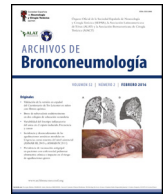




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## Letter to the Editor

**Alpha-1 Antitrypsin Deficiency and COVID-19 Infection**

**Deficiencia de Alfa-1 antitripsina e infección por COVID-19**

Dear Editor,

Andrea Vianello and Fausto Braccioni reported about a geographical overlap between Alpha-1-Antitrypsin deficiency and severe cases of a COVID-19 Infection in Italy.<sup>1</sup> This raises the question of the physiological background.

By search for early indicators of severe disease progression the proinflammatory cytokine IL6 in particular has proven to be prognostically unfavorable. McElvaney et al. showed that an increase in the ratio between IL-6 and alpha-1-antitrypsin is a negative prognostic factor for the course of the disease.<sup>2</sup>

The primary route of infection is by infecting the host cells via a coupling of the virus spike to the membrane protein TMRSS2 of the ACE2 receptor. Lukas Wettstein, Janis A. Müller, Tatjana Weil, Rüdiger Groß, Maximilian Hirschenberger, Alina Seidel et al.<sup>3</sup> could demonstrate that this mechanism is inhibited by alpha-1 antitrypsin in a dose-dependent manner. As the infection progresses, tissue proteases increase as part of the immune response. Especially trypsin and elastase enable virus absorption on the cell surface. This means a second, endosome-independent infection pathway. Here, the effectiveness is over 100 times higher.<sup>4</sup> At the same time, an increased protease level leads to an activation of the spike protein which facilitates the binding to the receptor of non-infected cells. Lysosomal proteases thus play a central role in the maintenance and spread of corona virus infection in the human body.<sup>5</sup> The inhibitory effect of alpha-1-antitrypsin on endogenous proteases has long been known and proven. Own investigations have shown that AAT suppresses the release of cytokines from stimulated fibroblasts in a dose-dependent manner. In the focus of an infection with a SARS-CoV 2 virus, a therapeutic increase of plasma AAT levels may be useful to reduce the spread of the virus in the body after initial infection.

Now the question arises to what extent these results can be integrated into the considerations for the development of new therapeutic concepts. The aim is to increase the local alpha-1-antitrypsin level in the lung tissue.

Besides their ability to act as immunomodulators, mesenchymal stem cells have the property to accumulate almost exclusively in lung tissue after application. First clinical results with single applications of stem cells at COVID-19 patients showed an unproblematic application without significant side effects. An increase of

lymphocytes as well as T-cells could be achieved within a period of two days. In addition, a significant decrease in serum levels of IL-6, TNF-alpha and CRP was found. Parallel to the normalization of the laboratory parameters an improvement of the clinical symptoms as well as the radiological findings was observed.<sup>6</sup>

Combining both principles in a genetically engineered stem cell expressing Alpha-1-Antitrypsin provides an effective therapy for severely ill patients.

In order to achieve high levels of AAT in the affected tissues (lung), MSCs are a suitable vehicle due to their "homing potential". Besides their modulating effect on immunological processes, mesenchymal stem cells show the ability to accumulate in diseased tissue. A modern therapy concept with a genetically modified stem cell expressing alpha-1 antitrypsin seems conclusive and reasonable.

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