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Clinical Immunology

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Letter to the Editor

Antibody-dependent enhancement and COVID-19: Moving toward acquittal

Dear Editor,

The recent review article published by Nguygen et al. nicely highlighted the promise and concerns surrounding the use of immunoglobulins to treat COVID-19 [1]. As several COVID-19 vaccine candidates enter human trials and the therapeutic use of convalescent plasma is explored, debate continues amongst clinicians over whether antibody-dependent enhancement (ADE) of SARS-CoV-2 infection represents a relevant concern. ADE is a well-recognized phenomenon whereby viral entry into cells is enhanced by binding of virus/antibody complexes to membrane Fc receptors or complement receptors, resulting in a worsening of disease. ADE was recently thrust into the spotlight with Dengue fever, though it has been observed for several clinically relevant viruses (RSV, HIV, Ebola).

Concerns of ADE with SARS-related coronaviruses are based primarily on experimental data with limited clinical evidence. Antibodies specific for the viral spike protein facilitated the entry of SARS-CoV-1 into human immune cells via Fc receptors and independent of ACE2 [2]. However, infection in these cells was abortive (no sustained replication or detectable release of infectious virus). High titers of spike-specific antibodies in macaques vaccinated with a live recombinant vaccine encoding the SARS-CoV-1 spike protein were associated with lung injury post-challenge [3], suggesting antibody enhancement. Though data from recent SARS-CoV-2 vaccine studies showing macaques that developed high titers of spike-specific antibodies were protected against infection with no increased lung pathology or ADE [4,5] support that spike-specific antibodies are predominately protective.

Early seroconversion following human SARS-CoV-1 infection was correlated with disease severity [6]. However, most early seroresponders were already high-risk (> 60 y.o.) and no difference in neutralization titers was noted between early seroresponders who died and those who survived. Early seroconversion and robust IgG responses during SARS-CoV-2 infection were recently associated with disease severity [7]. Neutralization titers were not measured, and the severe disease group contained a higher proportion of at-risk older individuals. Neither study quantitated viral loads, so the influence of viral inoculum and burden on study findings is unclear. As aging is associated with T-cell dysfunction [8], a role for aberrant T cell responses in these patients should not be excluded. Further, aging is characterized by heightened, low-grade chronic

inflammation [8]. Cytokine profiles were not characterized in either study, so early seroconversion might represent a poor prognostic factor in at-risk older patients rather than evidence for ADE. The presence of pre-existing antibodies against coronaviruses in patients is plausible. However, discordance between the epidemiology of severe COVID-19 cases and seroprevalence data for homologous betacoronaviruses [9], and the fluctuating circulation patterns of analogous human coronaviruses, cast doubts on roles for cross-reactive antibodies in pathology. Indeed, emerging safety data from a trial on convalescent plasma involving 5000 patients showing no evidence for ADE strongly suggests that protective neutralizing antibodies counteract the function of any enhancing antibodies found in patients [10].

Based on developing scientific data, ADE concerns with COVID-19 have significantly lessened. Thus, the primary risks associated with convalescent plasma therapy are those that are known (transmission of blood-borne pathogens, transfusion-related acute lung injury, and transfusion-associated circulatory overload), facilitating the development of risk-benefit assessments. Clinical research efforts should shift toward systematic analyses of antibody responses in convalescent patients. Data on the relationship between neutralization titer and recovery, antibody longevity, and the influence of age are needed to advance the development of antibody-based therapies. Though clinical data from studies using a variety of antiviral therapies (e.g., remdesivir) to treat COVID-19 have been promising, antibody-based therapies represent valuable treatment approaches since they can be used to treat symptomatic patients and be used prophylactically in at-risk individuals. Lastly, as data on the cellular correlates of disease protection and pathology are lacking, additional investigation into these areas is likely to provide valuable information for the development of vaccines and other immunotherapies.

Funding

None.

Declaration of Competing Interest

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