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TRANSPLANT INFECTIOUS DISEASE

EDITORIAL

SARS-CoV-2 vaccine clinical efficacy in SOT: What we know and our current gaps

Since the arrival of SARS-CoV-2 vaccines, solid organ transplant recipients' (SOTRs) protection from these vaccines has been under investigation. A number of studies have evaluated SOTR's adaptive immune response via measurement of spike protein IgG or receptor binding domain IgG.[1–4] Rates of detectable antibody after two doses of mRNA vaccine are variable, ranging from 0%–64%[1,5,6] but are subject to interpretation and variability due to a variety of confounding factors.[7] T-cell response ranges from 5–79% in various studies and may be present despite lack of measurable antibody.[6,8,9] Only a few studies have assessed clinical outcomes and demonstrate reduced rate of symptomatic COVID-19 and reduced mortality.[10–12] In one single center study, there was an almost 80% reduction in risk of symptomatic COVID-19 compared to unvaccinated SOTR.[12] However, these clinical effectiveness studies were done prior to the onset of the Delta and now Omicron variant-related surges.

Despite clinical benefit, vaccinated SOTRs do have greater risk of breakthrough COVID-19 than the general population.[13] Breakthrough infection is generally defined as COVID-19 infection occurring at least 14 days after the last vaccination dose in a series, such as after two doses of mRNA vaccines and a single dose of Janssen vaccine,[14] although this definition may change to include three-dose mRNA series and at least one additional vaccination dose following the initial Janssen vaccine. In a large multicenter study of 18 215 fully vaccinated SOTRs at 17 transplant centers, breakthrough infections occurred in 0.23%–2.52%, compared to 0.01% in immunocompetent vaccinated hosts.[13] Mortality among breakthrough cases was 9.3% (14/151).[13] Median onset of breakthrough infections ranged from 18 to 54 days from last vaccination.[15–19] Recent data from Israel demonstrate significant 88%–90% reduction in COVID-19-related mortality and reduced severity of illness with three-dose Pfizer vaccine series compared to two doses in the general population.[20–22] The extent of additional benefit in immunocompromised patient populations and outcomes of breakthroughs in this scenario are unknown at this time. Multicenter data regarding clinical course of breakthrough infections are lacking as well.

The paper by Saharia et al. evaluates characteristics of breakthrough COVID-19 infection among 43 fully vaccinated (completion of two mRNA vaccines) and nine partially vaccinated (at least one mRNA vaccination) SOTR. Thirteen cases in SOTR who received the second vaccine less than 14 days previously were reported as well. Cases were solicited from the Infectious Diseases Society of America Emerging Infection Network, resulting in 66 cases of COVID-19 infection in SOTR. Case definitions were not standard and probably resulted in over-estimation of severe disease, generally defined as oxygen saturation less than 94% on room air, based on National Institutes of Health Treatment Guidelines, but in this paper was defined as any illness resulting in hospitalization.[23] Among 66 cases, 43 (65.1%) occurred more than 14 days after the second dose of mRNA vaccination (i.e., true breakthrough infections). Among these 43, 25.8% had critical illness, and 15.2% required mechanical ventilation; with associated with 7% mortality. In other series of breakthrough infections, clinical outcomes are variable, with mortality ranging from 0%–22%.[15,24,25] Reported disease severity has been variable as well and may be related to use of monoclonal antibodies at some centers. At our institution, two of 12 breakthrough cases required supplemental oxygen, although five of 12 were admitted with one mortality; eight patients received monoclonal antibodies.[25]

The Saharia et al.'s paper is the first multicenter series detailing clinical manifestations of breakthrough COVID-19 in SOTR. However, significant bias exists both in the manner of case solicitation (in favor of hospitalized and more severe cases) and definitions of disease (again favoring more severe disease). With increasing variants of concern, in particular the Omicron variant currently, we need unbiased assessments of vaccine effectiveness and breakthrough risk in SOTR.[26] It is critical to develop a large multicenter database of breakthrough infections and to estimate incidence of breakthrough infections using clear denominators of all vaccinated SOTRs. Studies should ideally assess incidence of breakthrough cases based on type of vaccination, time since vaccination, variants of concern, as well as the organ transplanted, age of the transplant recipient, and disease severity and outcomes. Sophisticated statistical modeling is needed to account for a variety of confounding factors including the ebb and flow of the pandemic itself, survival bias, differing times of vaccination, and accurate case ascertainment. These studies will only be possible with large registry-based data collection. As we move forward with additional recommended vaccine doses, the definition of a "fully vaccinated" SOTR will need to be updated as well.[9,27] Lastly, duration of active viral replication in the setting of breakthrough infections remains unknown for immunosuppressed vaccinated patients and has implications for isolation duration and potential development of future viral variants; in particular short isolation periods may be insufficient.

As the pandemic continues to evolve, it is increasingly clear that our current vaccination strategy is not the only path for infection prevention in vulnerable patients, and additional strategies are needed. There are ongoing clinical trials that are investigating breakthrough COVID-19 rate following a fourth vaccine dose with simultaneous reduction

in immunosuppression. Recently, tixagevimab/cilgavimab (Evushield) combination monoclonal antibody has become available for use as pre-exposure prophylaxis in moderate to severely immunocompromised patients. Of the 5197 tixagevimab/cilgavimab clinical trial participants, at least 75% had high risk medical conditions, although the proportion of these who were SOTR is unclear, and thus effectiveness in this population will need to be determined.[28] Postexposure prophylaxis with casirivimab/imdevimab (REGEN-COV) monoclonal antibody combination may be used as another infection prevention strategy in high risk patients, but recent data demonstrate that it is less effective against the Omicron variant, thus limiting use.[26] Due to limited drug inventory, most centers are prioritizing very immunosuppressed individuals for these therapies.

Once a breakthrough case occurs, the goal should be to limit progression of disease with early use of monoclonal antibodies and/or antivirals. Data regarding early monoclonal antibody administration with subsequent reduction in hospitalization are robust with earlier SARS-CoV-2 variants although existing combinations do not neutralize the Omicron variant well.[26] A newer monoclonal antibody, sotrovomab, has in vitro neutralizing activity against Omicron and should be used when possible early after diagnosis. Early antiviral therapy with remdesivir, molnupravir, and paxlovid shows promise in preventing disease progression, although again data specifically in immunocompromised hosts are needed.[29–31]

Breakthrough COVID-19 in SOTR remains a major concern in all those who care for this population. Despite advances in vaccination recommendations, now including additional vaccines doses, and medical prevention with new monoclonal antibodies, SOTR should continue to follow precautionary measures as new viral variants emerge.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Rachel Sigler and Saima Aslam contributed to the study design, data collection and interpretation, and manuscript writing. These authors have reviewed the final manuscript draft for publication.

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