blood advances

On a collision course: SARS-CoV-2 variants and CAR T cells

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Comment on van Doesum et al, page 2645

In this issue of *Blood Advances*, van Doesum et al[1] present real-world data from the EPICCOVIDEHA survey showing improved 90-day event-free survival (EFS) in patients receiving CD19-directed chimeric antigen receptor (CAR) T cells, who subsequently become infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The authors attributed the observed reduction in coronavirus disease 2019 (COVID-19)-related deaths during the 3-year study period to patients receiving previous vaccination and postexposure, anti–SARS-CoV-2 monoclonal antibody (Mab) therapy, both made available later in the course of the COVID-19 pandemic.[1]

Sixty-four patients receiving CAR T-cell therapy and later developing COVID-19 were reported from 34 centers in 15 European countries before 1 July 2022, with equal distribution of patients reported across each study period. Of these 64 patients, 28 (43.8%) received at least 1 vaccination (97% SARS-CoV-2 messenger RNA vaccine) before (n = 11) or after (n = 17) CAR T-cell therapy and 14 (21.9%) received postexposure Mab. With respect to experiencing severe COVID-19, 50 patients (78.1%) were hospitalized and 18 (28.1%) received intensive care. Therapies received included convalescent plasma (n = 16), remdesivir (n = 18), steroids (n = 30), and tocilizumab (n = 6). Of the 26 patients receiving CAR T-cell therapy who died, 20 (76.9%) died of COVID-19 (31% attributable mortality rate) and the remaining 6 died of progressive malignant disease. Although EFS did not differ by vaccination status, patients receiving Mab therapy had greater EFS than those patients who did not receive Mab therapy ($P = .036$). In univariate analyses, age and infection with other viral variants besides omicron were associated with reduced EFS in patients receiving CAR T-cell therapy and having subsequent COVID-19. Restricted by low number of events, the authors performed a limited multivariate analysis using pairwise Cox regression, which showed that patient age was the only significant factor associated with less risk of dying of COVID-19.

The study is certainly not perfect, but studies analyzing real-world data never are. For example, use of nirmatrelvir/ritonavir (Paxlovid) and tixagevimab/cilgavimab (Evusheld) were not studied, given delayed approval from the European Medicine Agency and subsequent limited availability to centers until late 2022. The study also had a small patient size, and patient data were obtained via a retrospective survey. Therefore, missing data and potential reporting biases were/could be present. Furthermore, limited patient data restricted more robust analyses. Despite these limitations, the study serves as a harbinger for what may become a new reality as new variants continue to emerge and production of vaccines and effective Mab therapy stalls, leaving immunocompromised patients, in general, and patients receiving CAR T-cell therapy, in particular, precariously vulnerable to severe COVID-19.

Since the World Health Organization declared it a pandemic on 11 March 2020, COVID-19 has caused >7 million deaths worldwide and >1 million deaths in the United States.[2] Immunocompromised patients, especially patients receiving CAR T-cell therapy, are at high risk for poor outcomes after contracting COVID-19.[3] Moreover, SARS-CoV-2 associates with multiorgan sequelae, including long COVID and multisystem inflammatory syndrome, both of which remain largely unstudied in immunocompromised patients. The inherent instability of the SARS-CoV-2 RNA genome and the virus' replication in immunocompromised hosts induce mutations in the receptor binding domain (RBD), which combine to create viral variants.[4] In addition to conferring differences in virulence such as transmissibility and severity in infection, mutations importantly underlie immune escape mechanisms by variants, rendering them less susceptible to vaccination and Mab therapy.[5]

In the EPICCOVIDEHA survey, 32 (50%) patients receiving CAR T-cell therapy had COVID-19 caused by a SARS-CoV-2 variant, with the omicron variant (n = 18, 56.3%) being most common relative to the

alpha (n = 3) and delta (n = 4) variants. Omicron and its subvariants are associated with high transmissibility but lower severe COVID-19 infection.[6] Regarding severe COVID-19 infection, patients who received CAR T-cell therapy and subsequently infected with omicron had a significantly lower risk of death from COVID-19 compared to patients infected with previous SARS-CoV-2 variants (7% vs 58%; $P = .012$).

In the vaccinated patient group, the omicron variant was more common (10.3% vs 58.1%, $P < .001$), comorbidities less frequent (71.5% vs 41.9%, $P = .049$), and use of Mab more frequent (5.1% v 42.5%, $P < .001$) than the nonvaccinated group. In the 14 patients receiving Mab therapy, 10 received sotrovimab, 3 received casirivimab plus imdevimab, and 1 received bamlanivimab/etesevimab. Compared with those not receiving Mab therapy, patients receiving Mab were more often infected with an omicron variant (22% vs 50%, $P = .046$) and were more often vaccinated (86% vs 32%, $P < .001$). Of vaccination and Mab therapy, only Mab therapy was associated with a significant reduction in risk of death ($P = .036$). However, immune escape associated with omicron and its subvariants reduces vaccine-inducible immunogenicity as well as neutralizing effect of Mab, rendering the latter no longer authorized for use as prophylaxis[7] or treatment.[8]

Despite reduced vaccine-induced immunogenicity in immunocompromised patients, vaccination remains the best protection against severe COVID-19, even for patients receiving CAR T-cell therapy. Notwithstanding reductions in B cells and circulating antispike and RBD antibodies, vaccinated patients receiving CAR T-cell therapy have measurable antiviral T cells with preserved but variable neutralization against variants.[9] Given that current RBD–targeted messenger RNA vaccines have waning neutralizing protection against emerging omicron subvariants of SARS-CoV-2,[10] novel viral targets and forms of vaccine itself will be needed to confer protection against new variants.

On 30 January 2023, the Biden Administration announced its intent to end the national emergency and public health emergency declarations related to the COVID-19 pandemic on 11 May 2023.[11] Specifically, the US Department of Health and Human Services plans to dissolve the Public Health Emergency for COVID-19 based upon decreases in daily COVID-19 cases, hospitalizations, and deaths. As the pandemic transitions to an endemic phase, the vulnerability of the immunocompromised patient to severe COVID-19 must not be forgotten and instigate continued development of effective pharmaceutical interventions, including vaccination, antiviral therapies, and passive immune products. Given the inevitability that SARS-CoV-2 will continue to evolve and likely remain a cause for significant morbidity and mortality in the foreseeable future, the ecosystem's responsibility and response to study, prevent, and treat COVID-19 in immunocompromised patients must not waver.

Conflict-of-interest disclosure: J.J.A. reports providing consultancy for AscellaHealth and Takeda.

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https://doi.org/10.1182/bloodadvances.2023010371