Why COVID patients become critically ill

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Researchers at Amsterdam UMC have discovered why patients become seriously ill after being infected with the coronavirus. They identified that aberrant antibody responses are the main cause of becoming critically ill. In addition, they identified a drug that can counteract this derailed immune response, which may be used to treat seriously ill

COVID patients in the ICU. This drug is already FDA approved for treatment of particular autoimmune diseases.

Researchers Jeroen den Dunnen and Menno de Winther of Amsterdam UMC have discovered why COVID-19 patients can become seriously ill after infection with the coronavirus. It turns out that severe COVID-19 patients produce aberrant antibodies against the coronavirus, which dramatically worsen the course of the disease. The results were published today in the scientific journal *Science Translational Medicine*.

Extreme inflammatory response

Immunologist Den Dunnen explains: "During an infection, our immune system produces antibodies. Normally, these antibodies protect your body against viruses. This also holds true for most people that become infected with the Corona virus. But in COVID-19 patients that become seriously ill, the antibody response is derailed. These patients do not only make extremely high amounts of antibodies against the virus, but these antibodies also have an aberrant structure. This causes an extreme inflammatory reaction in the lungs."

De Winther, an expert on immune cells: "The antibodies that our bodies make are shaped like a Y. The top binds to the virus, while the tail binds to the immune cells in the lungs, thereby activating these cells. We now know that this tail is different in patients who are seriously ill. To put it simply, the sugars that are normally attached to antibodies are very different in these patients. The result is that the immune cells in the lungs are activated much too strong."

The different composition of the antibody's tail has three effects, Den Dunnen explains. "The immune system becomes completely over-activated, which is sometimes referred to as a cytokine storm. The inflammatory response that was meant to attack the virus now destroys

the patient's own tissues. In addition, the blood vessels become leaky, the lungs fill up, and platelets start to clump together. Admission to the ICU is often unavoidable and the prognosis for these patients is generally not good."

Treatment

Counteracting these serious consequences does not necessarily require antiviral drugs, but mostly require drugs that can suppress the immune response. Indeed, drugs such as dexamethasone and tocilizumab, are currently used to treat seriously ill patients. Den Dunnen: "These drugs do indeed have some effect, but the major disadvantage is that they suppress the immune system as a whole. And that is not really what you want, because you still want a good immune response against the virus."

The Amsterdam UMC has a lot of immunological expertise, and with that background knowledge in mind drugs were selected that specifically inhibit the inflammatory response caused by the abnormal antibodies, while leaving the rest of the immune system intact. "The drug we studied, fostamatinib, ensures that the immune cells in the lungs no longer react to the abnormal antibodies, but still react to the virus. This specificity makes this drug a promising candidate for treating seriously ill COVID patients."

Because this drug is already registered for another disease, it does not have to go through all kinds of procedures before it can be tested in humans. De Winther: "We now have the results of a phase 2 study in which the drug was tested in 59 patients. In the group of 30 who received the drug, fewer people died, there were fewer side effects and they recovered more quickly than the 29 patients who received a placebo. Meanwhile, based on this study, a large phase 3 study has started in more than forty hospitals, which should show whether this drug is indeed useful as a treatment for severely ill COVID patients."

De Winther and Den Dunnen, who work together at the Amsterdam Institute for Infection and Immunity, do not want to stop at just one drug. Last year they received a grant from ZonMw, a Dutch government funded organization, to further investigate this mechanism and to test several additional candidate drugs. "The goal is to find drugs that work just as well, or preferably even better, than fostamatinib. We have several already approved drugs that we suspect could work."

More information: Willianne Hoepel et al. High titers and low fucosylation of early human anti-SARS-CoV-2 IgG promote inflammation by alveolar macrophages, *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.abf8654

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