Intravenous Alpha-1 Antitrypsin: A Novel Therapy for Critically Ill Coronavirus Disease 2019 (COVID-19) Patients

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INTRODUCTION

There is an ongoing need for effective therapies for severe COVID-19.
Alpha-1 antitrypsin (AAT), also known as SERPINA1, is a circulating glycoprotein with a broad-spectrum antiproteinase activity, as well as various anti-inflammatory and tissue-protective properties.
It has demonstrated efficacy in several models of lung inflammation and injury from various causes, in preclinical studies and few clinical cases.

METHODS

Four critically-ill patients were treated with IV AAT (GLASSIA, Kamada, Ness Ziona, Israel), as compassionate therapy in addition to standard of care for COVID-19. Outcome measures included objective change in clinical status determined by the Sequential Organ Failure Assessment (SOFA) Score, PaO2/FiO2 (PF) ratio, successful extubation, mortality, hospital discharge and side effects.

OBJECTIVES

We hereby present our experience with intravenous human AAT therapy for critically-ill, mechanically ventilated patients with COVID-19.
Human liquid preparation of 2% AAT
Was administered intravenously over 2hours in three doses of 60mgl/kg each on time 0, and after 48 and 96 hours.

RESULTS

Three patients who received the treatment on an early stage showed significant signs of and were extubated within 9-13 days of treatment. The fourth patient was given the therapy as a rescue treatment at a very late and incurable state (hospitalization day 23, SOFA score=14) and succumbed the next day.
Improvement in SOFA score and PF ratio was noted following 48-hrs of initial dose of AAT.
No significant adverse effects were encountered.

TABLE: PATIENT CHARACTERISTICS

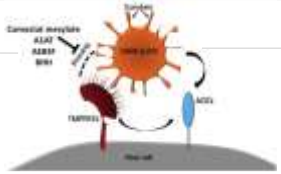
	Gender	Age	Comorbidities	Illness day of AAT 1st dose	Other COVID-19 medications	Outcome
1	Male	64	Morbid obesity, HTN, dyslipidemia	12	HCQ, dar-cob, hydro	Good
2	Male	56	Morbid obesity, HTN, DM, CKD, OSA	10	HCQ, lop-rit, tocilizumab, hydro	Good
3	Male	61	None	29	HCQ, dar-cob, lop-rit, tocilizumab, plasma, hydro	Death
4	Male	62	Obesity, urolithiasis	5	Dex, plasma	Good

MODE OF ACTION

1. SARS-CoV-2 cell entry requires attachment to the receptor ACE2 after priming of the viral S protein by the host cellular protease TMPRSS2. AAT effectively blocks TMPRSS2.

2. AAT inhibits the viral nonstructural protein 3-chymotrypsin-like protease.

3. AAT down-regulates several pro-inflammatory cytokines, including IL-6, implicated in severe COVID-19.



From: Azouz NP, Klingler AM and Rothenberg ME. Alpha 1 Antitrypsin is an Inhibitor of the SARS-CoV2–Priming Protease TMPRSS2. *bioRxiv* 2020.05.04.077826; doi: https://doi.org/10.1101/2020.05.04.077826.

Taken together, AAT may inhibit both the early "viral" phase of SARS-CoV2 cell infection, as well as the later inflammatory "cytokine storm" phase

From: Sanders JM, Monogue ML, Jodlowski TZ and Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020;323(18):1824-1836. doi:10.1001/jama.2020.6019

RESULTS

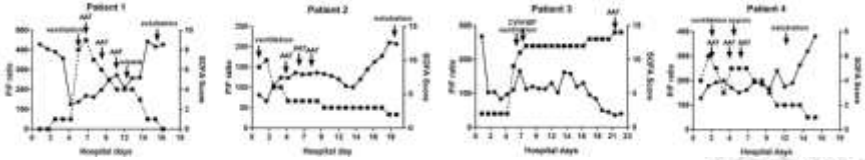


Figure: Hospitalization course of 4 patients treated with AAT for severe COVID-19
--- SOFA score, — P/F ratio of the patients
AAT time of AAT administration, CVVHDF initiation of continuous continuous venovenous hemodiafiltration for anuric renal failure

CONCLUSIONS

Given the extensive safety data and a high potential for positive effects, the risk/benefit ratio of treating severe COVID-19 patients with AAT seems favorable.
A phase II, prospective, randomized study of AAT in severe COVID-19 patients is currently under development.