Endotracheal Application of Ultraviolet A Light in Critically Ill Patients with Severe Acute Respiratory Syndrome Coronavirus 2: A First-in-Human Study

Ali Rezaie · Gil Y. Melmed · Gabriela Leite · Ruchi Mathur · Will Takakura · Isabel Pedraza · Michael Lewis · Rekha Murthy · George Chaux · Mark Pimentel

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ABSTRACT

Introduction: Our previous preclinical experiments show that under specific and monitored conditions, ultraviolet A (UVA) exposure reduces certain bacteria, fungi, and viruses including coronavirus-229E without harming mammalian columnar epithelial cells. The goal of this study was to evaluate the safety and effects of narrow-band UVA therapy administered by a novel device via endotracheal tube in critically ill subjects with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Methods: Newly intubated, mechanically ventilated adults with SARS-CoV-2 infection and an endotracheal tube size of at least 7.50 mm were eligible for inclusion in the study. Subjects were treated with UVA for 20 min daily for 5 days and followed for 30 days.

Results: Five subjects were enrolled (mean age 56.60 years, three male). At baseline, all subjects scored 9/10 on the World Health Organization (WHO) clinical severity scale (10 = death), with predicted mortality ranging from 21% to 95%. Average endotracheal viral load significantly reduced from baseline to day 5 (−2.41 log; range −1.16 to −4.54; Friedman p = 0.002) and day 6 (−3.20; range −1.20 to −6.77; Friedman p < 0.001). There were no treatment-emergent adverse events, with no changes in oxygenation or hemodynamics during the 20-min treatments. One subject died 17 days after enrollment due to intracranial hemorrhagic complications of anticoagulation while receiving extracorporeal membrane oxygenation. The remaining subjects clinically improved and scored 2, 4, 5, and 7 on the WHO scale at day 30. In these subjects, clinical improvement

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correlated with reduction of viral load (Spearman’s rho = 1, p < 0.001).

**Conclusions:** In this first-in-human study, endotracheal narrow-band UVA therapy, under specific and monitored settings, appears to be safe and associated with a reduction in respiratory SARS-CoV-2 viral burden over the treatment period. UVA therapy may provide a novel approach in the fight against COVID-19.

**Clinical Trial Number:** NCT04572399.

**Keywords:** SARS-CoV-2; Ultraviolet A light; Endotracheal administration; Viral load

### Key Summary Points

**Why carry out this study?**

- Preclinical data suggest that under specific and monitored settings, UVA light therapy can be an effective and safe antibacterial and antiviral treatment.
- Despite advances in treatment of coronavirus disease 2019 (COVID-19), mortality and morbidity remain high among critically ill patients.
- We hypothesized that endotracheal UVA therapy in ventilated patients might be feasible, safe, and capable of reducing respiratory viral load.

**What was learned from the study?**

- In this first-in-human study, endotracheal UVA therapy, under specific and monitored settings, appears safe and associated with a significant reduction in respiratory SARS-CoV-2 viral burden over the treatment period.
- UVA therapy may provide a novel approach in the fight against COVID-19.

### INTRODUCTION

Since the first report of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in December 2019, the global quest to find a highly effective modality to treat severe coronavirus disease 2019 (COVID-19) has been disappointing.

Despite advances in the care of patients with COVID-19, during the second surge in the USA approximately 20.10% of hospitalized patients required admission to an intensive care unit (ICU) [1], with 11.00% requiring mechanical ventilation and 3.50% mortality. This high burden of disease continues, despite current protocolized care for ventilated patients with COVID-19 including supportive care, steroids, remdesivir, and prompt treatment of known complications such as secondary infections and venous thromboembolism [2].

The ciliated airway epithelium serves as the main point of entry through binding of the SARS-CoV-2 spike (S) protein to the angiotensin-converting enzyme 2 (ACE) receptor, with infection of the upper respiratory tract then progressing to the lower respiratory tract [3]. Direct cytotoxic effects of SARS-CoV-2 along with dysregulated inflammatory responses and secondary respiratory infections inflict substantial morbidity and mortality in severe and critical cases of COVID-19 [4–6]. While the pathogenesis of COVID-19 has proven to be complex, one mechanism to explain SARS-CoV-2 virulence may be through impairment of mitochondrial antiviral signaling (MAVS) protein, which is responsible for host innate antiviral responses [7]. The MAVS protein transduces signals from cytoplasmic retinoic acid-inducible gene 1 (RIG-I)-like receptors (RLRs), which recognize viral RNA such as SARS-CoV-2. Activation of the MAVS protein induces an immune response to clear the virus from the host [8]. SARS-CoV-2 antagonizes the MAVS pathway, facilitating viral replication in infected cells [9].

Externally applied ultraviolet light therapy is an approved treatment for several atopic, inflammatory, and dysplastic dermatologic disorders [10]. In preclinical experiments,
Ultraviolet A (UVA) exposure under monitored conditions (i.e., specific intensity, peak wavelength, exposure time, and distance to target tissue) reduces bacteria, fungi, and RNA viruses including coronavirus-229E, but does not harm human columnar epithelial cells in vitro or murine columnar epithelial cells in vivo [11]. Moreover, narrow-band UVA (NB-UVA) exposure of coronavirus-229E-transfected human primary tracheal cells leads to activation of the MAVS protein, reduction in spike protein, and resumption of cell proliferation similar to uninfected cells, suggesting that NB-UVA may induce a beneficial antiviral state in infected human cells [11]. Interestingly, the beneficial effects of NB-UVA light in MAVS protein activation are not limited to cells directly exposed to UVA, but are also transmitted to cells that were not exposed to UVA [12]. This phenomenon could potentially increase the reach and magnitude of the antiviral effects of UVA light beyond the site of direct exposure.

Apart from a dysregulated inflammatory response, heightened viral replication has a critical role in the pathogenesis of severe and critical COVID-19 [13, 14]. Given the direct antiviral and immunomodulatory effects of UVA, we investigated the safety and treatment effects of a novel UVA-emitting device inserted into the endotracheal tube of critically ill subjects with SARS-CoV-2 infection.

METHODS

Trial Design

In this first-in-human open-label single-center trial, we aimed to recruit and treat five subjects. The trial protocol (ClinicalTrials.gov number NCT04572399) was approved by the institutional review board of Cedars-Sinai, Los Angeles, California, USA, and was overseen by an independent data and safety monitoring board (DSMB). Subjects’ legally authorized representatives provided written informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki. Inclusion criteria included age over 18 years, positive polymerase chain reaction (PCR) test result for SARS-CoV-2 on nasal swab, and mechanical ventilation with an endotracheal tube (ETT) inner diameter of at least 7.50 mm. Pregnant women were excluded. Subjects received all standard supportive care; concomitant use of any other COVID-19 treatments was permitted.

UVA Device

The UVA therapy device (Aytu Biosciences, Englewood, CO) consisted of a 5.40-mm-diameter sterile sealed multi-light emitting diode (LED) narrow-band UVA light catheter within a protective sheath and endotracheal adaptor, umbilical, and control unit (Fig. 1). The UVA catheter adaptor was connected to the ETT using a double-swivel multi-access port (Halyard Health, GA) to maintain a closed-loop system and prevent ambient exposure to exhaled air upon introduction of the catheter into the ETT.

Procedure

Within 24 h of enrollment, subjects underwent 20 min of endotracheal UVA therapy, which was repeated once daily for a total of five consecutive days. All subjects received 100% fraction of inspired oxygen (FiO₂) for 30 min prior to the procedure (see Supplemental Materials and Methods for detailed protocol). The UVA catheter was inserted to the distal end of the ETT, with concomitant ventilator adjustments to flow rate and tidal volume to maintain optimal oxygenation. A plastic clamp fixed the catheter base to the access port to ensure stability and consistent depth of catheter insertion throughout the 20-min treatment session. The procedural instructional video can be accessed at https://zenodo.org/record/4697987#.YHpAOJ-SmhM. UVA dosing was chosen on the basis of the optimal response of coronavirus 229E-infected human primary tracheal cells to UVA exposure observed in in vitro experiments [11]. Controlled narrow-band UVA emission (peak wavelength 340–345 nm) of maximum 2 mW/cm² was delivered at the level of tracheal mucosa. Predetermined criteria for treatment cessation and withdrawal of the UVA catheter...
included O₂ saturation drop below 88% or hemodynamic instability.

Endotracheal aspirates were taken prior to each UVA treatment and 24 h after the last UVA treatment for assessment of SARS-CoV-2 and absolute bacterial loads. Steps in preparation of the sampling traps and tracheal sampling, as well as sample processing and analysis for viral and absolute bacterial loads, are provided in the Supplemental Materials and Methods. Absolute quantification of bacterial load represented culturable and non-culturable, viable and non-viable, pathogenic, and non-pathogenic bacteria.

Baseline, hospital, and ICU admission-related information including relevant clinical, laboratory, and radiologic data were recorded for all patients until 30 days after enrollment. The World Health Organization (WHO) COVID-19 10-point ordinal severity scale [15] was calculated at enrollment, and on days 15 and 30 following enrollment. Sequential organ failure assessment (SOFA) [16] and Simplified Acute Physiology Score III (SAPSIII) [17, 18] scores were calculated from the worst values within 24 h of ICU admission.

Outcomes and Statistical Analysis

The primary endpoint was the change in endotracheal aspirate SARS-CoV-2 viral load from day 0 to the last day of treatment. Secondary outcomes included treatment-emergent adverse events (TEAEs), changes in endotracheal
absolute bacterial load, clinical outcomes and laboratory parameters including inflammatory markers, and changes in the WHO COVID-19 10-point ordinal scale of improvement from baseline to day 15 and 30.

GraphPad Prism 9.1.0 (GraphPad Software, San Diego, CA, US) and SAS 9.4 were used for statistical analysis. Freidman test was used to detect differences across daily viral and bacterial loads. One sample t test was used to analyze changes in inflammatory markers and microbial loads from day 0 to day 1 [19]. Spearman rank-order test was used to assess correlations between the reduction of viral load (log10) and the improvement of WHO scale. The reduction of viral load (log) from baseline to the final endotracheal sample was defined as the slope of the linear regression between log10 viral load and time point of viral load measurements. Similarly, the estimated improvement of WHO scale from baseline through day 30 was the slope of the linear regression between WHO scale and the time of WHO scale measurements. A significance level of $\alpha = 0.05$ was used.

### Table 1 Baseline characteristics on the day of intubation

| Subject | 1    | 2    | 3    | 4    | 5    |
|---------|------|------|------|------|------|
| Age     | 65.00| 38.00| 64.00| 62.00| 54.00|
| Sex     | M    | M    | M    | F    | F    |
| Race/ethnicity | White/ Hispanic | White/ Hispanic | White/Persian | African American | White/ Hispanic |
| BMI     | 26.00| 36.30| 25.50| 35.40| 34.00|
| PMH     | Type 2 DM | Prediabetes | Type 2 DM, HTN | Mechanical mitral valve, HTN, dyslipidemia | Type 2 DM |
| Symptom onset to intubation (days) | 14   | 18   | 11   | 5    | 10   |
| ETT size (mm) | 7.50  | 8.00  | 8.00  | 7.50  | 7.50  |
| PaO2/FiO2 | 70.00 | 51.00 | 50.00 | 50.00 | 82.00 |
| Pulmonary involvement | Bibasilar patchy opacities | Bilateral diffuse opacities | Bilateral peripheral opacities | Patchy bibasilar opacities | Bilateral patchy opacities |
| Vasopressor use | +     | +     | +     | +    | +    |
| ECMO    | –     | +     | –     | –    | –    |
| SOFA score/predicted mortality | 8/33.30% | 8/33.30% | 14/95.20% | 8/33.30% | 7/21.50% |
| SAPSIII score/predicted mortality | 62/34.00% | 62/34.00% | 85/67.00% | 68/43.00% | 57/26.00% |

**BMI** body mass index, **ECMO** extracorporeal membrane oxygenation, **DM** diabetes mellitus, **ETT** endotracheal tube, **HTN** hypertension, **PMH** past medical history, **SAPSIII** Simplified Acute Physiology Score III, **SOFA** sequential organ failure assessment

a Note that SOFA and SAPSIII scores do not account for the need for ECMO
RESULTS

Between October 30, 2020 and November 28, 2020, five subjects were enrolled (mean age 56.60 years, three male). Baseline characteristics of the enrolled subjects are summarized in Table 1, and a summary of the timeline and key events is presented in Fig. 2. At the time of intubation, all five patients were critically ill, with WHO COVID-19 ordinal scale scores of 9 in all subjects, and with SOFA scores predicting a 21–95% mortality rate. All patients received daily 20-min treatments starting within the first 36 h following intubation, for 5 days. Baseline and day 6 ET aspirates were taken in all patients except for study subject 1 who was extubated on day 6. Hence, a total of 29 ET aspirates were analyzed.

Primary Outcome

Subjects had elevated viral loads at baseline (range $3.40 \times 10^4$–$1.64 \times 10^7$ copies/ml) except daily for 10 days (all patients), tocilizumab 400 mg once (patient 2), venous thromboembolism prophylaxis (all patients) for study subject 2 who had an undetectable viral load at all time points, demonstrating that virus had cleared since the last nasal swab (Fig. 3). There was no significant correlation between symptom onset date and either baseline (Spearman rho = $-0.70$, $p = 0.23$) or day 6 viral loads (Spearman rho = $-0.21$, $p = 0.83$).

There was a significant reduction of SARS-CoV-2 levels in endotracheal aspirates during UVA treatment in all four subjects who had detectable SARS-CoV-2 loads at baseline. The average log_{10} changes in endotracheal viral load from baseline to day 5 and day 6 were $-2.41$ (range $-1.16$ to $-4.54$; Friedman $p = 0.002$) and $-3.2$ (range $-1.20$ to $-6.77$; Friedman $p < 0.001$), respectively (Fig. 3, Fig. 4).

Secondary and Clinical Outcomes

Among the secondary outcome measures, quantification of absolute endotracheal bacterial load at baseline ranged from $1.00 \times 10^3$ to $1.70 \times 10^6$ CFU/ml and remained statistically
unchanged during the UVA treatment sessions (Fig. S1).

The clinical course for each subject is shown in Fig. 2. WHO clinical severity scores improved by an average of 1.60 and 3.60 points on day 15 and day 30, respectively. Excluding subject 2 who had undetectable baseline viral load, WHO severity scores improved by an average of 4.75 points on day 30 (Table S1). All subjects survived except study subject 2, who was placed on comfort care following intracranial hemorrhage due to ECMO-associated anticoagulation and died on ICU day 17. Interestingly, there was an association between WHO clinical severity score outcomes and viral reductions during UVA treatment. Improvement in WHO severity scores by day 30 exhibited a positive correlation with the reduction of viral load during UVA therapy (Spearman’s rho = 1, *p* < 0.001) (Fig. 4c). Following UVA therapy, there was a significant drop in C-reactive protein (− 95.00 ± 48.00 mg/L, *p* = 0.04) within 7 days of enrollment. Observed reductions in interleukin-6 (− 258.90 ± 621.40 pg/mL, *p* = 0.47) and ferritin (− 563.60 ± 514.80 ng/mL, *p* = 0.12) did not reach statistical significance (Table S2).
Safety Outcomes

No treatment-emergent adverse events or need for treatment cessation was observed in the study. Oxygen saturations and hemodynamics during all treatment sessions remained stable. None of the subjects experienced pneumothorax, subcutaneous emphysema, venous thromboembolism, or endotracheal tube (ETT) dislodgment. Adverse events were deemed

Fig. 4  a Reductions in endotracheal SARS-COV-2 loads from day 0 through day 6 in patients with detectable viral load at baseline. Freidman test is used to analyze differences across daily viral load measurements. b Corresponding viral loads (log) for each subject at baseline, day 5, and day 6. All four subjects who had detectable SARS-CoV-2 loads at baseline showed a decrease in respiratory viral load. Average log changes from baseline to day 5 and day 6 were $-2.41$ (relative reduction $>99.00\%$) and $-3.20$ (relative reduction $>99.90\%$), respectively. c The individual slopes of reduction in SARS-CoV-2 loads during UVA therapy correlated with the slopes of reduction in WHO severity score by day 30
unrelated to UVA therapy (Table S3). Two sub-
jects eventually underwent bronchoscopy for
tracheostomy tube placement for prolonged
intubation which revealed normal-looking tra-
cheae without erythema or friability (Fig. 5). An
independent Data and Safety Monitoring Board
did not recommend any changes to the treat-
ment protocol for future planned trials.

DISCUSSION

The global challenge associated with the
COVID-19 pandemic is a bitter reminder that
safe and effective therapies are desperately
needed to treat resistant and/or novel patho-
gens. While externally applied UV therapy is
commonly used in dermatologic diseases, as a
result of technological limitations and knowl-
dge gaps, internal UV therapy has never pre-
viously been performed. In this first-in-human
study, endotracheal UVA light appeared safe in
critically ill patients with COVID-19. Further-
more, a significant reduction in endotracheal
SARS-CoV-2 levels was observed following 5 days of UVA therapy. Finally, the reduction of
viral load during UVA treatment correlated with
the reduction in the WHO clinical severity
scores.

Apart from a dysregulated inflammatory
response, heightened viral replication has a
critical role in the pathogenesis of severe and
critical COVID-19. There is a significant
association between respiratory SARS-CoV-2
load and mortality [13]. In addition, severe
cases of COVID-19 exhibit longer duration and
a later peak of virus in respiratory samples as
compared to mild disease [14]. Aligned with
these findings, four out of five of our subjects
had high viral loads in the endotracheal aspirate
at baseline ICU care without a significant cor-
relation with the time of symptom onset. In
addition, improvement of WHO clinical severity
scores by day 30 significantly correlated with
the reduction of viral load during UVA therapy.
Taken together, these suggest a temporal over-
lap between the viral replication and hyperin-
flammatory phases [5] in the disease course of
critically ill patients with COVID-19. Hence,
these patients may continue to benefit both
from viral load reduction and from improve-
ment of the innate immune response to SARS-
CoV-2. UVA potentially possesses the ability to
provide benefit in both areas. Firstly, we have
shown previously that UVA therapy exhibits
antiviral effects against positive sense, single-
stranded RNA viruses including coxsackievirus
and coronavirus-229E [11]. Secondly, in vitro
UVA exposure led to activation of MAVS pro-
tein in virally infected primary human tracheal
cells, a pathway that is directly impaired by
SARS-CoV-2. Activation of the MAVS protein
pathway by UVA exposure in SARS-CoV-2-in-
fected tracheal cells may be a mechanism
behind the significant reduction of viral load
along the respiratory tract in our study, despite

Fig. 5 Bronchoscopy pictures during tracheostomy for
patient 3 showing normal trachea without erythema,
edema, or friability (left panel). Full thickness penetration
of the tracheal wall did not lead to excessive bleeding or
hematoma (right panel).
only intermittent and localized UVA therapy in the upper airway. As activation of the MAVS protein by UVA is not only limited to cells directly exposed to UVA but also occurs in adjacent unexposed cells [12], this mechanism may explain the drop in viral loads beyond that which would have been expected following localized treatment in the trachea.

As compared to conventional microbial cultures, absolute bacterial load quantified by PCR detects a greater number of bacteria including normal non-pathogenic respiratory flora, along with unculturatable and non-viable bacteria, yielding higher loads of bacteria. We did not detect a significant change in endotracheal aspirate bacterial loads during UV therapy. This is encouraging and is likely due to leveraging a closed-loop system for introduction of the sterile UVA catheter. We previously have shown that UVA reduces several known pathogens linked to ventilator-associated pneumonia (VAP) including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Staphylococcus epidermidis*, and *Candida albicans* [20]. The potential role of UVA therapy in the prevention of VAP by decreasing or delaying tracheal and ETT colonization of pathogenic bacteria warrants further assessment, but the lack of rise in bacteria seen here is promising. If feasible, future studies should include conventional microbial cultures. No treatment-emergent adverse events occurred during the 25 UVA treatment sessions and serious/severe adverse events were unrelated to the treatment intervention. Oxygenation and hemodynamics remained stable during all treatments. Subsequent bronchoscopy in two subjects revealed normal-looking trachea, consistent with our preclinical in vivo and in vitro safety experiments [11]. Subject 2 died as a result of complications of ECMO-related anticoagulation (intracranial hemorrhage) despite stable oxygenation at the time of stroke. Bleeding occurs in approximately 50% of patients undergoing ECMO [21] with intracranial hemorrhage having an 85% risk of mortality [22]. Despite being in a highly critical state, four out of five subjects survived and had meaningful clinical improvements (Table S1). Further trials are needed to elucidate whether UVA therapy can improve clinical outcomes.

Our study has several limitations. As this was a first-in-human trial, the sample size was small. However, subjects had a diverse distribution of several known risk factors for severity of COVID-19 including age (range 38–65 years), sex (two women and three men), race (one non-Hispanic white, three Hispanic White, and one African American), and body mass index (BMI) (range 25–36). Of five patients, three had the smallest allowable ETT size (7.50 mm) without any treatment-emergent adverse events. With rapid advancements in LED and fiberoptic technology, future designs may accommodate patients with smaller diameter ETTs. Finally, the natural history of SARS-CoV-2 load in endotracheal aspirates is poorly defined. Zheng et al. observed a mean baseline respiratory viral load of $10^5$ copies/ml in 74 severe cases and a very gradual rate of viral clearance in lower respiratory tract (27.70 days from onset of symptoms) in 29 patients admitted to ICU [14]. The 3.20 log reduction in our study after 5 days of UVA therapy appears to outpace the natural decline of respiratory viral load. Further study may help characterize the natural history of SARS-CoV-2 levels in the respiratory tract of ICU subjects.

**CONCLUSION**

Using a novel device in a specific and monitored setting, endotracheal narrow-band UVA therapy in critically ill subjects appears to be associated with a reduction of respiratory SARS-CoV-2 viral load. Viral load reduction correlated with improvements in the WHO severity score by day 30. Finally, to date, there do not appear to be any treatment-emergent adverse outcomes from the direct effects of the UVA or the mechanical effects of endotracheal catheter insertion.
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**Author Contributions.** Study concept and design: AR, GYM, RM, MP, GC, IP, ML, RM. Acquisition of data: AR, GYM, WT, GL, GC, IP. Analysis and interpretation of data: AR, GYM, GL, RM, MP, WT, GC. Drafting of the manuscript: AR, GL, GYM, RM, MP. Critical revision of the manuscript for important intellectual content: all authors.

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**Compliance with Ethics Guidelines.** The trial protocol (ClinicalTrials.gov number NCT04572399) was approved by the institutional review board of Cedars-Sinai, Los Angeles, California, USA, and was overseen by an independent data and safety monitoring board (DSMB). Subjects’ legally authorized representatives provided written informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki.

**Data Availability.** All data generated or analyzed during this study are included in this published article or in the supplementary information files.

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