Intravenous Alpha-1 Antitrypsin Therapy for Critically Ill COVID-19 Patients

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The plasma serine protease inhibitor alpha-1 antitrypsin (AAT) is a circulating glycoprotein with a broad-spectrum antiproteinase activity. It also has various anti-inflammatory and tissue-protective properties [1]. A recent study showed that population differences in AAT deficiency allele frequencies may partially explain national differences in the COVID-19 epidemiology [2]. Currently, intravenous AAT is indicated as augmentation therapy in patients with emphysema and severe AAT deficiency. It has demonstrated efficacy in several preclinical and clinical studies [1]. Moreover, it exhibited benefit in various models of lung inflammation and injury. While various medications have been investigated to treat coronavirus disease 2019 (COVID-19), effective treatment, especially for severe cases, is still an unmet need. Recent theoretical reports, relying on the interplay between AAT with TMPRSS2, ADAM17, and immune molecules, have suggested the AAT as an interesting treatment option for COVID-19 [3].

All COVID-19 patients at our center were admitted to dedicated isolated wards, according to the Israeli guidelines. Thromboprophylaxis with low-molecular weight heparin is universal unless contraindicated. Indications for specific COVID-19 medications included a modified National Early Warning Score (modified NEWS) ≥ 5, age ≥ 65, and significant co-morbidities. Therapeutic options included lopinavir-ritonavir, darunavir-cobicistat, and dexamethasone. Additional therapies, such as tocilizumab and convalescent plasma from COVID-19 recovered individuals were offered to patients with severe COVID-19 on a case-by-case basis following a multidisciplinary discussion.

Human liquid preparation of 2% AAT (GLASSIA, Kamada, Ness Ziona, Israel) was administered intravenously over 2 hours in three doses of 60 mg/kg each on time 0, and following 48 and 96 hours. We present our experience with intravenous AAT therapy for four critically ill COVID-19 patients.

GLASSIA was given as compassionate care, following the approval of Clalit Health Services. Written Informed consent was obtained from close relatives since the patients were intubated. Ethics approval was given by the IRB (MMC-0320-20).

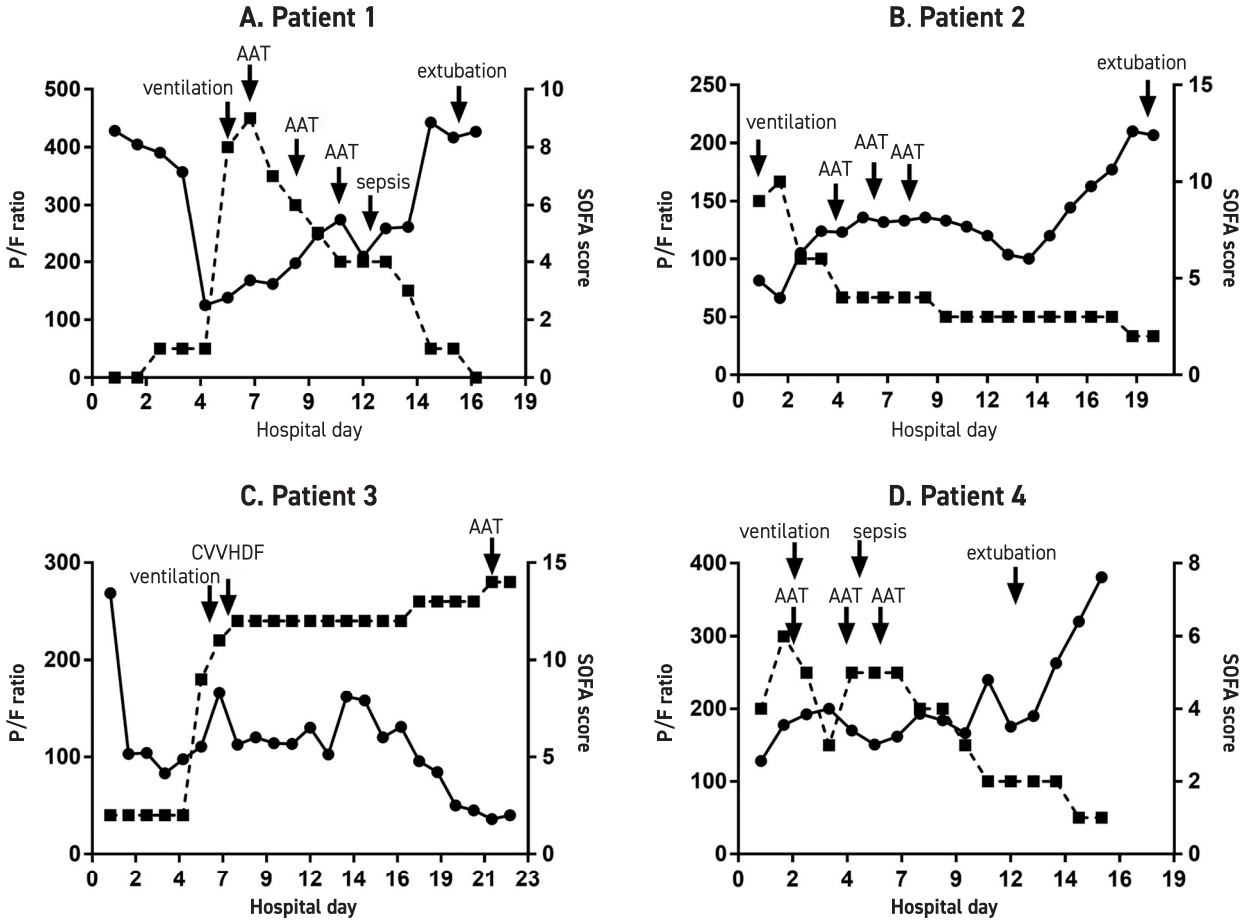
PATIENT DESCRIPTION

Four male patients with a median age of 61 years old (56–64 years) were treated with AAT and were included in this report. All were admitted with critical COVID-19 after a median of 5 days (4–7 days) presenting with fever and dyspnea. Disease course, including timing of AAT treatment, is shown in Figure 1. All developed severe hypoxemia requiring high-flow oxygen therapy initially and later mechanical ventilation, with hemodynamic instability requiring vasopressor support. Worsening gas exchange parameters required muscle relaxation, prone positioning, and inhaled nitric oxide (NO). Two patients were treated with two doses of intravenous tocilizumab (8 mg/kg) (patient 2 on day 3, patient 3 on day 6) but continued to deteriorate. One patient developed acute anuric kidney failure and required continuous venovenous hemodiafiltration. Two patients were also treated with convalescent plasma (patient 3 on days 15 and 16, patient 4 on days 1 and 2) [Figure 1], without improvement. Intravenous AAT, as compassionate therapy, was given in three doses. The median day for initiation of therapy was day 4 of hospitalization (range 2–22 days). Significant hemodynamic and respiratory improvements were noted following AAT treatment, with reduced need for vasopressors and oxygen support. Two patients developed an asymptomatic diffuse erythematous rash after the second dose of AAT, which resolved spontaneously, while their overall status continued to improve.

Patients 1 and 2 were extubated after 11 and 12 days of mechanical ventilation, respectively, and were discharged without need for supplementary oxygen. Patient 4 underwent successful decannulation following 6-weeks of inpatient rehabilitation, and regained full ambulation. Patient 3 developed multiorgan fail-

Figure 1. Hospitalization course of the patients, with the SOFA score (right Y axis, squares) and P/F ratio over time (left Y axis, circles)

AAT = initiation of alpha-1 antitrypsin treatment, CVVHDF = continuous venovenous hemodiafiltration, SOFA = sequential organ failure assessment



ure consisting of refractory hypoxemia and shock, left ventricular dysfunction, and protracted anuric kidney failure. On hospitalization day 22 he was treated with one dose AAT despite appearing terminally ill (sequential organ failure assessment [SOFA] score = 14) but succumbed within hours.

COMMENT

The pathophysiology of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection includes viral attachment to the angiotensin-converting enzyme 2 (ACE-2) receptor on cell membranes. This process of entry into host cells requires additional proteases, including cellular type II transmembrane serine protease and the viral essential nonstructural protein 3-chymotrypsin-like protease. Both proteins have already been implicated in other viral infections, and both can be effectively inhibited by AAT. In addition to its antiproteinase activity, AAT down-regulates several pro-inflammatory cytokines, including IL-6.

We think that AAT might be able to control viral burden while simultaneously inhibiting aberrant immune responses. Taken together, AAT may inhibit both the early viral phase of SARS-CoV-2 cell infection, as well as the later cytokine storm phase [4]. In a preclinical study, low concentrations of a protease inhibitor were sufficient to inhibit SARS-CoV-2 entry into host cells. In our trial, AAT was used at a relatively low dose, which was calculated based on previous trials.

GLASSIA, a plasma-derived AAT product for intravenous use, is approved as an augmentation or replacement therapy for patients with emphysema and severe AAT deficiency, showing a good safety profile [5].

All the patients given AAT in our study were critically ill and deteriorating. Three were given AAT treatment relatively early in their disease course (patients 1, 2, and 4, on days 5–12 of

symptoms). We witnessed significant improvement and stabilization within a day, manifested by objective measures, such as improvement in the SOFA score and PaO2/FiO2 ratio (P/F ratio). The forth patient (patient 3) was treated with AAT as a last resort at a very late and incurable state in which a fatal outcome was inevitable. Two of the patients developed a short-lived asymptomatic rash following the second dose of AAT. Dermatological disorders are frequent in critically ill patients, and in our cases may be the result of COVID-19 itself, of AAT therapy, or as a drug eruption or reaction to other medications. We are unaware of any previous reports of rash or drug-eruption resulting from administration of AAT. Skin manifestations of COVID-19, however, are common and diverse. Thus, we believe that the rash observed in those cases was probably the result of COVID-19 and should not preclude future treatment with AAT in similar cases.

Our results are, obviously, limited and difficult to generalize. In addition, due to the low sample size, outcome could have been confounded by co-morbidities of the patients. Given the complex nature of COVID-19, timing of therapy may also be crucial. In addition, drug therapy for COVID-19 continues to evolve as clinical data are accumulating. Thus, remdesivir was not available at the time our patients were treated, while trials which demonstrated the futility of hydroxychloroquine and lopinavir-ritonavir were published afterward. We cannot exclude effects of other medications on the outcome of our patients, or predict the results of combining AAT with current COVID-19 treatments.

CONCLUSIONS

To the best of our knowledge, this is the first report of intravenous AAT therapy for severe COVID-19. Given the extensive safety data and a high potential for positive effects, we believe that the risk/benefit ratio of treating severe COVID-19 patients with AAT is favorable, and warrants an adequately powered prospective trial. Altogether, AAT therapy might have great potential for severe COVID-19 patients, with minimal perils.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author on reasonable request.

FINANCIAL SUPPORT AND CONFLICT OF INTEREST DISCLOSURE

Naveh Tov is an employee at Kamada Ltd. GLASSIA was provided free of charge by Kamada Ltd. as compassionate therapy.

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Capsule

Pregnancy enables antibody protection against intracellular infection

Erickson et al. showed that pregnancy-induced post-translational antibody modification enables protection against the prototypical intracellular pathogen Listeria monocytogenes. Infection susceptibility was reversed in neonatal mice born to preconceptually primed mothers possessing L. monocytogenes-specific IgG or after passive transfer of antibodies from primed pregnant, but not virgin, mice. Although maternal B cells were essential for producing IgGs that mediate vertically transferred protection, they were dispensable for antibody acquisition of protective function, which instead required sialic acid acetyl esterase to deacetylate terminal sialic acid residues on IgG variable-region N-linked glycans. Deacetylated L. monocytogenes-specific IgG protected neonates through the sialic acid receptor CD22, which suppressed IL-10 production by B cells leading to antibody-mediated protection. Consideration of the maternal–fetal dyad as a joined immunological unit reveals protective roles for antibodies against intracellular infection and fine-tuned adaptations to enhance host defense during pregnancy and early life.

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