SARS-CoV-2 Vaccines in Kidney Transplant Recipients: Will They Be Safe and Effective and How Will We Know?

Madeleine R. Heldman and Ajit P. Limaye

Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, Washington

Coronavirus disease 2019 (COVID-19) has had a major effect on kidney and other solid organ transplant recipients. In addition to public health measures, improved access to testing, and therapeutic developments, vaccination has emerged as a key tool for controlling the ongoing pandemic. In December 2020, multiple regulatory agencies worldwide authorized the use of two mRNA vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and several other vaccine platforms are in advanced-stage clinical trials. Individuals who have received a transplanted kidney or other solid organ have been identified as high-risk populations and prioritized for vaccination in public health guidelines, but unfortunately have been excluded from major SARS-CoV-2 vaccine clinical trials. Thus, studies are urgently needed to characterize the safety, immunogenicity, and ultimately, efficacy of SARS-CoV-2 vaccines for such patients.

Below, we provide an overview of SARS-CoV-2 vaccines and highlight key concepts that should be considered in evaluating their safety in solid organ transplant recipients. Despite the theoretical concerns described below, we emphasize that available evidence from studies demonstrates safety and efficacy in the general population. Because of the known substantial risks of COVID-19-associated morbidity and mortality in recipients of kidney and other solid organs, and the long track record of safety of other vaccinations in such recipients, we anticipate the benefits of selected SARS-CoV-2 vaccines will far outweigh risks of vaccination. Accordingly, current guidance from multiple professional organizations recommend vaccination for all eligible organ transplant recipients.

Each vaccine platform has distinct safety considerations for kidney transplant recipients. Live (replication-competent) vaccines are generally contraindicated in immunocompromised individuals because of a risk of vaccine-acquired disease. The SARS-CoV-2 candidate vaccines that are furthest along in development do not contain replication-competent SARS-CoV-2 virus, and therefore do not carry risk of SARS-CoV-2 infection (Table 1).

However, viral vector–based vaccines that incorporate viruses other than SARS-CoV-2 are in advanced-phase studies, including adenovirus (AdV) vector–based vaccines that have been licensed in Europe. These vaccines consist of intact virions that are engineered to include the gene encoding the SARS-CoV-2 spike protein, a technique that leverages the viral vector’s ability to efficiently infect cells and enhances spike gene delivery. Vaccines that use viral vectors contain either replication-deficient or replication-competent viruses (Table 1). The majority of viral-vectorized vaccines in the most advanced phases of development have been rendered replication-deficient through deletion of genes essential for replication. By limiting vector replication, the potential for vaccine-associated AdV disease is greatly diminished.

There are, however, theoretical mechanisms by which replication-deficient viral vector–based vaccines could become replication competent and cause disease, especially in immunocompromised individuals. For example, in cells concurrently infected with two different AdVs, homologous recombination of genetic elements could occur and result in the emergence of new, pathogenic, replication-competent AdV types. This has been observed in patients with advanced HIV disease during natural AdV infections, and is theoretically possible with AdV vector–based vaccines in patients who are immunocompromised with a concurrent wild-type AdV infection. Although infrequent, severe AdV infections, including allograft nephritis, can occur in kidney transplant recipients during natural infection. Notably, vaccine-associated AdV disease has not been reported, albeit there is little experience in immunocompromised populations.

It should be emphasized that, despite the theoretical concerns with replication-deficient viral vector–based vaccines, immunosuppression is not considered a contraindication to their use. Replication-competent viral-vectorized vaccines carry a greater risk of vaccine-derived vector infection in...
Table 1. **Major SARS-CoV-2 platforms in development**

| Vaccine Platform | Vaccine Name (Manufacturer) | Vehicle | Phase of Development | Adjuvant | Safety and Efficacy in the General Population | Specific Considerations for Kidney Transplant Recipients |
|------------------|------------------------------|---------|----------------------|----------|--------------------------------------------|------------------------------------------------------|
| mRNA            | BNTb162b2 (Pfizer/BioNTech)  | mRNA encapsulated in lipid nanoparticles | Authorized for emergency use in the United States and other countries | Unadjuvanted, but lipid nanoparticles possess natural adjuvant activity | 95% efficacy in phase 3 trials. | Does not contain live virus. No evidence of vaccine-induced off-target immune responses in large phase 3 clinical trials. |
| mRNA            | mRNA-1273 (Moderna)          | mRNA   | Authorized for emergency use in the United States and other countries | Unadjuvanted | 95% efficacy in phase 3 trials. | Does not contain live virus. No evidence of vaccine-induced off-target immune responses in large phase 3 clinical trials. |
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GSK, GlaxoSmithKline; KTR, kidney transplant recipients.

*Does not include all candidate vaccines or platforms under investigation; limited to platforms in advanced stages of clinical development or authorized for use as of December 31, 2020.
patients who are immunocompromised and should only be administered under carefully controlled circumstances (specifically, clinical trials). Other vaccine candidates that are in advanced stages of development, including mRNA, protein subunit, or whole-virus–inactivated SARS-CoV-2 vaccines, do not contain intact virus and thus do not carry a risk of vaccine-associated infection.3

Induction of generalized systemic inflammation by either the vaccine antigen or an associated adjuvant, or by more specific cellular and humoral cross-reactivity between vaccine epitopes and allograft antigens, theoretically could promote undesired allograft-directed immune responses. AdV vectors elicit potent innate immune responses through complement activation and induce a diverse cytokine repertoire.10 Although this phenomenon is most prominent at the site of AdV-vector inoculation, systemic inflammation could promote vaccine-associated allograft rejection. Concern for autoimmunity related to the SARS-CoV-2 vaccine on the basis of a modified chimpanzee AdV vector (ChAdOx1) arose after two vaccine recipients developed transverse myelitis, although the possibility of an unrecognized preexisting demyelinating condition has raised questions about the significance of one of these events.8

In vitro reactivity between spike protein antibodies and human collagen has been demonstrated, but molecular mimicry has not been identified as a primary mechanism of kidney injury in COVID-19.14 Available data suggest acute allograft rejection is uncommon during COVID-19, despite frequent reduction in immunosuppression as a therapeutic strategy. In the absence of an observed association between natural SARS-CoV-2 infection and acute allograft rejection in kidney transplant recipients, it is unlikely that vaccine antigens would precipitate clinically significant immune responses to renal allografts.

In general, adjuvants used to enhance vaccine immunogenicity also elicit nonspecific inflammatory responses, and thus have the potential to induce acute allograft rejection. Concern about adjuvant safety in organ transplant recipients arose from observations of an unusually high incidence of anti-HLA antibodies in kidney transplant recipients who received the 2009 influenza A(H1N1) pdm09 vaccine, which contained the squalene-based AS03 adjuvant system.6,7 However, only a fraction of these anti-HLA antibodies were donor specific, and a subsequent investigation of >10,000 solid organ transplant recipients found no definitive association between the AS03 adjuvant system and acute allograft rejection.6 The AS01B adjuvant used in the recombinant varicella zoster virus vaccine contains a combination of monophosphoryl lipids and QS21, a saponin.13 This adjuvant induces a potent innate immune response and associated concerns for precipitating acute allograft rejection in kidney transplant recipients. Several recombinant spike protein SARS-CoV-2 vaccines contain adjuvants, such as AS03 and the novel Matrix M1 adjuvant, which contains the same QS21 saponin found in the recombinant varicella zoster vaccine.3 Viral-vectored and mRNA vaccines do not generally contain adjuvants, although lipid nanoparticle delivery devices used in the mRNA vaccines have natural adjuvant activity.13

Postmarketing surveillance will be essential to assess any potential association between SARS-CoV-2 vaccine components and acute allograft rejection. In the interim, theoretical concerns associated with any vaccine must be weighed against the benefits of preventing or mitigating the severity of a life-threatening infection in a vulnerable population. We emphasize that a broad range of vaccines have a substantial track record of safety in kidney and other solid organ transplant recipients. Furthermore, no definitive association between any vaccine or adjuvant and allograft rejection has been identified to date.2,6

Immunosuppression in kidney transplant recipients is anticipated to reduce the immunogenicity of SARS-CoV-2 vaccines, and immunogenicity may vary by vaccine platform. Available data across a broad range of vaccines in solid organ transplant recipients suggest they have relative humoral response rates that are approximately 50%–70% of those seen in nontransplant populations.5,7 Patients with ESRD may have more a robust response to vaccines before rather than after kidney transplant,6 and when possible, SARS-CoV-2 vaccines should be given before transplantation. In the post-transplant setting, age >65 years, more recent transplantation, use of mycophenolate and mammalian target of rapamycin inhibitors, and lower graft function are associated with decreased serologic responses to influenza vaccines.5,7 Despite the effects of lymphocyte-depleting immunosuppression in the early period after transplant or treatment for rejection, the benefits of even modest SARS-CoV-2 protection might outweigh the risk of delaying immunization during a pandemic.2 In general, vaccines are not recommended immediately post-transplant due to a presumed decrease in immunogenicity after recent high-level immunosuppression. Expert opinion advises that delaying SARS-CoV-2 vaccination of vaccine-naive transplant recipients until 3 months after transplant or receipt of T cell or B cell ablative therapies may be appropriate; for patients who received a first dose before transplant, administration of the second dose should be delayed until at least 4 weeks post-transplant.2 Higher doses, booster doses, adjuvants, and intradermal delivery have all been used with variable success to improve immunogenicity of commonly administered vaccines in solid organ transplant recipients.5,7 If immunogenicity of standard regimens in kidney transplant recipients is suboptimal, these alternative approaches should be considered.

The diversity of vaccine platforms and phased vaccine allocation present unique challenges for assessing the safety, immunogenicity, and efficacy of SARS-CoV-2 vaccination in kidney transplant recipients. Surveillance for adverse events related to each specific formulation through prospective multicenter registries of vaccinated solid organ transplant recipients is one potential approach to assessing safety, especially...
given that large population-specific studies of kidney transplant recipients may not be feasible. Prospective clinical trials should directly compare different SARS-CoV-2 vaccine platforms, assess the magnitude and durability of humoral and cellular responses, and utilize the same functional laboratory immunogenicity assays as the vaccine trials to facilitate direct comparisons between transplant recipients and general populations. It is hoped these investigations will identify relevant differences among the various vaccine platforms to guide future studies of alternative vaccination strategies, if warranted.

Because immunosuppression may increase SARS-CoV-2 viral load and prolong the duration of SARS-CoV-2 viral shedding and transmissibility, studies to monitor both symptomatic and asymptomatic infection in vaccinated kidney transplant recipients— with quantitation of viral loads, viral culture, or both—would complement studies of safety and immunogenicity. Large prospective studies of vaccine efficacy in kidney transplant recipients that include a placebo arm are likely not feasible and may not be ethically appropriate, depending on the final results of ongoing phase 3 studies. Case-control trials of kidney transplant recipients with COVID-19 that examine the effect of prior vaccination on disease severity, viral load, and duration of viral persistence, although less definitive, may offer a more practical approach.

SARS-CoV-2 vaccines have significant potential to reduce COVID-19–associated morbidity and mortality among recipients of solid organ transplants, including kidney transplants. Because transplant recipients’ responses to vaccines may be suboptimal, continued emphasis on nonvaccine preventive measures—use of face covers, hand hygiene, and physical distancing—will be needed, even after vaccination. Although the vaccines’ ability to disrupt viral transmission in either immunocompetent or immunocompromised individuals is not yet established, vaccination of caregivers and close contacts of kidney transplant recipients, recommended for influenza vaccination, would be an important strategy to reduce the risk of infection. Assessment of vaccine efficacy against emerging SARS-CoV-2 variants is necessary to establish optimal vaccine strategies for both immunocompetent and immunocompromised populations. Future evaluations of SARS-CoV-2 vaccine platforms in kidney transplant recipients are imperative to confirm safety and immunogenicity, but the expectation is that SARS-CoV-2 vaccines will add to the armamentarium of vaccines that have safely protected transplant recipients from serious infectious diseases for decades.

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