SARS-Cov2 variants and convalescent plasma: reality, fallacies, and opportunities

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In recent months genomic characterization of pandemic SARS-CoV-2 isolates identified viral variants that are less susceptible to neutralization by convalescent plasma (CP), vaccine-elicited plasma/sera, or SARS-CoV-2 mAbs than earlier SARS-CoV-2 strains. The emergence and spread of SARS-CoV-2 variants that evade vaccine immunity would be a cataclysmic development for a world expecting relief from the pandemic and a return to normality, since these could cause new cycles of infection in vaccinated individuals and those who recovered from COVID-19.

Some media reports have suggested that SARS-CoV-2 variants emerged as a consequence of CP use for COVID-19 (1, 2). This hypothesis followed a report that CP treatment in an immunosuppressed COVID-19 patient was associated with the emergence of new SARS-CoV-2 variant populations in that patient, some of which exhibited reduced susceptibility to antibody neutralization (3). This observation was confirmed in the laboratory, where serial passage of virus in the presence of CP selected for antibody resistant SARS-CoV-2 variants, including the E484K mutation associated with vaccine resistance (4). These findings established that CP could select for antibody-resistant variants, though this should not be regarded as a surprising result. As a powerful antiviral agent, CP is expected to exert selective pressure on viral populations in these types of in vitro evolution experiments. In this context, it is notable and reassuring that resistance-associated viral variants appeared very late, in the eighth passage (4).

RNA viruses exist in quasi-species populations including variants that may predominate under selective pressure from host immune systems, including both endogenous and passively administered specific antibodies. Specific monoclonal antibodies (MAbs) may exert consequential pressure that is even more consequential than from polyclonal preparations such as convalescent plasma (CP). This is because only a few amino acid changes are necessary to abrogate MAb binding to a single viral determinant (5). For example, exposure to the respiratory syncytial virus (RSV)-specific mAb palivizumab was associated with the emergence of variant viruses during experimental infection of rats (6, 7) as well as during treatment of human infants (8). However, administration of Mab combinations (oligoclonal “cocktails”) can abrogate the emergence of resistant viruses, as demonstrated for SARS-CoV-2 Mabs (9). Nevertheless, the broader array of immune system functions also influences the outcome of host-virus interactions.

Variant drug and/or antibody resistant viruses are more likely to arise with or without augmentation by specific antibodies (CP or Mabs) in immunocompromised patients because their generally high viral burdens provide greater opportunity for variant selection. Incidentally, MAbs are theoretically more likely to select for antibody-resistant variants simply because these bind to a single epitope that can be easily abrogated by one or more amino acid changes while CP contains antibodies of multiple specificities. The propensity of resistant variants to emerge in hosts with impaired immunity has been noted with other respiratory viruses such as influenza, for which oseltamivir-resistant influenza viruses were more likely to be identified in immunocompromised individuals (10).

We are now presented with news of globally emergent, antibody-resistant, SARS-CoV-2 variants alongside new laboratory evidence that CP can select for SARS-CoV-2 antibody-resistant variants in immunocompromised individuals. We must be wary of drawing fallacious, causative relationships between these new facts. SARS-CoV-2 variants associated with higher transmissibility emerged during a surge in the U.K (11). During that time, CP use was limited to hospitalized patients, who either die or resolve their infection. For CP to have been responsible for the observed SARS-CoV-2 variant, it would have had to emerge in patients who subsequently transmitted it to the community. This is possible, but extremely unlikely within the larger pandemic. A more likely explanation is that variants are emerging from the vast pool of replicating virus that is presently passaging through hundreds of millions of infected humans. This explanation posits that variants emerge spontaneously during viral replication and that some variants that are resistant to antibody-mediated neutralization are then selected by the developing immune response because they are more fit for survival in immune hosts. In other words, while CP is not the cause of mutations, it can select for resistant variants in immunocompromised hosts that lack normal immune mechanisms that clear virus. Such individuals are under medical care in isolation and thus represent a very unlikely source for the variants circulating in the population. Variants have arisen, and continue to arise (12), amid a backdrop of lack of adherence to public health measures, such as masking and distancing.

Importantly, humans with COVID-19 generate antibodies to the viral species with which they are infected, and these antibodies are found in CP, which is obtained from recovered patients. Notably, endogenous antibody contributes to SARS-CoV-2 clearance as demonstrated in Mab trials (13). The emergence of resistant variants in a population increases in probability with the number of infected hosts. With pandemic spread, particularly in settings where there is insufficient adherence to public health measures such as masking and distancing, SARS-CoV-2 is under substantial, population-wide pressure to generate antibody-resistant variants independently of the relatively miniscule CP-treated patient population. The selective pressures of community spread are also likely to yield antibody-resistant variants with preserved, or even enhanced, transmission potential relative to those arising from a patient with prolonged viremia. Although the emergence of antibody-resistant variants is a predictable outcome of viral evolution during the ongoing pandemic, there is currently no direct evidence to suggest that circulating variants are a consequence of CP use.

Some have suggested that CP use should be avoided in immunocompromised patients, in whom prolonged viremia is possible. However, CP administration has been repeatedly been shown to be an effective antiviral agent in this population and the FDA Emergency Use Authorization revised in February

2021 recognizes these patients (14) as a population that may derive special benefit from CP (15, 16). We believe that it is prudent to administer SARS-CoV-2-specific antibodies to these individuals early in monitored settings with good infection control practices and adherence to public health measures.

Effective COVID-19 therapies are very limited, especially for the viral phase of the disease and should not be withheld because we are concerned about emergence of antimicrobial resistance.

Only a very small proportion of all individuals who have been infected with SARS-CoV-2 have received CP or mAbs for COVID-19 therapy. In contrast, more than 100 million people have been infected with SARS-CoV-2 and the majority of these individuals have made antibodies similar to those found in CP or mAb preparations. Among these are neutralizing antibodies that put selective pressure on infecting virus to evade antibody-mediated neutralization and maintain a replicating population within the host. Each person who is infected and mounts an antibody response has a low probability of selecting for a resistant variant. However, when that low probability is multiplied by the hundreds of millions of people who have been infected, the likelihood of variant emergence is a near certainty. Occam's razor favors the simplest explanation, which is that antibody-resistant variants emerged spontaneously, were selected by natural immune responses in infected individuals, and are spreading because they offer a fitness advantage in a human population that is increasingly immune to the founder SARS-CoV-2 strains.

Within these emerging circumstances, important new opportunities for CP use arise. Although SARS-CoV-2 variants may elude antibodies elicited by earlier, ancestral SARS-CoV-2 strains, people who recover from variant-COVID-19 are likely to generate CP capable of neutralizing variants. Hence, variant-CP could be a potential antidote for variant-SARS-CoV-2. As variant SARS-CoV-2 strains spread in human populations, recently donated CP units will be especially efficacious for variant COVID-19 patients. Thus, strategies to deploy CP could be tailored to align with currently circulating viral strains. This provides an additional rationale for surveillance of viral strains, which is necessary to follow SARS-CoV-2 evolution just as it is for influenza. As we move towards a hopeful, but increasingly uncertain second quarter of 2021, every effort should be made to conduct real time viral surveillance with increased sequencing capacity designed to identify the emergence, type, and prevalence of variant-SARS-CoV-2 strains. The resulting knowledge should inform CP characterization by determining each unit's ability to neutralize relevant circulating viral variants. Going forward, matching CP characteristics to each patient's viral type may become a useful precision medicine approach at the front lines of the pandemic.

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