RECOVERY AND SURVIVAL IN COVID-19 RESPIRATORY FAILURE, WHEN TREATED WITH AVIPTADIL

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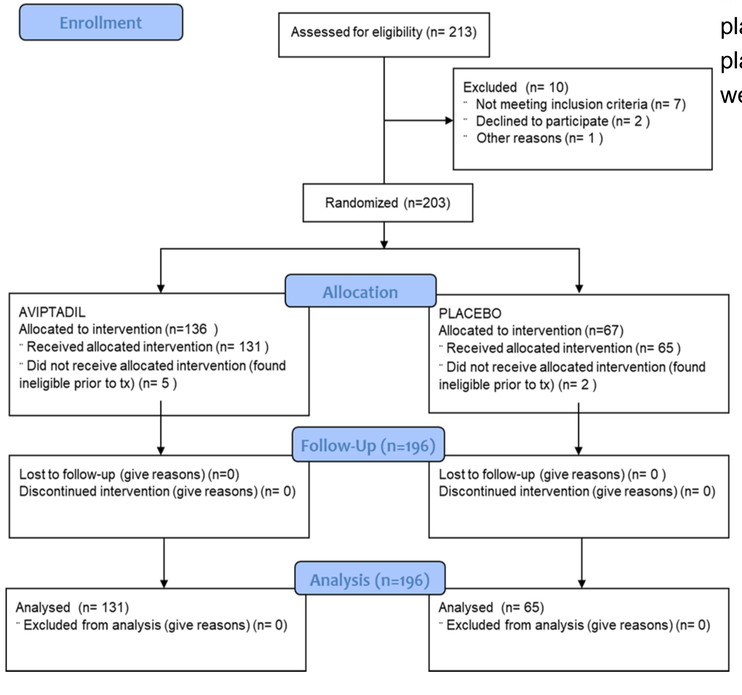
BACKGROUND

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Vasoactive Intestinal Peptide (VIP) blocks replication of the SARS-CoV-2 virus in alveolar type II cells, inhibits cytokine synthesis, prevents cytopathy, and upregulates surfactant production. Synthetic VIP-aviptadil is a novel strategy to treat patients with COVID-19 and respiratory failure.

METHODS

This was a prospective, multicenter, randomized, placebo-controlled trial in 196 patients, nasal swab PCR+ for COVID-19 receiving intensive care at 10 U.S. hospitals (6 tertiary care and 4 regional hospitals, conducted from May 2020 until Feb 2021 to determine if intravenous aviptadil is superior to placebo in achieving faster recovery from respiratory failure and survival at 60 days post treatment. The analysis was by modified intent to treat (ITT) using a proportional hazards model. The primary prespecified endpoint was being alive with no respiratory failure at day 60. Day 60 survival was a key secondary endpoint. All subjects were followed up to 60 days.



Aviptadil helps to resolve respiratory failure and extend survival at tertiary care sites in COVID-19

RESULTS

Baseline characteristics were comparable except for worse NIAID severity for aviptadil (Table 1).

Efficacy: An overall favorable trend (OR 1.6; CI 0.95-2.2 P=.08) was seen for the primary endpoint at 60 days. Patients treated with aviptadil experienced 2.0-fold increased odds of survival (95% CI 1.05-3.88; P<.035) at Day 60 compared to placebo controlling for baseline NIAID score which was the secondary end point.

In contrast to the overall results, those patients treated with aviptadil in tertiary care centers had significantly higher odds of meeting the primary endpoint (alive and free of respiratory failure at Day 60) and the key secondary endpoint (survival through Day 60) than patients treated with placebo. At tertiary care sites, the odds ratio was >2.5 times higher for Day 60 alive and free of respiratory failure and >4 times higher for Day 60 survival for patients treated with aviptadil than for patients treated with placebo. The subgroup (70% of subjects) who were progressing despite treatment with remdesivir demonstrated a significant 3-fold increased odds of meeting primary endpoint (P=.03) and 4-fold increased odds of day-60 survival (P=.006).

Aviptadil was associated with statistically significant (P=.02) improvement in PaO_2/FiO_2)(P/F ratio) and with a 5-fold reduction in Cytokine IL-6 increase from baseline through Day 7 compared with placebo (P=.02), suggesting that improving oxygenation and attenuation of cytokine storm are two plausible mechanisms of action. Both PF ratio improvement and prevention of Cytokine IL-6 release were highly correlated with both attaining the primary endpoint and with day 60 survival (P<.001),

Table 1 Patient Enrollment, Disposition and Baseline Characteristics.

	Aviptadil n (%)	Placebo n (%)	Total n (%)
Screened	--	--	213
Randomized	136	67	203
Randomized and Treated	131 (100)	65 (100)	196 (100)
Completed Day 28	85 (64.9)	45 (69.2)	130 (66.3)
Died between Day 1 and Day 28	41 (31.3)	18 (27.7)	59 (30.1)
Completed Day 60	80 (61.1)	34 (52.3)	114 (58.2)
Died between Days 29 and 60	5 (3.8)	12 (18.5)	17 (8.7)
Age (years, mean)	60.1	62.7	
Male (percent)	64.9	76.9	
Tertiary Care Sites	94 (71.8)	50 (76.9)	
NIAID 3	90 (68.7)	52 (80)	
HFNC	76 (58.0)	51 (78.5)	
On Vent	38 (29.0)	11 (16.9)	

RESULTS (continued)

Safety: Slightly over 75% of patients in both treatment groups had at least 1 Treatment-Emergent Adverse Event (TEAE) with 102 (77.9%) patients for aviptadil; 49 (75.4%) for placebo experienced TEAEs. (Table 2)

Table 2 TEAEs with Incidence ≥ 10% in At Least 1 Treatment Group Presented by Preferred Term

	Aviptadil n (%)	Placebo n (%)
Any TEAE	102 (77.9)	49 (75.4)
Diarrhoea	43 (32.8)	1 (1.5)
Hypotension	34 (26.0)	14 (21.5)
Acute kidney injury	31 (23.7)	13 (20.0)
COVID-19	22 (16.8)	10 (15.4)
Deep vein thrombosis	17 (13.0)	9 (13.8)
Respiratory failure	16 (12.2)	9 (13.8)
Hyperkalaemia	16 (12.2)	4 (6.2)
Atrial fibrillation	15 (11.5)	3 (4.6)
Multiple organ dysfunction syndrome	9 (6.9)	9 (13.8)
Constipation	9 (6.9)	7 (10.8)

Discussion

There are limited therapeutic options for patients with Critical COVID-19. Aviptadil, with its pleiotropic mechanism, represents a new additive therapeutic with evidence of mitigating cytokine storm, improving RDR / respiratory failure, subsequent clinical sequelae and has the potential to improve survival. Earlier treatment leads to improved outcomes. Aviptadil showed a manageable safety profile, with no unexpected serious adverse events.

Study limitations include:

- Initial risk assumptions made for the control group was underestimated, as such, the study was underpowered
- Higher proportion of mechanically ventilated patients in Aviptadil group, which may explain the lack of separation at 28 days
- At height of pandemic (patient care practice was rapidly evolving and ICU resource capacity at many sites were adversely impacted which may have impacted survival).

Conclusions

Patients infected with COVID-19, critically ill and hospitalized when treated with aviptadil, showed improvement which included, the likelihood of recovering from failure, surviving to 60 days, and reducing hospital stay when compared to placebo.

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