

Rapid Recovery from COVID-19 Respiratory Failure after treatment with Vasoactive Intestinal Peptide

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Abstract

Background: Vasoactive Intestinal Peptide (VIP) is known to bind to and protect the Alveolar Type II cell by blocking replication of the SARS-CoV-2 virus, upregulating surfactant production, blocking apoptosis, and blocking cytokine effects. RLF-100 (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. FDA has granted Emergency Use IND and Expanded Access Protocol approval for the use of RLF-100 in patients whose comorbidities render them ineligible for inclusion in the ongoing pivotal trial.

Methods: This report describes the first 6 patients with Acute Respiratory Failure in Critical COVID-19, enrolled under Emergency Use IND were treated with three successive 12-hour infusions of intravenous Aviptadil at 50/100/150 pmol/kg/hr, while continuing to receive maximal ICU care.

Results: Median patient follow-up time is 14 days. So far, all treated patients have survived. Improved radiographic appearance of typical “ground glass” COVID-19 features to varying degrees is seen in all patients within 72 hours. Improvement in blood oxygenation is seen in all patients, with complete remission from respiratory failure in 4 of 6 patients. An average 56% reduction in inflammatory markers was seen, together with a median 4 point reduction in the NIAID Ordinal Scale. 2/6 patients were discharged from the hospital and 1 patient was downgraded to the general medicine floor.

Comment: The short term survival of 6/6 patients with respiratory failure in the setting of COVID-19 and major comorbidity is the most dramatic response ever seen with an antiviral agent. Improvement in radiographic appearance, oxygenation requirement, and inflammatory markers is consistent with in vitro evidence of direct anti-viral effect.

Background

Vasoactive Intestinal Peptide (VIP) is the first COVID-19 therapeutic shown to block replication of the SARS-CoV-2 virus in human pulmonary epithelial cells and monocytes.¹ VIP further 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”.

RLF-100 (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). FDA has granted Emergency Use IND and Expanded Access Protocol approval NCT04453839 for the use of RLF-100 in patients whose comorbidities render them ineligible for inclusion in the ongoing pivotal trial. These comorbidities prognostic for poor outcomes in COVID-19, as enumerated below, were deemed to be sufficiently rare that enrollment could not adequately be balanced within the sample size of the randomized trial.

Since its discovery in 1970 by Said and Mutt² VIP has been shown to protect the lung against a broad array of caustic, immune, and infectious injuries^{3,4,5,6} through its binding to the VPAC₁ receptor of the Alveolar Type II cell. This is the same cell to which the SARS-CoV-2 virus binds via the ACE2 receptor⁷. VIP has previously demonstrated effectiveness in the treatment of ARDS related to sepsis⁸ by intravenous administration, sarcoid⁹, and pulmonary hypertension^{10,11}.

Patients and Methods

Six patients were identified with PCR-proven COVID-19 and respiratory failure who were ineligible for randomization in the phase 2/3 protocol.

Human subjects protection was overseen by the Institutional Review Board (IRB) of the Houston Methodist Hospital. Patients with Critical COVID-19 and PCR+ diagnosis of SARS-CoV-2 virus infection who were not eligible for NCT04311697 were offered the opportunity to be treated with IV RLF-100 under FDA Emergency Use IND on a named-patient basis. Following informed consent FDA approved the use of Aviptadil (NCT04453839). Following

informed consent, FDA was contacted prior to the treatment of each patient and approved the use of intravenous RLF-100. Drug product was donated by NeuroRx, Inc. (Wilmington, DE).

Each of the patients enrolled in this emergency use program was showing active signs of clinical deterioration at the time of enrollment despite receiving maximal intensive care for COVID-19 related respiratory failure at the Houston Methodist Hospital. The median age of patients was 71 (Interquartile range [IQR] = 25 years) and there were 3 male and 3 female patients (Table 1). All patients had known chronic diseases. The most common comorbidities prior to admission were hypertension (4/6) and chronic kidney disease (4/6). Two patients have known diabetes mellitus, with Patient 6 being insulin-dependent. Three of the patients had undergone solid organ transplants and were treated with immunosuppressive agents. Patient 2 received a double lung transplant and was treated for antibody-mediated rejection (AMR) one month before presentation. Patient 1 was also diagnosed with a non-ST-elevation myocardial infarction (NSTEMI) during her admission (Table 1). All patients had lab values suggestive of diffuse inflammatory processes including elevated ferritin (5/6), IL-6 (4/6), lactate dehydrogenase (3/6), and C-reactive protein (3/6).

Prior to enrollment, all patients received anticoagulation as well as dexamethasone without remission from respiratory failure. Patients were also treated with remdesivir, tocilizumab, and convalescent plasma as available and per physician discretion. However, supply shortages of these agents were such that only Patient 1 received convalescent plasma before Aviptadil with no clinical improvement following treatment. Following enrollment and informed consent, each patient received three 12-hour intravenous infusions of Aviptadil at graduating doses of 50, 100, and 150 pmol/kg/hr.

Table 1. Patient characteristics and treatment modalities prior to Aviptadil therapy

Patient	Age	Sex	Comorbidities	Presenting Illness	Treatments Prior to Aviptadil	Respiratory Support
1	71	F	HTN CAD s/p CABG in 2015 CKD	3-days diarrhea, Generalized weakness, Bilious vomiting, Dry cough NSTEMI	Convalescent plasma Anticoagulation Dexamethasone	HFNC/NIPPV
2	54	M	Rheumatoid arthritis with interstitial lung disease, S/p double lung transplant (2019), Subclinical AMR Pulmonary HTN CKD	Dyspnea, Fever Hypoxemia	Tocilizumab Dexamethasone Anticoagulation	HFNC
3	77	M	Pulmonary fibrosis S/p left lung transplant (May 2020), Contracted COVID in Rehab Facility HTN	Respiratory distress Hypogammaglobulinemia Hypoxemia Shock AKI	Dexamethasone Tocilizumab CRRT Nitric oxide Anticoagulation	Ventilator
4	71	F	HTN DM	Dry cough, Dyspnea, Hypoxemia (SaO ₂ 90%), Fever 102 F AKI	Tocilizumab Dexamethasone Anticoagulation	Ventilator
5	49	F	CKD s/p kidney transplant, on immunosuppression, HTN	Chest Pain, Headache, Dyspnea, Fatigue	Tocilizumab Dexamethasone Anticoagulation	Ventilator
6	81	M	Parkinson's Disease, Systolic heart failure, Pulmonary valve vegetations, CKD Seizure disorder Cervical spondylosis Insulin-dependent	Fever 102.5F Hypoxemia	Dexamethasone Tocilizumab Anticoagulation	BiPAP

DM,
CAD
HTN
HLD
Recent sepsis (3/2020)

Clinical Results

Each patient showed clinical improvement following administration of Aviptadil, as documented on radiographic imaging and blood oxygenation values (Figure 1). In all cases, clearing of the “ground glass” parenchymal changes associated with COVID-19 pneumonitis was apparent and was noted by the radiologists who read the chest x-rays. Similarly, in all cases a marked decrease in oxygen requirement was seen. Four of six patients recovered from respiratory failure and were weaned off of high-flow nasal cannula (HFNC) to low-flow nasal cannula (LFNC) or room air. All patients demonstrated improvement in blood oxygenation. Available data from blood gases showed stark 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). Three patients achieved ratios greater than 200 during the week following treatment and no patient showed deterioration of oxygenation below baseline during subsequent measurements. Furthermore, all patients showed improvements in inflammatory markers. At present, 3/6 patients have been discharged to home with minimal supplementary oxygen (Table 2).

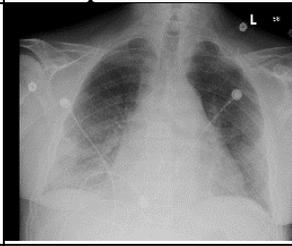
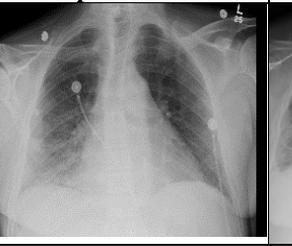
Patient 2	Before Aviptadil	24-hr post 3rd Dose	48-hr post 3rd Dose	2 weeks s/p Aviptadil
Portable Chest X-Ray				
PaO ₂ :FiO ₂	146	146	285.19	
SaO ₂	98	89	95	97
Ventilation	HFLNC 30 L/min, FiO ₂ 50%	6 L/min	2 L/min	2 L/min

Figure 1 (Representative Radiographic Appearance and blood oxygen saturation before and after treatment. In all 6 patients resolution of “ground glass” parenchymal changes typical of COVID-19 was apparent on chest x-ray and ascertained by radiologist review

A laboratory panel of inflammatory markers, including LDH, troponin, C-reactive protein, ferritin, D-Dimer, and interleukin 6 was obtained prior to and post treatment with aviptadil (figure 2). In all patients, improvement can be seen on each of the inflammatory markers (see online supplement). The largest average percent decrease was seen in C-reactive protein (88%) and interleukin 6 (84%). No patient demonstrated an increase in any of the inflammatory markers.

Hospital course and adverse events. The time to ICU discharge ranged from 1 – 14 days in the 4 of 6 patients so far discharged from intensive care (Table 2). No Serious Adverse Events (SAEs), including mortality were recorded. Only one patient developed a drug-related (non-serious) adverse event. Patient 1 developed diarrhea (an expected treatment emergent event associated with VIP) during the third infusion, which was successfully managed with loperamide and fluid replacement. There were various complications in hospital courses following completion of the Aviptadil regimen (Table 2) 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 but remains in the ICU requiring intermittent ventilatory support.

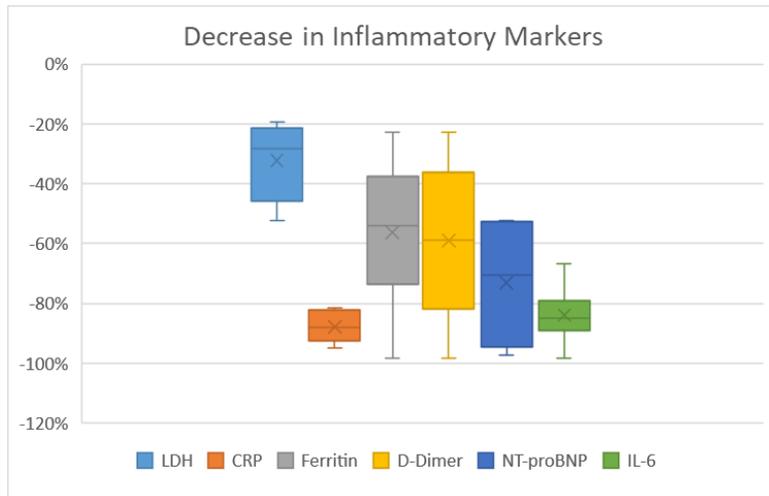


Figure 2: Decrease in Inflammatory Markers seen following treatment with Aiviptadil. In all patients, all markers were seen to decrease following treatment (see on-line supplementary material).

Table 2. Hospital course and current disposition of patients following treatment with Aiviptadil

Patient	Side Effects	Time to Resolution of Respiratory Failure	Time to ICU Discharge	Time to Hospital Discharge	Current Disposition	Respiratory Support
1	Diarrhea	15 days	14 days	32 days	Discharged to home	LFNC with exertion
2	None	3 day	1 day	3 days	Discharged to home	LFNC with exertion
3	None				ICU s/p tracheostomy CRRT Respiratory Muscle Weakness	Ventilator
4	None				ICU CRRT Prolonged ventilation from pneumothorax	Ventilator
5	None	12 days	9 days		Discharged to floor	LFNC
6	None	3 days	3 days		Ready for discharge, awaiting placement	LFNC

Discussion

This is the first reported treatment of Acute Respiratory Failure in patients with Critical COVID-19 using Vasoactive Intestinal Peptide (Aiviptadil). The six patients in this report had serious comorbidities that made them ineligible for participation in the ongoing FDA phase 2/3 pivotal study of RLF-100 (aiviptadil) in the treatment of COVID-19 respiratory failure. All six patients demonstrated rapid clinical improvement in both blood oxygenation and radiographic features, although respiratory failure persists in 2 of the 6 patients. The substantial decrease in inflammatory markers seen in all patients, particularly in ferritin, D-Dimer, and IL6 which are increasingly associated

with poor prognosis in COVID-19 suggests that the radiographic and oxygenation improvement seen in these patients may be tied to an etiologic effect of Aviptadil. The fact that all patients have, so far, survived is highly unexpected in COVID-19 patients with this degree of comorbidity and the fact that four of the six have been discharged from acute care is equally remarkable. Patient 3 remains on mechanical ventilation not because of oxygenation failure but rather because of respiratory muscle weakness. Patient 4 was scheduled for extubation when a pneumothorax developed requiring additional ventilatory support.

This is the second similarly-sized case series in which aviptadil has been associated with a remarkable degree of improvement in patients with Acute Respiratory Distress. In the 2005 time frame, 8 patients with sepsis-related Acute Respiratory Distress Syndrome were treated with the same intravenous protocol.¹² All 8 patients demonstrated clinical improvement, 7 were discharged from intensive care and life support was terminated in the 8th for neurologic, rather than pulmonary reasons. Although the case series was not reported until recently because of the retirement and subsequent demise of the senior author, the clinical care was managed and results recorded by one of our authorship (JGY). Similar clearing of pneumonitis with aviptadil (delivered by nebulizer) was recently reported in a patient with checkpoint inhibitor pneumonitis.¹³

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 mis-named) for the gut where it was first isolated, 70% of VIP is localized to the lung and binds primarily to Alveolar Type II cells (ATII) cells via VPAC₁.¹⁴ ATII cells comprise only 5% of the pulmonary epithelium but are critical to surfactant production and recycling as well as the maintenance of type I epithelial cells. The SARS-CoV-2 virus specifically attacks ATII via their ACE2 surface receptors and does not enter the Type I pneumocyte.¹⁵ VIP preserves the function of lung allografts and may have been particularly beneficial in this patient who was suffering active graft rejection.^{16,17}

Unlike synthetic anti-cytokines, such as anti-IL6 drugs, VIP is shown to have a specific role in preserving surfactant production in the lung.^{18,19,20,21} Accordingly, VIP and longer acting modifications of VIP have been proposed in the past as respiratory therapeutics²². 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 cytidylyltransferase¹⁶. VIP upregulates C-Fos protein expression in cultured type II alveolar cells, which is instrumental in promoting synthesis of pulmonary surfactant phospholipids¹⁷ and induces surfactant protein A expression.

Conclusion:

The rapid clinical improvement seen in these six patients treated with intravenous RLF-100 (Aviptadil), is consistent with the finding that VIP not only blocks viral replication in the pulmonary epithelium but creates a “bystander effect” whereby nearby monocytes secrete soluble antiviral agents to further protect ATII cells, blocks cytokine storm, and improves oxygenation in a lung that is under attack by the SARS-CoV-2 virus. This highly specific role of VIP in the lung may be key to combating the lethal effects of SARS-CoV-2 infection. A randomized prospective trial is underway, which will attempt to demonstrate that intravenous RLF-100 improves survival, oxygenation, and clinical course of Critical COVID-19 with respiratory failure. The independent Data Monitoring Committee of that trial has conducted the first unblinded look at the study data and identified no safety signals. Moreover, the DMC has determined that the study is not futile in its objective to identify a statistically significant difference between aviptadil and placebo in remission from COVID-19 respiratory failure.

The patients reported here were deemed too ill to be randomized in the ongoing phase 2/3 clinical trial of RLF-100 for treatment of Critical COVID-19. Yet their clinical course, particularly the rapidity with which resolution in COVID pneumonitis with improvement in oxygenation and radiographic appearance within days is highly atypical for COVID-19 and suggests that Aviptadil has substantial potential to demonstrate clinical effectiveness in placebo-controlled trials.

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