

VIP in the Treatment of Critical Covid-19 with Respiratory Failure in Patients with Severe Comorbidity: A Prospective Externally Controlled trial

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Abstract

Importance: There is currently no meaningfully effective drug for Critical COVID-19 with respiratory failure, particularly in highly comorbid patients with mortality in excess of 30%. Vasoactive Intestinal Peptide (VIP) blocks replication of the SARS-CoV-2 virus, inhibits cytokine synthesis, prevents cytopathy, and upregulates surfactant production in human pulmonary cells.

Objective: To determine the safety and efficacy of intravenous Aviptadil (synthetic Vasoactive Intestinal Peptide) for improving the survival and recovery from respiratory failure in patients with Critical COVID-19 and severe comorbidity.

Design: Prospective, open label, administratively controlled trial, measuring objective endpoints only. Patients were treated in June and July 2020 and followed for 60 days or more post ICU admission.

Setting: Intensive care unit and step down units of a quaternary care hospital

Participants: 21 consecutively admitted patients with Critical COVID-19, treated with intravenous Aviptadil (synthetic VIP), compared to all patients with comparable comorbidity (n=24) from the same ICU, treated by the same clinical team, in the same time frame who received maximal standard of care (SOC).

Intervention: 3 successive 12 hour intravenous infusions of Aviptadil at 50/100/150 pmol/kg/hr.

Main outcome measures: Survival, Recovery from Respiratory Failure, WHO 10 point ordinal scale.

Results: Seventeen of 21 patients survived to day 60 in the aviptadil treated group compared to 5 of 24 control patients (81% vs 21%; P<0.0001). Kaplan-Meier analysis demonstrates a 4 fold advantage in the probability of survival (80% vs. 20%; P<0.0006). The Hazard Ratio 0.149 (95% CL:0.050, 0.445). A similar 9 fold advantage was seen in the cumulative probability of Recovery from Respiratory Failure (Hazard ratio: 0.115; 95% CL: 0.0254, 0.5219). Between Day 28 and day 60 a mean 6.1 point difference in the 10 point WHO Ordinal Scale for COVID-19 was seen between aviptadil treated patients, who exhibited a 2.6 point mean improvement from the time of ICU admission vs those treated with standard of care who exhibited a mean 3.5 point mean decrement (Wilcoxon rank-sum:P<0.001). Improved radiographic appearance was seen in both lungs of 17 patients and in one lung of 2 treated patients. Four of five aviptadil treated patients initially on Extracorporeal Membrane Oxygenation (ECMO) have been decannulated, compared to 3 of 13 ECMO treated controls (80% vs 23%; P=0.045). A 75% (95% CI ± 3%; P<0.001) reduction in IL-6 was seen. At day 60, a similar 5.5 fold advantage was seen in the cumulative probability of Recovery from Respiratory Failure (55%

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vs 10%; $P=0.002$) at 60 days. The hazard ratio is 0.115 (95% CI: 0.0254, 0.5219). Patients treated with Aviptadil were 7 times more likely (% WHO 0-1 57.1% (12/21) for aviptadil vs 8.3% (2/24) control, P -value= 0.0008 to achieve resolution of their symptoms.

Comment: A dramatic multi-dimensional treatment effect was observed, consistent with FDA and ICH-10 guidance for acceptance of externally controlled, open label trials in high lethality conditions

Keywords: Vasoactive Intestinal Peptide (VIP); SARS-CoV-2; COVID-19; Acute Respiratory Distress Syndrome (ARDS); Acute Lung Injury (ALI); Surfactant; Alveolar Type II

Introduction

Critical COVID-19 with Respiratory Failure in patients with advanced comorbidity is a highly lethal condition with a known mortality in excess of 70%, despite intensive care with ventilation and extracorporeal membrane oxygenation (ECMO). Remdesivir is shown to be ineffective in patients on ventilation, as have monoclonal antibodies. Convalescent plasma, steroids, and anti-coagulants have yet to show effectiveness in Critical COVID-19. 50 years ago, Nature published the first report of a novel peptide discovered in the gut of patients with atypical presentation of diarrhea and flushing. Said and Mutt named it Vasoactive Intestinal Peptide (VIP). Over the subsequent 50 years, VIP has been shown to protect the lung against a broad array of caustic, immune, and infectious injuries, through its binding to the VPAC1 receptor of the Alveolar Type II cell. This is the same pulmonary cell to which the SARS-CoV-2 virus binds via the ACE2 receptor. VIP by intravenous administration has previously demonstrated effectiveness in treating ARDS related to sepsis. Promising results have been shown with inhaled administration in treating sarcoid, and pulmonary hypertension [1-10].

COVID-19 is distinct from ARDS in that it begins with alveolar collapse, caused by a failure of surfactant production, producing a unique “ground glass” appearance on radiography. Surfactant is manufactured by the ATII cells and selective viral attack on ATII cells is sufficient to produce the lethal manifestations of Critical COVID-19.

Recently, VIP was shown to block replication of the SARS-CoV-2 virus in human pulmonary epithelial cells and monocytes while also demonstrating clinical improvement on radiographic and laboratory parameters. In addition to its antiviral effect, VIP protects the Alveolar Type II (ATII) cell by upregulating surfactant

production, blocking apoptosis, and blocking cytokine effects. In vitro evidence suggests that human monocytes treated with VIP secrete soluble agents that further protect ATII cells via a “bystander effect”. In addition to blocking viral replication, VIP blocks cytokine synthesis and cytopathy in human pneumocytes and upregulates surfactant production [11-15].

VIP, thus, has a mechanism of action that directly addresses Mason’s articulation of the site and mechanism of viral injury to the pulmonary epithelium [6].

Aviptadil, a synthetic form of Vasoactive Intestinal Peptide (VIP) has been granted Fast Track Designation and is currently in phase 2/3 placebo controlled trials (NCT04311697) for the treatment of Critical COVID-19 with Respiratory Failure. The protocol is based on the Phase 1 ARDS data with Aviptadil [8].

It was agreed with FDA and the IRB that the most highly comorbid patients (e.g. transplant patients, those on Extracorporeal Membrane Oxygenation (ECMO), and those with malignancy or serious cardiac conditions) with a mortality expectation in excess of 70% would be excluded from randomization and treated under Expanded Access Protocol (NCT04453839). In addition, FDA guidance identifies the appropriateness of a non-randomized design in highly lethal conditions where there is the potential to observe a dramatic treatment effect [16].

In this prospective trial, consecutive patients were assigned to Aviptadil+maximal Standard of Care (SOC) vs maximal SOC alone based on their admission to the ICU by one of two pulmonary medicine teams and by the week in which they were admitted. Once admitted to the ICU, all patients were treated by the same intensivist physicians according to the same protocol.

Patients and Methods

Standard of Care patients were enrolled between May 23 and August 15, 2020 in the ICU’s of the Houston Methodist Hospital System (Houston, TX). Aviptadil treated patients were enrolled between June 11 and July 30, 2020. Inclusion criteria for both cases and controls are noted in Table 1. The study follows the CONSORT rules for reporting pragmatic trials (see online checklist and CONSORT diagram). The primary endpoint was survival as measured by Kaplan Meier life table, with Recovery from Respiratory Failure, WHO 10 point ordinal scale, and PaO₂: FiO₂ ratio while on a ventilator as secondary endpoints [17].

Human subjects’ protection was overseen by Advarra IRB, the Institutional Review Board (IRB) of the Houston Methodist

Table 1 Inclusion criteria

Consort rules for reporting pragmatic trials	
1	Pregnancy
2	Mechanical ventilation for more than 7 days in primary cohort. Mechanical ventilation > 21 days in the exploratory
3	Mean Arterial Pressure <65 mm Hg with use of presser per ICU protocol
4	Irreversible condition (other than COVID-19) with projected fatal course
5	ECMO
6	Current or recent (within 30 d) enrolment in another investigational trial of anti-IL6 drug
7	Active diagnosis of Acquired immune deficiency syndrome
8	Transplant patients currently immunosuppressed
9	Chemotherapy induced neutropenia (granulocyte count <1000/mm ³)
10	Cardiogenic shock; congestive heart failure NYHA Class 3 or 4
11	Recent myocardial infarction - within last 6 months and troponin >0.5 uria (urine output <50 ml/d) or other sign of multi-organ failure
12	Severe liver disease with portal hypertension
13	Recent stroke or head trauma within last 12 month
14	Increased intracranial pressure or other serious neurologic disorder

Hospital, and by an independent Data Monitoring Committee. Patients enrolled in the treatment group were given informed consent approved by the FDA and the IRB. Data on control patients was incorporated into the study based on their consent for de-identified data to be used in research given at the time of hospital admission in a manner approved by the IRB (PRO00025607). Participants in this study are typical of those treated in a highly specialized tertiary care center experienced in managing transplant patients (Figure 1).

Standard of Care therapy were screened for NCT04311697 but deemed ineligible based on the basis of exclusionary comorbidity were offered enrollment into this study. Specifically, they were offered treatment with Aviptadil, initially under FDA Emergency Use IND, which FDA subsequently converted to an intermediate population size Expanded Access Protocol (EAP), NCT04453839. In addition, control patients comprised a series of all patients who were similarly ineligible for NCT04311697, either admitted by ICU physicians who were not study investigators over the same time frame or admitted by physicians who were study investigators in the two weeks before and after recruitment of the aviptadil treated patients.

All patients in this study were treated by the same ICU team (regardless of admitting team) and received maximally available therapy, which included steroids, anti-coagulants, remdesivir, and, in some cases convalescent plasma. As required in the CONSORT description, no additional resources were added or removed from the usual care setting other than treatment or non-treatment with VIP. No patients offered participation in this clinical study declined to participate. In order to identify potential referral bias and confounding based on severity, Rothman score and WHO ordinal scale upon admission, together with Sequential Organ Failure Assessment Score (SOFA), at time of ICU admission was compared between aviptadil-treated and control patients (Table 2).

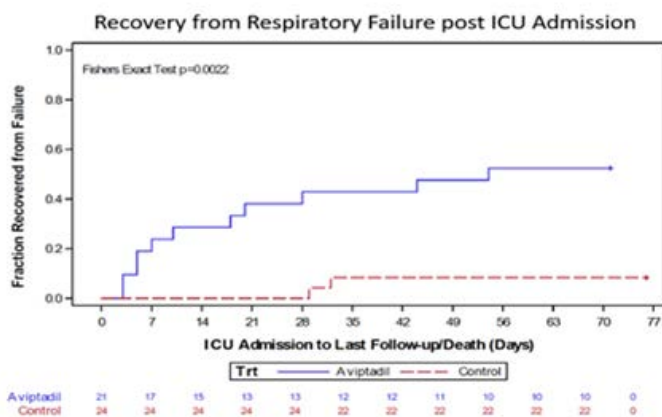
Table 2 Baseline Characteristics-Aviptadil vs SOC

Figure 1 Survival of aviptadil (n=21) vs. SOC (n=24) patients from time of ICU admission. The hazard ratio is 0.113; 95% CL 0.037, 0.343.

A consecutive series of 21 patients with PCR-proven COVID-19 and respiratory failure who did not respond to maximum

	Aviptadil+SOC (n=21)		Standard Care (n=24)	
	Mean	STD	Mean	STD
Age	57	14	56	10
% Female	48%		29%	
BMI	29.5	7	33.2	7
Rothman on Admission	54.9	26.2	59.9	26.1
Rothman on ICU Adm	16.5	23.7	56.9	26.1
SOFA on ICU Adm	10.6	3.7	4.3	2.2
PaO ₂ :FIO ₂ at baseline	91.6	36.1	108.2	47.9
WHO Ordinal on Adm	4.8	11.5	5.1	1.2
WHO Ordinal at ICU Adm	7.6	1.5	6.3	0.5

The Rothman index (RI) is a continuous predictor of impending mortality that is implemented as part of the electronic medical record system. At hospital admission; there were no significant differences in age gender, or RI. Both groups received systemic anticoagulation as well as intravenous corticosteroids. In addition, 19 out of 20 Aviptadil versus 20 out of 24 received Tocilizumab. However, 50% of the control group received Remdesivir compared to only one patient in the Aviptadil group. At ICU admission, however the RI (16.5) (SD 23.7) vs 56.9 (SD 26.1); $P < 0.001$ and SOFA score (10.6) (SD 3.7) vs 4.3 (SD 2.2); $P < 0.001$ for aviptadil treated patients was significantly worse than for control patients. Patients had a critical level of respiratory distress (PaO₂:FIO₂ ratio=91.6) at study entry with radiographic evidence of severe COVID-19 pneumonitis. The median WHO ordinal scale at admission was 9 (mean 7.6), denoting patients in the highest risk category for mortality. Sixteen were treated with various forms of ventilation at the time of enrollment and 5 with mechanical ventilation plus ECMO [18,19].

Following informed consent, each patient received three 12 hour intravenous infusions of Aviptadil over three days at graduating doses of 50, 100, and 150 pmol/kg/hr. One of the three aviptadil treated patients (Patient 10) who did not survive received only the first two infusions because he developed hemorrhagic shock caused by a chest tube inserted to treat a spontaneous pneumothorax while on ECMO. Patients received background

treatment with remdesivir (n=6), Tocilizumab (n=18), and convalescent plasma (n=2) as available and per the treating physician's discretion. All patients were treated with systemic steroids and anticoagulation.

Statistical methods

Sample size and study power were calculated using an exact binomial distribution where it was assumed that 28 day survival in the control group was 25% or less based on historical data and that treatment with VIP might increase 28 day survival to 70% or more. This difference was chosen to fulfill the FDA guidance that non-randomized design is appropriate only when the treatment effect is "dramatic". Survival was ultimately calculated at 60 days because of a change in FDA guidance. There was 80% power to detect a 45% absolute improvement in any success fail outcome according to a two sided test with 5% Type 1 error.

All analysis was by "intention to treat". No subjects were excluded from any analyses. Contingency (2 × 2) tables for 60 day survival and resolution of respiratory failure were analyzed by a two sided Fisher exact test. Survival from the time of ICU admission was assessed via the standard Kaplan-Meier method and compared using a log rank test. Subjects last reported as alive were censored at the time of the last follow up (Figure 1).

In contrast, the resolution of respiratory failure (RRF) was evaluated conservatively using all patients as an "ever never" outcome since subjects could die without RRF, the cumulative distribution of RRF timing was displayed without censoring for death since death was not missing at random with RRF timing compared using a log rank test. WHO Score change from baseline distributions for the differences between treated and control groups were tested by the Wilcoxon rank sum test. Change from baseline in PaO₂:FIO₂ ratio was compared by Student's t test. Because of the added risk of bias and confounding associated with historical control vs. randomized prospective studies, the null hypothesis was rejected only at a Type I error of 0.001 or less. All performed analyses are reported. Specifically, there were no analyses that yielded negative results, which have not been reported.

Clinical Results

The Consort diagram for this non-randomized prospective study documents that all 21 patients identified as eligible for treatment with VIP gave consent either directly or via their legally responsible party per IRB guidelines. There were no losses to follow up, and all patients were followed through day 42.

Hospital course and adverse events

The time to resolution of respiratory failure ranged from 3-20 days (mean 10.5) and time to ICU discharge ranged from 1-21 days (mean 8.1) in the 14 of 21 patients so far discharged from intensive care.

Clinical narratives are included in the online supplementary material. There were various complications in hospital courses following completion of the aviptadil regimen, as would be expected in patients with this degree of comorbidity. For instance, patient 2 was scheduled for discharge to home 3 days following completion of treatment but fell in the hospital and suffered a retroperitoneal bleed which led to a subsequent 10 day course of inpatient care. Patient 4, who was about to be treated with extracorporeal membrane oxygenation (ECMO) successfully demonstrated improvement in respiratory distress but developed line sepsis with confirmed *S. Epidermidis*, which has led to chronic respiratory distress and continued ventilation. Patient 4's hospital course was complicated by an apical pneumothorax attributed to prone positioning that occurred 24 hours after completing Aviptadil therapy. The pneumothorax spontaneously resolved after discontinuation of prone positioning, and no chest tube was required. Vasopressors were administered for continued acidosis and hypotension and were subsequently weaned. The patient was started on inhaled nitric oxide and CRRT. The patient had slow clinical and radiologic improvement and was discharged to LTAC on Tracheostomy/Ventilator for rehab. No drug-related Serious Adverse Events (SAEs), including mortality, were recorded. Only one patient developed a drug related (non-serious) adverse event. Hypotension was seen in two patients that was successfully managed with pressors and did not require cessation of infusion. Diarrhea was observed in 4 aviptadil treated patients, consistent with the known metabolic effects of VIP, compared to 3 control patients (19% vs 10%; $p=0.2$). Clinical experience shows that diarrhea is minimized when patients are pre-treated with loperamide and albumin for diarrhea and hypotension. Nevertheless, ICU staff should be prepared to use a fecal management system and monitor fluid/electrolyte loss when treating with high doses of intravenous VIP.

Outcome of care

By Kaplan-Meier life table analysis, Aviptadil treated patients were 4 fold more likely to survive to 60 days than were those treated with Standard of Care (80% vs 20%; $P<0.0006$). (Hazard Ratio:0.149; 95% CL:0.050, 0.445). The difference is dramatic (As identified in FDA guidance 15). Time to recovery from respiratory failure was similarly analyzed by life table analysis (Figure 2).

Respiratory failure was defined by the FDA resource based criteria of requirement for mechanical ventilation, non-invasive ventilation, or high flow nasal oxygen at 20 L or greater. A similar 5.5 fold increase in the likelihood of recovery from respiratory failure from the time of ICU admission was seen (55% vs 10%; $P=.002$) at 60 days. The hazard ratio is 0.115 (95% CL: 0.0254, 0.5219). The hazard ratio is 0.115 (95% CL:0.0254, 0.5219). Patients treated with Aviptadil were 7 times more likely (% WHO 0-1 57.1% (12/21) for aviptadil vs 8.3% (2/24) control, P value=0.0008 to achieve resolution of their symptoms. Four of the five aviptadil treated patients on ECMO were successfully decannulated, compared to 3 of 13 control patients who developed the need for ECMO (80% vs 23%; $P<0.05$). The decannulation rate on ECMO seen among control patients in this study is consistent with survival rates for COVID-19 patients treated with ECMO across the country. A substantial and meaningful 6.1 point difference in the 10 point WHO Ordinal Scale for COVID-19 was seen between aviptadil treated patients, who exhibited a 2.6 point median improvement from the time of ICU admission vs. those treated with standard of care who showed a mean 3.5 point median decrement (Wilcoxon signed rank: $P<0.001$).

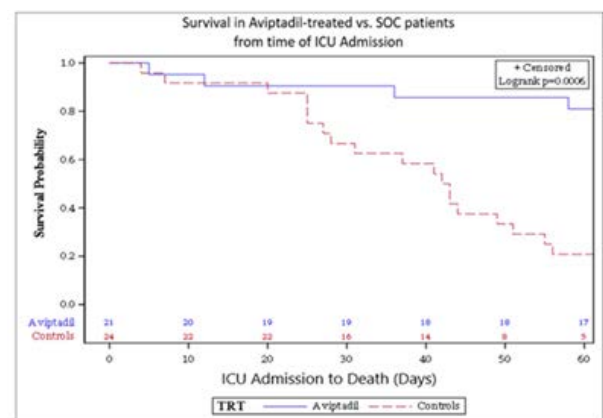


Figure 2 Time to recovery from respiratory failure. The hazard ratio is 0.115 (95% CL:0.0254, 0.5219).

Aviptadil treated patients demonstrated significant, nearly 3 fold improvement in oxygenation as measured by the PaO₂:FiO₂ ratio, while control patients demonstrated no significant mean improvement (164 (SD 134) vs 3 (SD 86); $P<0.001$) (Figure 3). Fifteen of 21 aviptadil treated patients demonstrated 100 point or greater improvement in blood oxygenation compared to 4 of 30 controls ($P<0.001$). No aviptadil treated patient demonstrated significant worsening in blood oxygenation, whereas 5 control patients showed 100 points or greater decrement ($P<0.05$). The improvement in patients on ECMO was similar to that seen in patients treated with conventional mechanical ventilation. Available data from blood gases showed clear increases in

PaO₂:FiO₂ ratio after the 2nd dose (Median increase=92.5, IQR=74) and at 24 hours after the 3rd dose (Median increase over baseline 84.5, IQR=110).

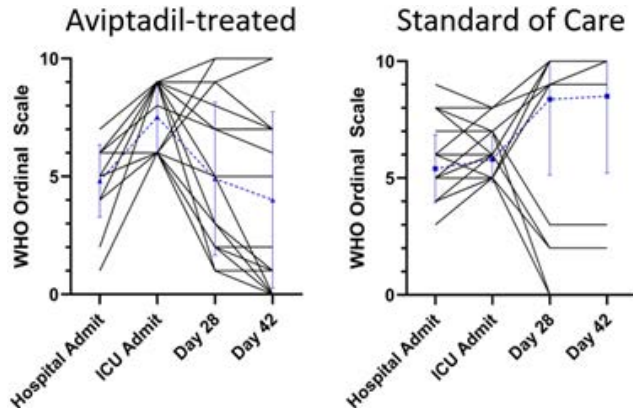


Figure 3 Change in 20 point ordinal scale from enrolment through day 42 (=mean:SD). Aviptadil-treated patients demonstrated a median 2.6 point Improvement compared to control patient who demonstrated a 3.5 point median decrement at 42 days (Wilcoxon signal rank, P<0.0001).

Radiographic evidence on all patients is included in the online supplementary material. Full or partial resolution of the “ground glass” parenchymal changes associated with COVID-19 pneumonitis in 17 of 21 aviptadil treated patients. Quantitative analysis of radiographic changes by a panel of radiologists will be the subject of a future report (Figure 4). A laboratory panel of inflammatory markers, including LDH, troponin, C-reactive protein, ferritin, D-Dimer, and Interleukin-6 (IL-6), was obtained prior to and post-treatment with Aviptadil (Figure 5).

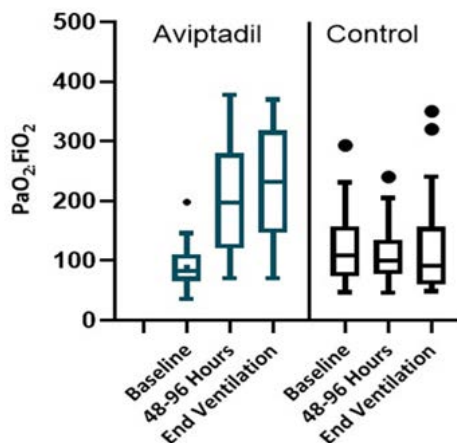


Figure 4 Blood oxygenation in aviptadil-treated vs control patients. A statistically-significant difference in mean improvement is seen in aviptadil-treated patients vs. controls (164 vs 3:P<0.001).

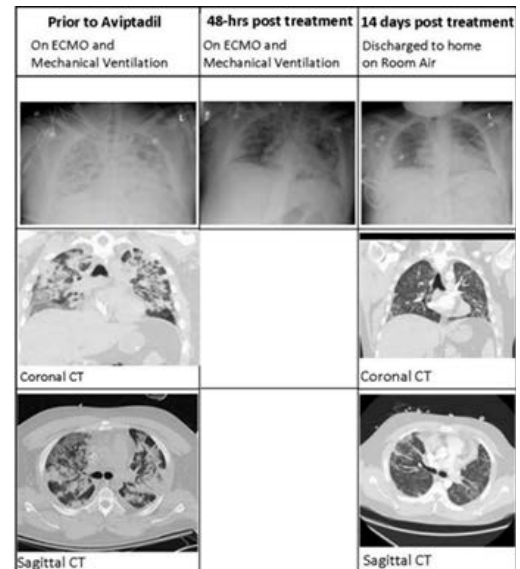


Figure 5 Chest x-ray and CT imaging of a patient initially treated while on mechanical ventilation and extracorporeal membrane oxygenation for Critical COVID-19 with respiratory failure (see supplemental online material for radiographic documentation of all patients).

In all patients, improvement can be seen on each of the inflammatory markers. C reactive protein (76% ± 3%) and IL-6 (75% ± 3%) was the largest average percent decrease. No patient demonstrated an increase in any of the inflammatory markers because of the high mortality rate in the control group, an accurate comparison (Figure 6).

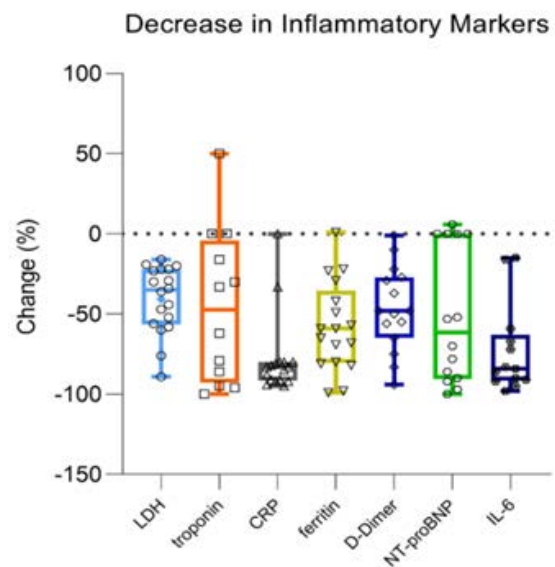


Figure 6 Decrease in inflammatory markers as a percent change from pretreatment value. The decrease is both clinically and statistically significant (P<0.001).

Discussion

Assignment to Aviptadil+SOC vs SOC alone in this prospective

study was not according to a formal randomization structure. It was based on the admitting team to which a patient was assigned at hospital intake or the week in which a patient was admitted. However, once admitted to the ICU, all patients were cared for by the same intensive care physicians and nurses, using the same ICU protocols. In addition, patients admitted to this study had previously been treated with all approved treatments for COVID-19, and no new therapies were approved during the study time frame.

FDA's guidance (harmonized with ICH 10) for use of historical controls state: "The inability to control bias restricts use of the external control design to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable. In addition, use of external controls should be limited to cases in which the endpoints are objective and the impact of baseline and treatment variables on the endpoint is well characterized". Clearly, mortality, recovery from respiratory failure, and ordinal scale are objective. The finding of a 4.5 fold increased odds of survival among critically ill patients with COVID-19 have now been replicated for those treated in tertiary care medical centers.

The 45 patients enrolled in this study were at the highest possible risk for mortality based on serious comorbidities that rendered them ineligible for participation in the ongoing FDA phase 2/3 pivotal study of Aviptadil in the treatment of COVID-19 respiratory failure. In addition, they had failed to respond to all treatments approved for COVID-19 in the June 2020 time frame. Indeed, the 10% survival probability seen in the standard of care group is clear evidence of the lethality of COVID-19 in the setting of severe comorbidity.

Despite comparable age and RI at the time of hospital admission, the aviptadil treated patients had worse RI and SOFA scores at the time of ICU admission, which biases against finding a survival and recovery advantage in the Aviptadil treated group.

Indeed, there may be unknown and therefore unappreciated sources of bias and confounding associated we did not appreciate in choosing sequentially admitted patients for both the treatment and control group, who were also seen to be comparable on RI, SOFA score, and underlying major comorbidity. However, when dealing with patients at this level of comorbidity and mortality risk, it is not reasonable to expect that formal randomization will more readily insure balanced allocation or risk factors between drug and placebo groups absent an inordinately large sample size. Therefore, because of the potential for bias and confounding associated with administrative assignment based on admitting

physician, we set our criteria for rejecting the null hypothesis at $P < 0.01$.

In an open label study, one must always be concerned about the placebo effect. However, the patients in this study were unconscious when they were treated with Aviptadil and unable to know which medication they were receiving through their multiple intravenous lines. Thus, the study endpoints (survival and recovery from respiratory failure) are completely objective and not subject to ascertainment bias from clinical personnel who are aware of treatment assignment. However, we cannot absolutely rule out the unlikely possibility that clinical personnel somehow treated patients who received VIP in a manner different from how control patients were treated.

All of the study outcomes were pre-specified, and no negative analyses were unreported. Therefore, we believe that there is no issue with multiplicity and no need for p-value adjustment. Furthermore, were p-value adjustment to be employed, it would not affect the statistical significance of the results. Readers should be cautioned that this study was conducted in a highly skilled ICU that is well-experienced in managing ultra high risk patients. When given at the intravenous doses required to produce this magnitude of clinical effect, Aviptadil is known to cause hypotension and diarrhea in approximately 20% of treated patients. It should not be administered to patients who have a mean arterial pressure of less than 65 despite treatment with pressors. It should only be administered by board certified Critical Care physicians who are adept at managing these side effects.

This is the second clinical report in which Aviptadil has been associated with a remarkable degree of improvement in patients with Acute Respiratory Failure. In 2005, 8 patients with sepsis related Acute Respiratory Distress Syndrome were treated with the same intravenous VIP protocol [20].

Early COVID-19 lung injury is characterized by a remarkable degree of hypoxemia in the absence of overwhelming pneumonia, suggesting a primary injury to the pulmonary gas exchange mechanism. Although named (or misnamed) for the gut where it was first isolated, 70% of VIP is localized to the lung and binds primarily to Alveolar Type II (ATII) cells via VPAC1 [21]. ATII cells comprise only 5% of the pulmonary epithelium but are critical to surfactant production and recycling and the maintenance of type I epithelial cells. The SARS-CoV-2 virus specifically attacks ATII via ACE2 surface receptors and does not enter the Type I pneumocyte. VIP preserves the function of lung allografts and May have been particularly beneficial in this patient who was suffering active graft rejection [22-24]. Unlike synthetic anti-

cytokines, such as anti-IL6 drugs, VIP is shown to have a specific role in preserving surfactant production in the Lung [12-15].

Accordingly, VIP and longer acting VIP modifications have been proposed as respiratory therapeutics in the past. Li demonstrated in rat lung explants that VIP increased the incorporation of methylcholine into phosphatidylcholine. The major component of the pulmonary surfactants by enhancing the activity of the enzyme choline-phosphate cytidyltransferase [16,17]. VIP upregulates C-Fos protein expression in cultured type II alveolar cells, which is instrumental in promoting synthesis of pulmonary surfactant phospholipids and induces surfactant protein A expression [25-27].

Conclusion

The significant clinical improvement seen in these 21 patients treated with intravenous Aviptadil compared to contemporaneous patients treated with standard of care, is consistent with the finding that VIP both blocks viral replication in pulmonary AII cells and creates a “bystander effect” whereby nearby monocytes secrete soluble antiviral agents to protect AII cells further, block cytokine storm, and improve oxygenation in a lung that is under attack by the SARS-CoV-2 virus. Furthermore, the rapidity and magnitude of clinical effect has not been reported to our knowledge in association with any other COVID-19 therapeutic agent, suggesting a highly specific role of VIP in combating the lethal effects of SARS-CoV-2 infection.

Our findings raise the possibility that patients with earlier stage disease and an intact pulmonary epithelium may benefit from inhaled Aviptadil to prevent progression to respiratory failure. FDA has granted an inhaled use IND and a phase 2/3 trial of inhaled Aviptadil (NCT04360096) is currently underway. Aviptadil may have further value as a nasopharyngeal drug to prevent SARS-CoV-2 from successfully infecting nasopharyngeal cells and starting the pathogenic process of COVID-19. Moreover, Aviptadil may have promise in treating a broad array of pulmonary inflammatory conditions.

Study Limitations

The generalizability of our findings to patients with Critical COVID-19 but without severe underlying comorbidity is unknown. A randomized prospective study in these ultra-high risk patients would not have been feasible and a quasi-experimental design is supported by FDA and ICH-10 guidelines. Indeed, the patients selected for this study were deemed ineligible for enrolment in a phase 2/3 clinical trial during the FDA Pre-IND process, as they were previously deemed ineligible by FDA in its

2001 issuance of IND 52,088 to Stony Brook University for the use of VIP in ARDS. However, for Aviptadil to be adopted more broadly to treat patients with Critical COVID-19, a traditional multi-center randomized controlled trial is required and was concluded. Recently published, but not peer-reviewed data from this clinical trial suggests that treatment with Aviptadil improves the likelihood of recovery from respiratory failure and survival at 60 days post-treatment in critically ill patients with respiratory failure caused by COVID-19. [20]

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Disclosure

Author JCI is employed by NeuroRx, Inc., a pharmaceutical company currently conducting clinical trials of RLF-100 in patients with COVID-19. The investigational product was provided for expanded access use by NeuroRx, Inc.

Key Points

Question

Does intravenous aviptadil (Vasoactive Intestinal Peptide) improve survival and recovery from respiratory failure in patients with Critical COVID-19 and significant comorbidity?

Findings

In this administratively controlled clinical trial, intravenous Aviptadil, administered as three successive 12 hour infusions of 50/100/150 pmol/kg/hr, resulted in a 9 fold advantage in both survival and recovery from respiratory failure compared to standard of care (with all approved therapy for COVID-19 among patients treated in the same ICU by the same clinical care team). Notably, 4 out of 5 patients treated with Aviptadil on Extracorporeal Membrane Oxygenation were successfully decannulated and survived. This is in comparison to the 3 out of 13 control patients who survived. In addition, although 20% of patients exhibited hypotension and/or diarrhea, no drug-related serious adverse events were observed.

Meaning

Intravenous Aviptadil demonstrated a dramatic level of efficacy that is consistent with FDA guidance for administratively controlled clinical trials and may be warranted for use in highly comorbid patients with Critical COVID-19 and respiratory failure.

References

1. Beigel KM, Tomashek LC, Dodd AK, Aneesh KM, Barry S, et al. (2020) Remdesivir for the treatment of COVID-19—Final Report. *NEJM* 383: 1813-1826.
2. Said SI, Mutt V (1970) Potent peripheral and splanchnic vasodilator peptide from normal gut. *Nature* 225: 863-864.
3. Said SI (1988) Vasoactive intestinal peptide in the lung. *Ann NY Acad Sci* 527: 450-460.
4. Said SI (1988) VIP as a modulatory of lung inflammation and airway constriction. *Am Rev Respir Dis* 143: S22-S24.
5. Said SI, Dickman KG (2000) Pathways of inflammation and cell death in the lung: Modulation by vasoactive intestinal peptide. *Regul Pept* 93: 21-29.
6. Javitt J, Youssef JGVIP (2020) A COVID-19 therapeutic that blocks coronavirus replication.
7. Mason R (2020) Pathogenesis of COVID-19 from a cell biologic perspective.
8. Said SI, Youssef JG, Youssef G, Javitt MJ, Javitt J, et al. (2020) Treatment of sepsis related acute respiratory distress syndrome with vasoactive intestinal peptide. *Am J Respir Crit Care Med* 203: 2490.
9. Prasse A, Zissel G, Lützen N, Schupp J, Schmiedlin R, et al. (2010) Inhaled vasoactive intestinal peptide exerts immunoregulatory effects in sarcoidosis. *Am J Respir Crit Care Med* 182: 540-548.
10. Petkov V, Mosgoeller W, Ziesche R, Raderer M, Stiebellehner L, et al. (2003) Vasoactive intestinal peptide as a new drug for treatment of primary pulmonary hypertension. *J Clin Invest* 111: 1339-1346.
11. Leuchte HH, Baezner C, Baumgartner RA, G Bacher C, Neurohr J, et al. (2008) Inhalation of vasoactive intestinal peptide in pulmonary hypertension. *Eur Respir J* 32: 1289-1294.
12. Temerozo JR, Sacramenta Q, Fintelman RN (2020) The neuropeptides VIP and PACAP inhibit SARS-CoV-2 replication in monocytes and lung epithelial cells, decrease the production of proinflammatory cytokines, and VIP levels are associated with survival in severe Covid-19 patients.
13. Li L, Luo ZQ, Fu-wen Z, Dan-dan F, Guang CX, et al. (2004) Effect of vasoactive intestinal peptide on pulmonary surfactants phospholipid synthesis in lung explants. *Acta Pharmacol Sin* 25: 1652-1658.
14. Li L, She H, Yue SJ, Qun QX, Xia CX, et al. (2004) Role of C-Fos gene in vasoactive intestinal peptide promoted synthesis of pulmonary surfactant phospholipids. *Regul Pept* 140: 117-124.
15. Li L, Hua S, Yue S, Luo Z, Dandan F, et al. (2010) Vasoactive intestinal polypeptide induces surfactant protein A expression in ATII cells through activation of PKC/c-Fos pathway. *Peptides* 31: 2016-2051.
16. FDA Guidance for Industry. E10 Choice of Control Group and Related Issues in Clinical Trials. US Department of Health and Human Services.
17. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, et al. (2008) For the CONSORT and pragmatic trials in healthcare (practihc) group. Improving the reporting of pragmatic trials: An extension of the CONSORT statement. *BMJ* 337: 2390.
18. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, et al. (1996) The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European society of intensive care medicine. *Inten Car Med* 22: 701-710.
19. Rothman MJ, Rothman SI, Beals J (2013) Development and validation of a continuous measure of patient condition using the electronic medical record. *J Biomed Informatics* 46: 837-848.
20. Youssef JG, Said S, Youssef G, Javitt MJ, Javitt JC (2021) Treatment of acute respiratory distress syndrome with vasoactive intestinal peptide.
21. Youssef JG, Said S, Youssef G, Javitt MJ, Javitt JC (2021) Intravenous aviptadil is associated with increased recovery and survival in patients with COVID-19 respiratory failure: Results of a 60 day randomized controlled trial.
22. Virgolini I, Kurtaran A, Raderer M, Leimer M, Angelberger P, et al. (1995) Vasoactive intestinal peptide receptor scintigraphy. *J Nucl Med* 36 : 1732-1739.
23. Mossel EC, Wang J, Jeffers S, Shuanglin W, Gregory P, et al. (2008) SARS-CoV replicates in primary human alveolar type II cell cultures but not in type I-like cells. *Virology* 372: 127-135.
24. Alessandrini F, Thakkar M, Foda HD, Said SI, Lodi R, et al. (1993) Vasoactive intestinal peptide enhances lung preservation. *Transplant* 56: 964-973.
25. Pakbaz H, Berisha H, Sharaf H, Foda HD, Said SI, et al. (1994) VIP enhances and nitric oxide synthase inhibitor reduces survival of rat lungs perfused ex vivo. *Ann N Y Acad Sci* 723:

- 426-428.
26. Onoue S, Ohmori Y, Endo K, Yamada S, Kimura R, et al. (2004) Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide attenuate the cigarette smoke extract-induced apoptotic death of rat alveolar L2 cells. *Eur J Biochem* 271: 1757-1767.
27. Mathioudakis AG, Chatzimavridou GV, Evangelopoulou E, Mathioudakis GA (2013) Vasoactive intestinal peptide inhaled agonists: Potential role in respiratory therapeutics. *Hippokra* 17: 12-16.