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EDITORIAL COMMENTARY

Implications of Coronavirus Disease 2019 (COVID-19) Antibody Dynamics for Immunity and Convalescent Plasma Therapy

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(See the Major Article by Wang et al on pages e531–9.)

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The article by Wang et al in this issue of *Clinical Infectious Diseases* reports that neutralizing antibody titers to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus peak 4–5 weeks after the onset of symptoms and decline by 3 months [1]. A lentiviral pseudovirus expressing the SARS-CoV-2 spike protein was used as a surrogate for measurement of SARS-CoV-2 neutralizing antibodies. Although this assay does not use live SARS-CoV-2 virus, it has a good correlation with assays that use native virus [2]. The results reported by Wang et al [1] match those of plasma donors in the United Kingdom, in whom antibody titers declined over the first 3 months after resolution of COVID-19 [3]. These findings have important implications for immunity and ongoing efforts to deploy convalescent plasma for prevention and therapy of COVID-19, as well as for the generation of antibody products from plasma, such as specific immunoglobulins.

The implications of the results of this study for immunity to SARS-CoV-2 are not surprising: for most, if not all infectious diseases, immunity, as reflected by antibody levels, wanes with time. Should this be the case for COVID-19, what will matter is the slope by which immunity declines over time, something that varies for different pathogens. For example, measles confers lifelong immunity [4], whereas a bout of norovirus disease results in immunity that lasts from 6 months to 2 years [5]. As discussed by Wang et al [1], coronaviruses are notorious for eliciting short-lived immunity. The decline in neutralizing antibody titers measured by Wang et al [1] in 93.5% of the patients studied is concerning for it raises the possibility that like other coronaviruses, COVID-19 may not result in the establishment of long lasting immunity. However, such a conclusion is premature at this time because the relationship between different components of the immune response and resistance to re-infection has not been established. Furthermore, it is very early in the COVID-19 epidemic and conclusions about long-term immunity will have to wait for longitudinal studies of susceptibility as a function of time.

At present, it is not known if SARS-CoV-2 antibody titers will plateau at a lower level sufficient to prevent reinfection. We also do not know the specificity or functional activity of antibodies that may prevent reinfection. For example, antibodies to SARS-CoV-2 determinants that are not identified by current assays and/or nonneutralizing antibodies may prevent infection by potentiating other antiviral mechanisms such as antibody-dependent cellular cytotoxicity, as has been described for other viruses. Furthermore, antibody-mediated humoral immunity is only one component of successful immune responses that also include T-cell immunity, which can exert antiviral effects. In addition, together with B cells, T cells help provide memory for future encounters with SARS-CoV-2. Importantly, the amount of antibody needed to protect a recovered person from reinfection in the setting of immunological memory of SARS-CoV-2 is likely to be only a small fraction of the amount of antibody generated in the immediate convalescent period. Therefore, the conclusion that there is a causal relationship between declining titers of neutralizing antibody and susceptibility to reinfection is currently premature. Medicine has known of SARS-CoV-2 for less than 1 year and correlates of immunity are not well understood. More time and research are needed to inform our knowledge of the duration and durability of immunity to SARS-CoV-2 following asymptomatic infection as well as symptomatic COVID-19.

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It is also difficult to extrapolate the results of Wang et al [1] to the type of immune response that should be elicited by SARS-CoV-2 vaccines. Although the goal of most current vaccine formulations is to elicit neutralizing antibodies to SARS-CoV-2 that might recapitulate the response to natural infection, it is important to note that protective immune responses elicited by vaccines and natural infection can differ [6]. Perhaps the most extreme example of this phenomenon are vaccines for diphtheria and tetanus, whereby toxoids produced from their toxins elicit long-lasting protection, but these diseases do not induce immune responses that confer immunity [6]. Any conclusions concerning SARS-CoV-2 vaccine design or efficacy drawn from the findings of the work of Wang et al should be cautious yet optimistic. Wang et al [1]. show that infection with SARS-CoV-2 does elicit neutralizing antibodies with some durability, and this is good news for the prospect of a successful vaccine.

Whereas implications of the kinetics of the antibody response to SARS-CoV-2 for long-lasting and vaccine-mediated immunity are uncertain, the results of Wang et al [1] are important for the development and use of antibody therapies. Antibody therapies rely on donor B cells, which are used to isolate monoclonal antibodies (mAbs), and plasma, which is used for therapy and production of hyper-immune globulin. Convalescent plasma has emerged as a promising therapy for COVID-19, and there is evidence that its administration early in the course of hospitalization is associated with reduction in viral load, clinical improvement, and reduction in mortality [7–9]. Studies reporting a reduction in viral load following plasma administration have used plasma with high titer neutralizing antibody, with the caveat that these studies were observational and dose-response data are not available. Hence, the finding by Wang et al [1] that neutralizing antibody titers can drop rapidly after recovery from COVID-19 means that there may be a narrow window when a recovered patient is a suitable convalescent plasma donor. Similar concerns apply to donations of plasma for the generation of hyper-immune globulin preparations, which are produced from human convalescent plasma. Although not analyzed in the Wang et al [1] study, similar kinetics apply to circulating B cells that are used to isolate human mAbs or serve as the source of variable region genes for construction of human antibodies.

The finding that SARS-CoV-2 neutralizing titers declined relatively quickly in the Wang et al study [1] means that efforts to collect convalescent plasma with high titers of neutralizing antibody for therapy and hyper-immune globulin preparation need to be highly organized such that potential donors are contacted early in the weeks following COVID-19. A prior report from China found that antibodies to the SARS-CoV-2 protein peaked at 4 weeks [2]. Given that current recommendations for plasma donation advise waiting 4 weeks after the resolution of symptoms to ensure viral clearance and a rise in convalescent antibody titer, the preferred window for plasma collection begins at 4 weeks and could narrow rapidly by 12 weeks. This short collection window means that ensuring a plentiful supply of high-quality plasma requires making it a priority that individuals diagnosed with COVID-19 recruited for donation during the relatively short time window between resolution of symptoms, clearance of virus (to eliminate chance of infecting transfusion personnel), and the decline in antibody titer. This is important information for the blood banking community that is producing and supplying convalescent plasma for therapeutic use and the hyper-immune globulin purveyors in the pharmaceutical industry.

In addition to studies of the kinetics and durability of SARS-CoV-2-binding B cells, an important issue that should be addressed by future longitudinal studies is the quality of the antibody response as a function of time. The observation that COVID-19 patients who received convalescent plasma late in their course of disease exhibited a reduced viral load [7], even though most individuals make their own neutralizing antibody by day 10–12 of disease [2], suggests that there are qualitative differences between the type of antibodies made during the endogenous response and convalescent plasma [10].

In summary, Wang et al [1] show that immunity as measured by neutralizing antibody wanes rapidly in the months after infection. At present, the implications of this finding for individual susceptibility to re-infection are unknown. Nonetheless, this report has major implications for the timing of harvesting of convalescent plasma for therapeutic use and hyper-immune globulin production because it implies there is a narrow window of time between recovery from COVID-19, viral clearance, and still having high levels of neutralizing SARS-CoV-2 antibody. Hence, convalescent plasma collection efforts for COVID-19 need to be organized around the temporal dynamics of the immune response to ensure that optimal plasma is obtained from donors.

Notes

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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