

Hyper-inflammation in severely ill COVID-19 is induced by early phase anti-SARS-CoV-2 IgG and can be specifically counteracted by FDA/EMA-approved small molecule inhibitors

^{1,2} Hoepel W, ³ Chen HJ, ^{1,2} Geyer CE, ⁴ Manz XD, ⁵ de Taeye SW, ⁴ Bogaard HJ, ⁵ van Gils MJ, ⁶ Vidarsson G, ³ de Winther M, ^{1,2} den Dunnen J

¹dept. of Rheumatology and Clinical Immunology, ²dept. of Experimental Immunology, ³dept. of Medical Biochemistry, ⁴dept. of Pulmonary Medicine, ⁵dept. of Medical Microbiology, ⁶dept. of Experimental Immunohematology

Patients diagnosed with COVID-19 become critically ill primarily around the time of activation of the adaptive immune response. Here, we provide evidence that antibodies play a key role in this worsening of disease at the time of seroconversion. We show that early phase IgG against the Spike protein of SARS-CoV-2 in serum of critically ill COVID-19 patients induces excessive inflammatory responses by human alveolar macrophages. We identified that this inflammatory response is dependent on two antibody features that are specific for patients with severe COVID-19, i.e. extremely high titers of anti-spike IgG, and aberrant glycosylation of the Fc tail of anti-spike IgG, particularly low fucosylation. We identified Fcγ receptor (FcγR) IIa and FcγRIII as the two primary IgG receptors that are responsible for this excessive inflammation. Strikingly, we show that the hyper-inflammatory response induced by anti-Spike IgG can be specifically counteracted by fostamatinib, an FDA- and EMA-approved therapeutic small molecule inhibitor of the kinase Syk, which is now tested in phase III clinical studies involving 42 different hospitals worldwide. In addition, we show that hyper-inflammation induced by low fucose anti-Spike IgG is dependent on a novel interferon-dependent pathway. Finally, we applied this knowledge to identify FDA- and EMA-approved small molecule inhibitors that are even more specific to counteract inflammation in severely ill COVID-19 patients than fostamatinib. These drugs may be highly valuable to treat individuals that have not been vaccinated, or for the treatment of (future) SARS-CoV-2 mutants to which the current vaccines do not provide sufficient protection.