyngeal and/or nares swab sample were considered for inclusion if they demonstrated mild to moderate hypoxia ($SpO_2 \leq 96\%$ on $\geq 1$ L/min $O_2$ by nasal cannula) but not on mechanical ventilation.

### Treatments

After informed consent was obtained, subjects were randomized 1:1 into the treatment arm (ARB) or standard of care (SOC) control arm. SOC consisted of the subject remaining on or being eligible for any treatment not part of a randomized clinical trial and considered standard of care at the time of enrollment. On May 13, 2020, and afterwards, this included the use of remdesivir. Patients were also eligible to receive convalescent plasma therapy as part of the nationally available compassionate use registry, which was informally accepted in our region as SOC. The ARB treatment arm consisted of the subject receiving an ARB (losartan—generic brand was locally sourced) 12.5 mg orally every 12 h for 10 days, beginning on the day of randomization, in addition to SOC. The treating physician had the option to titrate the dose upward if blood pressure allowed. Subjects were monitored for progression to the endpoint of (1) respiratory failure requiring receipt of mechanical ventilation (a composite of either receiving ventilation or the patient status changed to a do not resuscitate/do not intubate resulting in progressive respiratory failure and death) or (2) death from non-respiratory causes prior to receipt of mechanical ventilation. If the subject progressed to mechanical ventilation, receipt of off-label agents and/or enrollment in other clinical trials was allowed. The subject's hospital course was followed until hospital discharge.

### Clinical Data Extraction and Analysis

Relevant clinical and laboratory information was captured to allow for group comparisons, including the calculation of the Charlson comorbidity index (https://www.mdcalc.com/charlson-comorbidity-index-cci).

### Statistical Analysis

Statistical differences in rates of receipt of mechanical ventilation and other categorical or ordinal variables were calculated using Fisher exact test, and differences in continuous variables were calculated using the Mann-Whitney $U$ test. $p < 0.05$ was considered statistically significant.

## RESULTS

### Baseline Patient Demographics and Clinical Characteristics

Thirty-two patients were randomized with the intent to treat (ITT) between March 30 and July 4, 2020, 16 to receive ARB plus SOC and 15 to SOC alone. One patient in the ARB group did not receive losartan and was excluded from the analysis. Hypotension (SBP < 100) was similar in both groups (3/16 in ARB and 4/15 in SOC groups). Oxygen flow rate requirements were similar between the groups at enrollment (median ARB 0.5 L/min vs. SOC 2.0 L/min, $p = 0.41$,

Mann-Whitney *U* test) and at 48 h post-enrollment (median ARB and SOC 0 L/min, $p = 0.37$, Mann-Whitney *U* test). Total oxygen consumption (total liters) during the enrollment period was also similar between the two groups (median 5832 L ARB vs. 8208 L SOC, $p = 0.31$ Mann-Whitney U test).

The remaining patient characteristics are listed in Table 1, demonstrating median age of 53 years in both groups, overall 61% males and a majority of Hispanic/Latino patients, consistent with the local demographics of COVID-19 in Southern California. Diabetes mellitus, hypertension and obesity were the most common comorbidities. The mean body mass index in the ARB and SOC groups were 31 and 29 kg/m$^2$, respectively. Concomitant COVID-19 therapies received are also listed in Table 1. Notably, because the vast majority of these patients were enrolled early in the pandemic (April and May 2020), only a minority of patients received glucocorticoid and remdesivir therapies. Thereafter, study enrollment dropped off considerably because of a rise in competing clinical trials.

### Clinical Outcomes, Safety and Tolerability

Fifteen of 16 (94%) ARB and 13/15 (87%) SOC patients were discharged to home without need for ICU transfer or mortality. Two SOC patients (13.3%) and 1 ARB patient (6.3%) progressed to requiring ICU care. One patient in each group progressed to mechanical ventilation and died prior to discharge. Lengths of hospital stay were also similar between the groups (9 days for ARB, 10 days for SOC). No patient required ARB discontinuation because of tolerability or safety concerns.

## DISCUSSION

Preclinical studies suggested the potential for either benefit or harm from renin-angiotensin system blockers in COVID-19 [13]. Initial concerns stemmed from the hypothesis that angiotensin-converting enzyme inhibitors (ACE-Is) and ARBs may upregulate angiotensin converting enzyme 2 (ACE2), which is used by

**Table 1** Patient characteristics and outcomes

| | **ARB (*n* = 16)** | **SOC (*n* = 15)** |
|---|---|---|
| Mean age (years) | 59 | 55 |
| Median age (years) | 53 | 53 |
| Male *N* (%) | 10 (62.5) | 9 ((60) |
| Race *N* (%) | | |
| White | 1 (6.3) | 2 (13.3) |
| Black/African American | 1 (6.3) | 0 (0) |
| Hispanic | 2 (75) | 13 (86.7) |
| Asian | 0 (0) | 0 (0) |
| Unknown | 2 (12.5) | 0 (0) |
| Median days | | |
| Admission to enrollment (range) | 2 (1–6) | 2 (1–4) |
| Mean Charlson Comorbidity Index | 2 | 2 |
| Comorbidities *N* (%) | | |
| Diabetes mellitus | 3 (18.8) | 5 (33.3) |
| Hypertension | 7 (43.8) | 5 (33.3) |
| Obesity (BMI $\geq$ 30 kg/m$^2$) | 8 (50) | 5 (35.7) |
| Mean BMI (kg/m$^2$) | 31.1 | 28.8 |
| Mean BMI of obese (kg/m$^2$) | 35.8 | 35.0 |
| Tobacco use | 4 (25) | 2 (13.3) |
| Cardiovascular disease | 1 (6.3) | 0 (0) |
| Concomitant SARS-CoV-2 medications *N* (%) | | |
| Remdesivir | 4 (25) | 5 (33) |
| Glucocorticoids > 2 doses | 2 (12.5) | 5 (33) |
| Azithromycin | 2 (12.5) | 3 (20) |
| Hydroxychloroquine | 2 (12.5) | 1 (6.7) |
| Convalescent plasma | 1 (6.3) | 1 (7) |
| Anti-thrombotics | 16 (100) | 15 (100) |
| Outcomes *N* (%) | | |
| Discharge without progression to ICU | 15 (93.8) | 13 (86.7) |
| ICU transfer | 1 (6.3) | 2 (13.3) |

**Table 1** continued

| | ARB ($n$ = 16) | SOC ($n$ = 15) |
|---|---|---|
| In-hospital mortality | 1 (6.3) | 1 (6.7) |
| Mean length of stay (days) | 9 | 10 |

SARS-CoV-2 as an entry portal into pneumocytes and other cells, thereby facilitating viral infection and increasing illness severity. Mechanisms have been proposed by which ARB may upregulate ACE2 and decrease viral entry by formation of complexes between angiotensin II type 1 receptors and membrane-bound ACE2. This would offer potential therapeutic benefit, particularly in early COVID-19. Retrospective observational studies are marked by bias and other methodologic concerns so the overall neutral findings are of limited value [14–21]. Two recent meta-analyses have shown no benefit or harm of ARBs in COVID-19 [22, 23]. Interestingly, however, ACE-I and ARBs have been documented to be lung protective, suggesting possible benefit in renin angiotensin system blockade in pneumonia [24].

This study enrolled 32 ITT COVID-19 subjects who were randomized to receive losartan ARB in addition to SOC at the time versus SOC alone. We noted no significant differences in progression from mild hypoxia to severe disease requiring ICU transfer, mechanical ventilation or in-hospital mortality with addition of ARB. This is consistent with the overall neutral findings of retrospective observational studies and fully supports the recommendations early in the COVID-19 pandemic by the American Heart Association, American College of Cardiology, Heart Failure Society of America, Canadian Heart Failure Society, Canadian Heart Failure Society and European Society of Cardiology to not discontinue or alter therapy on patients already on ACE-I or ARB to mitigate the risk of COVID-19 infection or to affect COVID-19 treatment outcome.

Although limited by its small size, unblinded design and being restricted to three hospitals in close proximity in one geographic area, this study suggests that ARB therapy may not influence COVID-19 pathogenesis. This may be less surprising now than it was at the beginning of the COVID-19 pandemic given what we have learned about the pathophysiology of severe COVID-19 infection, namely that progressive more severe disease is driven by system immunologic and coagulopathic mechanisms in the setting of a waning viral presence [2, 3, 5, 6]. Furthermore, given the evolution of SOC therapy over the past year, with the introduction of remdesivir in mid-May 2020 [25–27] and the mainstream adoption of glucocorticoid therapy in mid-June 2020 [28], it is likely that potentially small signals of ARB clinical benefit that might have been captured in a more treatment-naïve background will be much more difficult to capture in the setting of current treatment paradigms. Other up and coming COVID-19 therapies such as SARS-CoV-2 monoclonal antibodies [29] and the use of intravenous immunoglobulins [11] will likely further hamper the study of ARB in the future. Indeed, the limited clinical utility of direct antiviral therapies is coming to light in larger scale assessments [30].

## CONCLUSIONS

This small prospective study of ARB (losartan) therapy L mildly hypoxic COVID-19 patients early in the pandemic, largely before the adoption of remdesivir and glucocorticoid therapies, showed no clinical benefit or harm in hospitalized patients with COVID-19. While larger randomized studies are needed to provide more definitive validation of these findings, we believe that it is unlikely that the evolving COVID-19 treatment paradigms will allow for any small signals of potential benefit or harm of ARB to be captured among hospitalized COVID-19 patients. Future studies of ARB therapy likely should focus on outpatients very early in their COVID-19 illness.

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***Authorship.*** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published. All authors were active participants in at least one category of study design, study execution, data gathering and organization, data analysis and statistics, or manuscript preparation.

***Authors' Contributions.*** Matthew Geriak: Study design, execution, data gathering and organization, data analysis, manuscript preparation. Fadi Haddad: Data analysis, subject referrals. Ravina Kullar: Data analysis and statistics. Kristina L. Greenwood: Data gathering and organization, data analysis. MacKenzie Habib: Data gathering and organization. Cole Habib: Data gathering and organization. David Willms: Data analysis,. George Sakoulas: Study design, subject referrals, data analysis, manuscript preparation, study team oversight.

***Disclosures.*** Matthew Geriak: has nothing to disclose. Fadi Haddad: has nothing to disclose. Ravina Kullar: has nothing to disclose. Kristina L. Greenwood: has nothing to disclose. MacKenzie Habib: has nothing to disclose. Cole Habib: has nothing to disclose. David Willms: has received speaking honoraria from La Jolla Pharmaceutical Company. George Sakoulas: has received speaking honoraria from Allergan, Sunovion and consulting fees from Allergan and Paratek Pharmaceuticals.

***Compliance with Ethics Guidelines.*** The research protocol was approved by the Sharp Healthcare Institutional Review Board (IRB # 2003902) for all three sites prior to patient enrollment. The study was performed in accordance with the Declaration of Helsinki. All participants and/or legally authorized representatives were provided complete information about the risks and benefits of participation prior to informed consent being obtained. All participants and/or legally authorized representatives signed to participate in this study on the informed consent form, and the signing to participate in this study was documented via DocuSign™. Subjects were made aware that results of the study would potentially be published free of any subject identifiers. We are extremely grateful to our study participants for allowing us to participate in their care, especially during the most challenging of times of great uncertainty during the COVID-19 pandemic.

***Data Availability.*** Datasets generated during and/or analyzed during the current study are available in collaboration upon communication with the corresponding author and approval of Sharp IRB.

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