COVID-19 vaccines and kidney disease

Martin Windpessl[1,2,18], *Annette Bruchfeld*[3,4,18], *Hans-Joachim Anders*[5,18], *Holly Kramer*[6,7], *Meryl Waldman*[8], *Laurent Renia*[9,10], *Lisa F. P. Ng*[9,10,11,12], *Zhou Xing*[13,14,15] *and Andreas Kronbichler*[16,17]✉

Patients with kidney diseases should be prioritized for COVID-19 vaccination and the available data suggest that replication-defective viral-vectored vaccines and mRNA vaccines are safe to use. As vaccine responses are likely to be lower in patients with kidney diseases than in the general population, highly potent vaccines should be preferred.

> “Kidney disease substantially increases the risk of severe COVID-19”

Kidney disease substantially increases the risk of severe COVID-19. As medications to reduce COVID-19 hospitalizations and mortality largely remain elusive and are unlikely to be developed in the near future, effective and safe vaccines and continuous infection mitigation strategies are currently the only realistic options to curb the ongoing pandemic and drive down SARS-CoV-2 infections. As we move into 2021, several vaccines have either received or are about to receive emergency use authorization, with many more in development (TABLE 1; Supplementary Table 1).

Given the vulnerability of people with chronic kidney disease (CKD) to COVID-19, major nephrology societies such as the UK Renal Association and the US National Kidney Foundation have issued statements calling for prioritization of these patients for vaccination. Whether COVID-19 vaccines confer the same high level of protection in patients with kidney disease as has been reported for participants in recent trials, who were generally healthy, is not yet known. A recently initiated phase III trial evaluating the vaccine candidate NVX-CoV2373 (Novavax) is prioritizing the enrolment of patients with underlying medical conditions, including CKD[1]. Similar trials for other vaccine candidates are needed to accrue information to guide selection of the most appropriate vaccine delivery platforms for these patients.

Choice of COVID-19 vaccine

As patients with kidney disease commonly have compromised immune systems, live replicating microbial-vectored vaccines should be avoided. However, replication-defective viral-vectored vaccines such as ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and the mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) are safe to use. The potency of approved COVID-19 vaccines in patients who are immune compromised is currently unknown, but data for established vaccines, such as those for influenza, suggest that vaccine potency in such individuals can vary substantially in terms of the titres of neutralizing antibodies that are induced and the duration of specific immunity. In phase 3 trials, BNT162b2, mRNA-1273 and ChAdOx1 nCoV-19 prevented COVID-19 in 95%, 94.1% and 70.4% of participants[2–4], respectively, suggesting that the mRNA vaccines might induce protective immunity more reliably than ChAdOx1 nCoV-19. Use of these vaccines might therefore be preferable for patients who are immune compromised.

Compared with inactivated vaccines, both mRNA vaccines and viral-vectored vaccines have the advantage of inducing balanced humoral and T cell immunity[5]. The immune correlates of vaccine-induced protection against COVID-19 are poorly defined but likely include both humoral and cellular mechanisms[6]. Cytotoxic CD8+ T cells are involved in viral clearance in many respiratory viral diseases[7] and protracted T cell immunity may reduce the risk of SARS-CoV-2 infection. A potent CD8+ T cell response is usually induced by viral-vectored vaccines[4] and is expected for mRNA vaccines (TABLE 1). T cell immunity assays to test for adequate vaccine responses would therefore be desirable for routine practice.

Patient characteristics such as age, gender, type of kidney disease and treatment regimen might also influence the protective capacity of vaccines. In patients with no or weak induction of seroconversion and/or T cell immunity after vaccination, theoretical options include an additional booster dose, administration of a different vaccine platform (e.g. prime-boost strategies) or respiratory mucosal vaccination. The latter approach, in contrast to intramuscular administration, induces strong immunological memory mediated by tissue-resident innate and adaptive immune cells that are adept at offering protection in early stages of SARS-CoV-2 infection. Mucosal vaccination might therefore be an effective vaccine strategy for patients who are immune compromised.

✉*e-mail: andreas.kronbichler@i-med.ac.at*

https://doi.org/10.1038/s41581-021-00406-6

> mRNA vaccines might induce protective immunity more reliably than ChAdOx1 nCoV-19

Patients receiving chronic dialysis

Dialysis units are particularly high-risk locations for infection with SARS-CoV-2. Seroconversion after confirmed infection approaches 100% in the dialysis population, but the durability of this immune response and the extent to which it translates into protective immunity remains unclear. Some studies indicate that SARS-CoV-2 IgG titres decline substantially by 3 months after diagnosis[8]. Thus, it is critical that as dialysis units begin to vaccinate their patients, post-vaccination antibody levels are monitored to determine optimal immunization schedules. Moreover, ongoing research should elucidate whether particular vaccines offer specific advantages for people on chronic dialysis.

Patients receiving immunosuppression

Patients with autoimmune kidney diseases on chronic immunosuppression were excluded from all major trials of COVID-19 vaccine candidates (Supplementary Table 1). Thus, no data are currently available regarding short-term and longer-term vaccine safety, immunogenicity and protective efficacy in these patients. Specific issues that impact vaccination decisions in certain subgroups of patients also need to be addressed. Timing of vaccination and vaccine readiness is relevant in this regard, particularly in patients receiving treatment with anti-CD20 therapy (e.g. rituximab), which is known to abrogate immune responses to vaccinations[9]. Decisions on whether to delay or interrupt non-urgent treatment with rituximab to find an appropriate vaccination window or to use alternative immunosuppressive therapies need to be considered in addition to weighing the potential risk of autoimmune disease relapse versus risk of infection with SARS-CoV-2 if vaccination is deferred. In patients with active autoimmune disease, treating this disease should take priority and vaccination should be delayed.

The immunogenicity of SARS-CoV-2 vaccines in patients receiving other common immunosuppressive regimens requires further investigation. Among transplant recipients, the seroresponse to a trivalent influenza vaccination was significantly lower in those receiving mycophenolate mofetil[10]. This finding might suggest that such patients may need modification of vaccination regimens. Some COVID-19 vaccines require adjuvants to increase their immunogenicity; comparison of the seroconversion and safety of these vaccines with those that do not require adjuvants, such as replication-defective viral-vectored vaccines, will be informative.

Concerns have been raised that vaccines can trigger autoimmunity but causation is difficult to prove and statistically significant associations have not been reported. Furthermore, there is currently no evidence that vaccines provoke potentially fatal disease relapses or acute rejection episodes (Supplementary Table 2). Vaccine-triggered antiviral immunity (IFNα) might theoretically provoke disease flares in patients with systemic lupus erythematosus. However, the risk–benefit assessment for potentially fatal COVID-19 versus a treatable disease flare or rejection episode may still favour vaccination in most cases. We need to be vigilant regarding these risks and robust pharmaco-epidemiologic post-marketing studies are needed for each of the vaccine delivery systems.

Conclusions

Based on the available data for inactivated vaccines such as those against influenza, one can reasonably assume that the safety of current SARS-CoV-2 candidate vaccines does not differ between individuals in the various registration studies and the CKD population. The suitability of new COVID-19 vaccine platforms such as mRNA and viral-vectored vaccines for this heterogeneous population is unknown, but the response rates are expected to be lower than in the key studies published so far, hence, highly potent vaccines should be preferred. Another important consideration is vaccine hesitancy, which might differ by socioeconomic and demographic factors. Long-term relationships between patients and health-care providers should enable frank and balanced discussions of the benefits, risks and uncertainties regarding COVID-19 vaccination. Such discussion together with referral to reliable online resources, such as those provided by NephCure, will hopefully result in increased vaccine uptake.

Dedicated prospective COVID-19 vaccine studies involving patients with advanced stages of kidney disease and kidney transplant recipients are urgently needed and are likely to emerge in the near future. Meanwhile, patients should be counselled about the importance of continuing to practise safety measures such as social distancing and using personal protective equipment.

Author addresses

[1]Department of Internal Medicine IV, Section of Nephrology, Klinikum Wels-Grieskirchen, Wels, Austria.
[2]Medical Faculty, Johannes Kepler University, Linz, Austria.
[3]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden.
[4]Department of Renal Medicine, Karolinska University Hospital and CLINTEC Karolinska Institutet, Stockholm, Sweden.
[5]Division of Nephrology, Medizinische Klinik und Poliklinik IV, LMU Klinikum, Munich, Germany.
[6]Department of Public Health Sciences and Medicine, Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA.
[7]Hines VA Medical Center, Hines, IL, USA.
[8]Kidney Disease Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health, Bethesda, MD, USA.
[9]A*STAR Infectious Diseases Labs, Agency for Science, Technology and Research, Singapore, Singapore.
[10]Singapore Immunology Network, Agency for Science, Technology and Research, Singapore, Singapore.
[11]Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore.
[12]Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK.
[13]McMaster Immunology Research Centre, McMaster University, Hamilton, ON, Canada.
[14]Department of Medicine, McMaster University, Hamilton, ON, Canada.
[15]Michael G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton, ON, Canada.
[16]Department of Medicine, University of Cambridge, Cambridge, UK.
[17]Department of Internal Medicine IV, Nephrology and Hypertension, Medical University Innsbruck, Innsbruck, Austria.
[18]These authors contributed equally: Martin Windpessl, Annette Bruchfeld, Hans-Joachim Anders

Table 1 | **COVID-19 vaccine candidates currently approved or in phase III trials***

Vaccine (manufacturer)	Type of immune response	Efficacy	Storage	No. of doses	Status
Killed whole virus					
CoronaVac (Sinovac)	IgM/IgG	NA	2–8 °C	2	Approved in countries including China, Turkey and Brazil
COVAXIN (Bharat Biotech)		NA			Approved in India
BBIBP-CorV (Sinopharm)		NA			Approved in China, Bahrain and UAE
Purified virus components					
NVX-CoV2373 (Novavax)	IgM/IgG	NA	2–8 °C	2	Phase III trials
ZF2001 (Chinese Academy of Sciences)		NA			Phase III trials
Replication-defective viral vector carrying pathogen gene(s)					
ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	IgM/IgG	Two full doses, 62%; one half and one full dose, 90%; overall, 70.4%[4]	2–8 °C	1–2	Approved in UK and by the EMA
Ad5-nCOV (CanSino)	IgA, cell-mediated immunity	NA			Phase III trials
Sputnik V (Gamaleya Research)		NA			Approved in countries including Russia, Belarus and Argentina
Ad26.COV2.S (Janssen)		NA			Phase III trials
mRNA vaccines					
BNT162b2 (Pfizer-BioNTech)	IgM/IgG, IgA, cell-mediated immunity	95% in all age groups[2]	−70 °C permanently; 2–8 °C for 5 days	2	Approved by the FDA and EMA and in countries including Canada and UK
mRNA-1273 (Moderna)		94.1%[3]	−20 °C for 6 months; 2–8 °C for 30 days	2	Approved by the FDA and EMA, in Canada and UK

*All of the listed candidates are suitable for people with immunodeficiency but no efficacy data are currently available for this population. EMA, European Medicines Agency; FDA, US Food and Drug Administration; NA, not available; UAE, United Arab Emirates.

1. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT04611802 (2021).
2. Polack, F. P. et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N. Engl. J. Med.* **383**, 2603–2615 (2020).
3. Baden, L. R. et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2035389 (2020).
4. Voysey, M. et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* **397**, 99–111 (2021).
5. Jeyanathan, M. et al. Immunological considerations for COVID-19 vaccine strategies. *Nat. Rev. Immunol.* **20**, 615–632 (2020).
6. Poland, G. A., Ovsyannikova, I. G. & Kennedy, R. B. SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates. *Lancet* **396**, 1595–1606 (2020).
7. Schmidt, M. E. & Varga, S. M. The CD8 T cell response to respiratory virus infections. *Front. Immunol.* **9**, 678 (2018).
8. Labriola, L. et al. A longitudinal, 3-month serologic assessment of SARS-CoV-2 infections in a Belgian hemodialysis facility. *Clin. J. Am. Soc. Nephrol.* https://doi.org/10.2215/CJN.12490720 (2020).
9. Baker, D. et al. COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. *Clin. Exp. Immunol.* **202**, 149–161 (2020).
10. Scharpé, J. et al. Influenza vaccination is efficacious and safe in renal transplant recipients. *Am. J. Transplant.* **8**, 332–337 (2008).

Acknowledgements
H.J.A. is supported by the Deutsche Forschungsgemeinschaft AN372/24-1. The authors' research was supported in part by the Intramural Research Program of the NIH, NIDDK.

Competing interests
A.B. received grants and personal fees from AstraZeneca and personal fees from ChemoCentryx, Merck/MSD, Vifor and Abbvie, all unrelated to the context of this article. H.J.A. received honoraria from AstraZeneca, GSK, Bayer, Boehringer Ingelheim, Novartis, Previpharma, Inositec and Noxxon, all unrelated to the context of this article. A.K. received honoraria from Miltenyi Biotech, Vifor, TerumoBCT and Novartis, all unrelated to the context of this article.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1038/s41581-021-00406-6.

RELATED LINKS
National Kidney Foundation Position Statement on Kidney Patient Prioritization for COVID-19 Vaccines and Therapeutics: https://www.kidney.org/sites/default/files/nkf_statement_vaccine_distribution_final_20201216.pdf
NephCure Kidney International COVID-19 vaccine FAQs for kidney patients and caregivers: https://nephcure.org/wp-content/uploads/2021/01/nc.COVID-QA_210111.pdf
Renal Association COVID-19 vaccination for adult patients with kidney disease: a position statement from the UK renal community: https://renal.org/health-professionals/covid-19/ra-resources/covid-19-vaccination-adult-patients-kidney-disease