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REVIEW

Recommendations for the use of COVID-19 vaccines in patients with immune-mediated kidney diseases

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ABSTRACT

Coronavirus disease 2019 (COVID-19) vaccine platforms are becoming available and are the most promising strategy to curb the spread of severe acute respiratory syndrome coronavirus 2 infections. However, numerous uncertainties exist regarding the pros and cons of vaccination, especially in patients with (immune-mediated) kidney diseases on immunosuppressive drugs. Here, members of the Immunonephrology Working Group of the European Renal Association–European Dialysis and Transplant Association discuss 13 frequently asked questions regarding the safety and efficacy of the most promising vaccine candidates. Post-marketing surveillance should be performed to estimate the rate of vaccine response (humoral and cellular) of different vaccine platforms and disease activity following the administration of COVID-19 vaccines. Some of the candidates induce signalling pathways, which also promote autoimmune kidney diseases, e.g. type I interferons in systemic lupus erythematosus. Efficacy estimates would thus far favour the use of selected COVID-19 vaccines, such as BNT162b2, mRNA-1273 or Gam-COVID-Vac. Humoral immune response after vaccination should be monitored using appropriate assays. Even in the absence of neutralizing antibodies, patients might be protected by a sufficient cellular immune response capable of reducing the severity of COVID-19. A reduced vaccine response after the use of CD20-depleting agents is anticipated and it is particularly important to discuss strategies to improve vaccine response with these patients. Distancing and shielding measures remain important, as not all vaccines fully protect from coronavirus infection. In-depth information about the most pressing vaccine questions is essential to reduce vaccine hesitancy of patients.

Keywords: COVID-19, glomerulonephritis, immunity, immune response, vaccine

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) remains a global threat. Risk factors predicting a severe disease course have been defined for kidney transplant recipients, patients with chronic kidney disease (CKD) and dialysis patients. There is a paucity of information about the risk for patients with immune-mediated kidney diseases [1]. A first analysis of the International Registry of COVID Infection in Glomerulonephritis (IRoc-GN) reported the outcomes of 40 patients with glomerulonephritis and COVID-19. Compared with control cases, mortality was higher (15%) and acute kidney injury more frequently present (39%) in cases with glomerulonephritis [2]. Medications to reduce COVID-19 mortality remain largely elusive. Dexamethasone at a dose of 6 mg prevented COVID-19-related death in the RECOVERY trial [3]. In contrast, investigations involving immune-mediated diseases have provided evidence that a corticosteroid dose $\geq$10 mg prior to infection is an independent risk factor for mortality [4]. These findings suggest that the underlying mechanisms leading to severe COVID-19 may differ in these patients and, in combination with high mortality rates, provides a strong argument that patients with immune-mediated kidney diseases should be prioritized to receive a COVID-19 vaccine [5].

Different vaccine candidates have received emergency use authorization by agencies around the globe. The reported efficacies are variable, ranging from 50.4% for an inactivated vaccine candidate to 91.6, 94.1 and 95% for Gam-COVID-Vac, mRNA-1273 and BN162b2, respectively (Tables 1 and 2) [6–8]. Exclusion criteria in these vaccine studies included autoimmune conditions requiring immunomodulatory therapy or the chronic use of immunosuppression. Thus no information on efficacy in patients with immune-mediated kidney diseases is available to date. Here, board members of the Immunonephrology Working Group of the European Renal Association–European Dialysis and Transplant Association discuss 13 frequently asked questions relevant to this context (Table 3).

Is vaccination recommended to patients with kidney disease?

We do recommend vaccination for everyone (except for those with known allergic reactions to any of the vaccine components).

Patients with immune-mediated disease have typically been excluded from all major trials and data on vaccine efficacy, particular safety (relapse/recurrence risk) and specific adverse events will only become available during the ongoing pharmacovigilance studies. The Centers for Disease Control interim clinical guidance states: 'Immunocompromised individuals may still receive COVID-19 vaccination if they have no contraindications to vaccination. However, they should be counseled about the unknown vaccine safety profile and effectiveness in immunocompromised populations, as well as the potential for reduced immune responses' [9]. The potential of COVID-19 vaccines to induce immunity protecting from severe COVID-19 should outweigh potential risks in most cases.

Table 1. COVID-19 Vaccines and their efficacy in phase 3 trials, including the storage temperature and the number of doses used

Vaccine (manufacturer)	Participants (vaccine/control group)	Efficacy (%)	Infections (vaccine versus control arm)	Duration (months)	Countries involved in trial	Number of doses	Storage
Inactivated virus							
CoronaVac (Sinovac)	–	50.7[a,b]	–	–	Brazil	2	2–8°C
BBIBP-CorV (Sinopharm)	–	79.34[a]	–	–	UAE	2	2–8°C
Purified protein							
NVX-CoV2373 (Novavax)	–	89.3[a]	6 versus 56		UK	2	2–8°C
Replication-defective viral vector vaccine							
ChaAdOx1 nCoV-19 (Oxford-Astra Zeneca)	5807 versus 5829	70.4 (LD/SD: 90.0; SD/SD: 62.1)	30 versus 101[c]	3.4	UK, Brazil	1–2	2–8%
Gam-COVID-Vac/Sputnik V (Gamaleya)	16 501 versus 5476	91.6	16 versus 62[d]	1.6	Russia	2	2–8%
Ad26.COV2.S (Janssen/ Johnson & Johnson)		72, 66, 57[a] (USA, Latin America, South Africa)	116 versus 348		USA, Central/ South America, South Africa	1	2–8%
mRNA vaccines							
BNT162b2 (Pfizer/BioNTech)	18 860 versus 18 846	95	8 versus 162[e]	2	USA, Brazil, Argentina, South Africa	2	–20%/–70%
mRNA-1273 (Moderna)	15 181 versus 15 170	94.1	11 versus 185[c]	2.1	USA	2	–20%

[a]Based on press releases.
[b]83.7% if very mild cases were excluded.
[c]Fourteen days after second dose.
[d]Twenty-one days after receiving the first dose (day of the second dose).
[e]Seven days after second dose.

Table 2. Relevant endpoints of COVID-19 vaccine trials

Vaccine (manufacturer)	Positive cases (%)	Protection from symptomatic/severe COVID-19	Protection from hospitalization
Inactivated virus			
CoronaVac (Sinovac)	50.7	83.7	100
BBIBP-CorV (Sinopharm)	79	–	–
Purified protein			
NVX-CoV2373 (Novavax)	89.3	–	100
Replication-defective viral vector vaccine			
ChaAdOx1 nCoV-19 (Oxford-Astra Zeneca)	70.4	64.1	100
Gam-COVID-Vac/Sputnik V (Gamaleya)	91.6	–	100
Ad26.COV2.S (Janssen/Johnson & Johnson)	66	85	100
mRNA vaccines			
BNT162b2 (Pfizer/BioNTech)	95	90	100
mRNA-1273 (Moderna)	94.1	100	100

Table 3. Thirteen frequently asked questions related to COVID-19 vaccines

Question number	Specific question?	Answers
1	Is vaccination recommended to patients with kidney disease?	We do recommend vaccination for everyone (except for those with known allergic reactions to any of the vaccine components)
2	Is one vaccine better than others?	Full trial publications of BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna) and Gam-COVID-Vac (Sputnik V, Gamaleya) showed a high efficacy on preventing symptomatic and severe COVID-19, while the duration of protection and the potential of the available vaccines to prevent asymptomatic SARS-Cov-2 infection has not yet been fully explored. It is also not known, if any single vaccine offers advantage for specific patient populations
3	I had COVID-19 recently. Should I be vaccinated?	Antibodies are decreasing over time, so theoretically there is a benefit, but data on the number of booster injections and an optimal time point for vaccination after infection are scarce
4	Can I be vaccinated while taking immunosuppression?	States of immunodeficiency, hereditary or acquired, can reduce vaccine responses. A recent dose of rituximab or higher doses of other immunosuppressants may specifically impair vaccine responses. Likely, it is wise for many patients to wait with vaccination until steroid doses are tapered to <20 mg prednisone equivalent per day and 6 months have eclipsed since last rituximab dose
5	Are there specific side effects of vaccines?	The approved vaccines are generally well tolerated. Some report 'flu-like symptoms' one or several days following the second dose. Local reactions are frequently reported as with other vaccines
6	Is there a possibility that the vaccine induces an activation of my disease?	Patients with autoimmune diseases were excluded in the early studies. There are insufficient data, but the vaccines seem to be safe and experience from previous vaccine studies does not indicate an increased risk for relapse/recurrence
7	Should I get vaccinated even if there are existing allergies?	In general, 'yes', the whole process is supervised. We advise against the use of currently available vaccines in patients with known PEG or polysorbate allergies
8	Am I having a lifelong protection against COVID-19 after vaccination?	For now, there is no information about the longevity of immunity following vaccination. Booster injections may become necessary to maintain anti-SARS-CoV-2 immunity. Viral mutations are frequent, and newer/modified vaccines may be used to protect against these variants
9	I failed to mount an adequate immune response to my first COVID-19 vaccine. Is it possible to receive another vaccine platform?	Yes, with the approval of more vaccines, there could be other options (such as respiratory booster vaccines under investigation), which might induce immunity
10	Can I expect interference of the COVID-19 vaccine with my medication?	No, no such interactions are expected
11	After receiving my first vaccine shot, do I still need to shield and can I infect others?	Vaccinated patients should continue to follow current guidance to protect themselves from exposure to COVID-19. While providing the vaccine to patients and their caregivers will reduce risk for infection or clinical COVID-19 disease, they must continue practices of wearing masks, social distancing and maintaining good hand hygiene even after vaccination
12	I received another vaccine a week ago. Should I get vaccinated against COVID-19 now?	There should be a delay of at least 2 weeks before you should receive your COVID-19 vaccine. We advise that non-urgent vaccinations may be postponed, with the exception of meningococcal/pneumococcal vaccination when eculizumab/ravulizumab is used
13	Does the formation of antibodies reflect antiviral immunity?	This is unclear at the moment. The formation of antibodies is perceived as a surrogate biomarker for antiviral protection but whether the detected antibodies are of a neutralizing type or whether protective immunity is present even at low or absent antibody levels will remain uncertain. Therefore antibody testing has not generally been recommended

Is one vaccine better than others?

Full trial publications of BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna) and Gam-COVID-Vac (Sputnik V, Gamaleya) show a high efficacy in preventing symptomatic and severe COVID-19, while the duration of protection and the potential of the available vaccines to prevent asymptomatic severe acute respiratory syndrome coronaviorus 2 (SARS-CoV-2) infection has not yet been fully explored. It is also not known if any single vaccine offers an advantage for specific patient populations.

Published trials with efficacy estimates included a 'healthy' population, with comorbidities present in 20.9% of participants in the BNT162b2 trial (0.7% with 'renal disease') [7], in a small proportion of participants in the mRNA-1273 trial (9.5% with diabetes, 5.0% with significant cardiac disease and chronic lung disease in 4.7%) [6] and a similar frequency in the ChAdOx1 nCoV-19 trial (respiratory disease 9.9%, cardiovascular disease 12.6% and diabetes in 2.8%) [10, 11] and Gam-COVID-Vac trial (concomitant diseases in 24.7%) [8]. Vaccine efficacy in patients with immune-mediated diseases needs to be defined. Estimates of vaccine protection of different platforms are summarized in Table 1. A specific discussion about differences in trial design and the differences between cellular and humoral immunity is necessary to reduce the existing uncertainty whether a specific vaccine is more effective than others. Importantly, all vaccine candidates showed high efficacy to prevent severe COVID-19, including hospitalizations (Table 2). The total number of severe/hospitalized cases was low, given the selection of the study population.

Efficacy endpoints in the BNT162b2 trial included development of COVID-19 7 days after the second dose (28 days after the administration of the first dose) as the primary endpoint and severe COVID-19 after the first dose as a major secondary endpoint. COVID-19 occurred in eight patients after the second dose in the BNT162b2 arm compared with 162 trial participants in the placebo arm. These results were consistent among older participants (≥65 years or 75 years) and those considered at risk, defined by having a comorbidity. Severe COVID-19 occurred in one participant randomized to receive the vaccine as compared with nine in the control arm [7].

The primary endpoint in the mRNA-1273 vaccine trial was defined as SARS-CoV-2 infection 2 weeks after the second dose (42 days after the first dose). The endpoint was reached by 196 cases, 11 in the mRNA-1273 arm and 185 in the placebo group. These findings were consistent across defined subgroups (age, sex, race and ethnic group). Severe COVID-19 occurred in 30 participants, of whom all were assigned to receive placebo. Seven COVID-19 cases were reported after the first mRNA-1273 dose compared with 46 cases in the placebo arm [6].

The primary objective of the ChAdOx1 nCoV-19 trial was to evaluate the efficacy of the vaccine against nucleic acid amplification test–confirmed COVID-19. Combined efficacy analysis 14 days after the second dose included patients receiving a low-dose/standard-dose (LD/SD) and SD/SD vaccine strategy. Thirty cases (0.5%) among 5807 participants in the ChAdOx1 nCoV-19 group and 101 cases (1.7%) in the control group contracted symptomatic COVID-19, resulting in a vaccine efficacy of 70.4% [10]. Further investigations indicated that a higher vaccine efficacy can be obtained with a longer prime-boost interval, with a vaccine efficacy of 82.4% when the second dose was delayed by 12 weeks or more compared with 54.9% in those with a delay of <6 weeks. A similar frequency of asymptomatic infections was reported in both arms, indicating that there is suboptimal protection against transmission of SARS-CoV-2 [11]. However, no peer-reviewed information is currently present in participants >55 years of age. Concerns have been raised that the ChAdOx1 nCoV-19 trials included too few elderly trial participants to inform about efficacy. Relevant data will be obtained from real-world experience and ongoing investigations in the UK and Israel that started their vaccination programs earlier than others. Several authorities have advised against its use in people >65 years of age [12]. This hesitancy to use ChAdOx1 nCoV-19 in the most vulnerable age groups might also be extended to people with underlying medical conditions, such as patients with immune-mediated kidney diseases, where a lower seroconversion rate to vaccination should be expected. Nonetheless, preliminary real-life data from Scotland indicate that ChAdOx1 nCoV-19 prevents COVID-19-related hospitalizations even in elderly populations.

Twenty-one days after the first dose of Gam-COVID-Vac (Sputnik V, rAd26 at Day 0 and rAd5 at Day 21), a 91.6% vaccine efficacy was shown. The observed vaccine efficacy was consistent among different age groups, with 91.8% efficacy reported in participants >60 years of age. Importantly, no moderate or severe cases of COVID-19 were reported in the vaccine arm, while 20 such events were recorded in the placebo group [8].

Based on the efficacy estimates provided by the published Phase 3 trials, patients with immune-mediated kidney diseases should receive the most effective vaccines to improve their chances of adequate protection from COVID-19. Based on this criterion, we would recommend the use of BNT162b2, mRNA-1273 or potentially Gam-COVID-Vac.

I had COVID-19 recently, should I be vaccinated?

Antibodies decrease over time, so theoretically there is a benefit, but data on the number of booster injections and an optimal time point for vaccination after infection are scarce.

As vaccine rollout is slow in most countries and vulnerable patient groups are not being vaccinated at a satisfactory speed, it may be argued that it is unethical to prioritize patients with recent infection and the presence of antibodies. An argument to pursue vaccination is the possibility of reinfection. Single reinfection cases have been reported. These patients did not exhibit immunodeficiency and antibodies to SARS-CoV-2 after the first infection were either absent or not tested. Two of the four cases had a worse disease outcome at reinfection, further underlining that the first infection does not provide lifelong immunity [13]. However, with new mutations evolving, the risk of reinfection is real [14]. Persistence of SARS-CoV-2 infections has been reported in patients receiving immunosuppressive drugs, and in particular with rituximab therapy [15, 16].

It has to be determined whether a single dose as a 'booster' is sufficient to mount an adequate response and protect against

reinfection. Recent data suggest that administration of a single vaccine dose of BNT162b2 or mRNA-1273 in individuals with pre-existing immunity leads to an antibody response, which is equal to or even exceeds titres found in naïve individuals following their second dose [17].

Can I be vaccinated while taking immunosuppression?

States of immunodeficiency, hereditary or acquired, can reduce vaccine responses. A recent dose of rituximab or higher doses of other immunosuppressants may specifically impair vaccine responses. Likely it is wise for many patients to wait on vaccination until steroid doses are tapered to <20 mg prednisone equivalent per day and 6 months have elapsed since the last rituximab dose.

There is a paucity of data regarding COVID-19 vaccine responses in patients with immune-mediated kidney diseases. A study of 56 patients with systemic lupus erythematosus (SLE) with low SLE Disease Activity Index (SLEDAI) scores indicated that patients had fewer seroconversions or 4-fold titre increases for influenza A/H1N1 and A/H3N2 compared with healthy controls. Response defined as titres ≥40 to influenza A/H3N2 was especially diminished in patients receiving azathioprine [18]. Similarly, in patients with granulomatosis with polyangiitis with a good disease control, high seroconversion rates were reported, while seroconversion to A/H1N1 and geometric mean titres were lower compared with controls. Patients were either off or had a low intensity of immunosuppression during the study period [19]. Based on these findings, the response to COVID-19 vaccines may be sufficient in patients with low grades of disease activity and no or minimal immunosuppression.

A particular concern during the COVID-19 pandemic is the use of rituximab in several immune-mediated kidney diseases. Analysis of the COVID-19 Global Rheumatology Alliance indicated that 42/192 (21.9%) of rituximab users died of COVID-19, corresponding to a >4-fold higher odds ratio of death when methotrexate is used as a reference. No in-depth information about diagnoses, disease state (new diagnosis, flare or maintenance stage) or concomitantly used treatment is given [4]. It is important to acknowledge that most patients survive COVID-19 after rituximab treatment, while there is a need to determine risk factors that are indicative of a poor disease course following rituximab. Rituximab impairs humoral immunity, and vaccine response is diminished within the first months of administration. Subdividing patient groups in early vaccination (4–8 weeks) and late vaccination (6–10 months) following rituximab in rheumatoid arthritis showed that the early vaccination group did not exhibit an immunoglobulin M (IgM) or IgG response following influenza vaccine administration, while a significant IgG response (2.82-fold) was observed in patients receiving the vaccine 6–10 months after rituximab [20]. A 4-fold titre increase was achieved in only 2/12 patients receiving an influenza vaccination 7–9 months following rituximab [21]. Thus a few months should have elapsed between rituximab administration and vaccination, with an ongoing B-cell repopulation that indicates the potential of a humoral vaccine response [22]. Nonetheless, it is unclear thus far if an impaired humoral vaccine response is tantamount to no protection against COVID-19 at all or if patients may still be protected against severe disease forms by other mechanisms such as cellular immunity. Vaccination early after rituximab should be weighed against the individual risk of infection with all potential sequela.

In kidney transplant recipients, the seroresponse rate after influenza vaccination decreased in a dose-dependent manner in patients receiving mycophenolate mofetil (MMF), while seroprotection was comparable to non-MMF users [23]. This implies that response to vaccines may be appropriate, but the quality of immune response may be impaired and likely depends on the dose of MMF used. Belimumab, which is increasingly used in the management of SLE, was not associated with increased odds of death (1/27), although cautious interpretation is necessary given the number of studied patients [4]. Analysis of an SLE cohort indicated that the addition of belimumab to other treatment modalities did not further impair vaccine response to a 13-valent pneumococcal conjugate vaccine [24].

Limited information is available on the vaccine response in patients currently taking high doses of corticosteroids. In patients with chronic obstructive pulmonary disease, a systemic corticosteroid dose >10 mg/day did not impair the response to a 23-valent pneumococcal polysaccharide vaccine [25]. In children with nephrotic syndrome, the response to a hepatitis B vaccine was comparable among children without and with (0.4–0.5 mg/kg body weight on alternate days) corticosteroid prescription [26].

Taken together, vaccine antibody response can be expected to be blunted in patients who recently received rituximab, while the impact on cellular immunity needs to be determined. Antimetabolites impaired the quality of vaccine response following influenza vaccination. The effects of high doses of corticosteroids on immune response need to be determined but we do not recommend administrating a COVID-19 vaccine in situations where high doses of steroids are needed.

Are there specific side effects of vaccines?

The approved vaccines are generally well tolerated. Some report 'flu-like symptoms' for one or several days following the second dose. Local reactions are frequently reported as with other vaccines.

Based on the currently available data, COVID-19 vaccines in the general population seem to be safe. Pharmacovigilance is essential to obtain information about side effects in a real-life setting. In Norway, 23 very frail elderly patients died following BNT162b2 administration [27], but this might have been coincidental. In this regard, a discussion on approved vaccines with a focus on the safety profile is essential to provide relevant information and reduce vaccine hesitancy. In the BNT162b2 Phase 3 trial, systemic reactogenicity to the vaccine was more frequent in recipients in the younger age group (16–55 years of age). Fatigue and headache were reported in >50% of trial participants following the second dose. Fever ranging between 38.9°C and 40°C was reported in 0.2% and 0.8% after the first and second vaccine dose, respectively. Serious adverse events related to BNT162b2 were reported in 4 (0%) of the trial

participants, while the overall rate of severe and life-threatening adverse events did not differ between groups [7]. An increase in severity of systemic events was also found following the second dose in trial participants receiving mRNA-1273, and both injection site and systemic adverse events were more common among younger participants (16–<65 years of age). Serious related adverse events were reported more frequently in the mRNA-1273 group compared with the placebo arm (6 and 4, respectively). A similar frequency of serious adverse events was reported for mRNA-1273 and placebo-treated participants (147 and 153), with no reported increase in autoimmunity [6]. Serious adverse events were reported in 79 (0.7%) participants receiving ChAdOx1 nCoV-19 compared with 89 events (0.8%) in the control group receiving MenACWY (meningococcal group A, C, W and Y conjugate vaccine). Potential immune-mediated conditions (such as Crohn's disease, ankylosing spondylitis and vasculitis rash) were reported in 13 participants in the ChAdOx1 nCoV-19 arm, while 16 such events were recorded in the comparator arm [10]. 'Flu-like illness' was the most common side effect following Gam-COVID-Vac administration. Allergic reactions were balanced and no increase in immune-mediated disease was reported [8].

Is there a possibility that the vaccine induces an activation of my disease?

Patients with autoimmune diseases were excluded in the early studies. There are insufficient data, but the vaccines seem to be safe and experience from previous vaccine studies does not indicate an increased risk for relapse/recurrence.

Most immune-mediated kidney diseases have a relapsing–remitting disease course. The benefits of vaccination outweigh the risk of relapse/recurrence induced by a specific COVID-19 vaccine, as there is a high probability to be protected against severe COVID-19 disease.

No increase in SLEDAI scores was found 30 days after influenza vaccination in SLE patients, independent of prescribed treatment modality [18]. Thirty-one patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis in remission were randomized to receive either an influenza vaccine or no vaccine. During the follow-up period, there was no change in ANCA titre or inflammatory parameters, and only a single disease relapse episode was recorded in a patient with microscopic polyangiitis 6 months after influenza vaccination [28], an event unlikely to be associated with the vaccine. A post-marketing surveillance study found a 3.6-fold higher incidence of nephrotic syndrome in the year after vaccination with the 4CMenB vaccine, with the report of 4 cases among 49 000 vaccinated patients [29].

In conclusion, the risk to develop *de novo* or relapsing/recurring disease following COVID-19 vaccine administration seems to be low. Several pathways known to be implicated in vaccine response, i.e. toll-like receptor 7 or production of type I interferon [30], are also induced in autoimmunity (i.e. in SLE) [31] and thus might predispose patients to disease relapse. Follow-up within registries focusing on immune-mediated kidney diseases (IRoc-GN, COV-GN or others) is necessary to estimate the individual risk of disease flare following COVID-19 vaccination.

Should I get vaccinated even if there are existing allergies?

In general, 'yes', the whole process is supervised. We advise against the use of currently available vaccines in patients with known polyethylene glycol (PEG) or polysorbate allergies.

Authorities have issued warnings that individuals with a known history of severe allergic reactions to any of the components of the COVID-19 vaccines should not be vaccinated. In case of known other allergies, patients should be monitored for a period of 30-min post-vaccination and all others should be observed for 15 min. Post-marketing experience revealed that among the first 1.9 million doses of BNT162b2 administration, 21 events consistent with anaphylaxis were reported. Anaphylaxis is a rare event, but a risk assessment prior to vaccination should be performed and if allergic to PEG, patients may be ineligible to use an mRNA vaccine. Both, BNT162b2 and mRNA-1273 use excipient PEG to stabilize the lipid nanoparticle containing the mRNA, while the ChAdOx1 nCov-19 and Ad26.COV2.S vaccines use excipient polysorbate 80 as a stabilizer. If a patient develops anaphylaxis after the first dose, it may be justified to withhold the second dose or perform PEG skin testing to evaluate if a second dose can be administered or not [32]. As there is an expanding COVID-19 vaccine platform, patients with known severe anaphylaxis may be vaccinated once other candidates become available.

Will I have lifelong protection against COVID-19 after vaccination?

For now, there is no information about the longevity of immunity following vaccination. Booster injections may become necessary to maintain anti-SARS-CoV-2 immunity. Viral mutations are frequent and newer/modified vaccines may be used to protect against these variants.

In patients with immune-mediated diseases, a significant decline in antibody levels can be expected between 3 and 6 months (as discussed above). Antibody levels may be measured during routine testing, as we need to understand the impact of the presence of neutralizing antibodies on the risk of SARS-CoV-2 infections and severity.

A particular concern are the development of 'escape mutations', a change in the Spike protein shape and a potential loss of specific neutralizing antibody binding sites induced by COVID-19 vaccines. Widespread sequencing has revealed new variants that have been detected worldwide and are characterized by higher transmissibility. These new variants include B.1.1.7 (the 'UK' strain) and B.1.351 and N501Y.V2 (the 'South African' variant). A reported lower activity and efficacy of mRNA vaccine–induced neutralizing antibodies and a lower efficacy in trials has been reported for other vaccines (NVX-CoV2373, ChAdOx1 nCoV-19 and Ad26.COV2.S) [33, 34]. It is likely that COVID-19 vaccines need to be adjusted to accommodate key sequence changes of these new variants [34]. Thus regular vaccinations comparable with seasonal influenza vaccination combating new variants may be necessary.

I failed to mount an adequate immune response to my first COVID-19 vaccine—is it possible to receive another vaccine platform?

Yes, with the approval of more vaccines there could be other options (such as respiratory booster vaccines under investigation), which might induce immunity.

We expect that patients on immunosuppressive drugs develop reduced and sometimes insufficient vaccine responses compared with individuals without these treatments. Strategies to overcome such impaired response need to be determined and are speculative at this time. Different COVID-19 vaccines will allow administration of several candidates. The absence of seroconversion may not reliably indicate a lack of protection from severe COVID-19. Cellular immunity may still be present, but it is more difficult to assess. Cytotoxic $CD8^+$ T cells are involved in viral clearance. The relevance of $CD8^+$ T cells was underlined by the finding that subjects with milder COVID-19 disease exhibited a greater number of memory $CD8^+$ T cells in the respiratory tract compared with severe cases. A potent $CD8^+$ T-cell response is induced by replication-defective viral-vectored vaccines, while it depends on the adjuvant used and formulation of mRNA-based vaccines and shows a weak response upon vaccination with a protein subunit [35]. T-cell responses to a variable degree were shown for BNT162b2, mRNA-1273 and ChAdOx1 nCoV-19 [36–38]. In non-human primates, the intranasal administration of adenovirus-vectored vaccines resulted in reduced shedding, a reduction in viral load in the respiratory tract and prevention of SARS-CoV-2 infection [39–41]. Thus in patients with a non-detectable humoral immunity, T-cell response may be measured when possible (i.e. by ELISPOT techniques [42]), as a cellular immune response may protect against infection or eventually reduce the probability of severe disease courses.

Can I expect interference of the COVID-19 vaccine with my medication?

No such interactions are expected.

Based on our current understanding of the mode of action of approved vaccines, no interactions between the COVID-19 vaccines and immunosuppression used in patients with immune-mediated kidney diseases are expected.

After receiving my first vaccine shot, do I still need to shield and can I infect others?

Vaccinated patients should continue to follow current guidance to protect themselves from exposure to COVID-19. Providing the vaccine to patients and their caregivers will reduce the risk of infection or clinical COVID-19 disease, but they must continue practices of wearing masks, social distancing and maintaining good hand hygiene even after vaccination.

At present, there is no evidence that mounting an adequate vaccine response protects others and one might still transmit and contract COVID-19, even if the severity of infections might be reduced. It is important to continue shielding measures, and these should be adapted according to one's individual risk. Vaccination protects the vaccinated person from severe COVID-19. To what extent the currently available vaccines can help to reduce viral transmission, and hence case numbers, in the population as a basis for public containment measures is currently unclear.

I received another vaccine a week ago—should I get vaccinated against COVID-19 now?

There should be a delay of at least 2 weeks before you receive your COVID-19 vaccine. We advise that non-urgent vaccinations may be postponed, with the exception of meningococcal/pneumococcal vaccination when eculizumab/ravulizumab is used.

We advise that annual or regular vaccinations should still be performed. The year 2020 has seen a dramatic decrease in cases with influenza [43], presumably due to measures such as washing hands and wearing a mask. Influenza vaccination during the 2019–20 winter season led to significantly fewer SARS-CoV-2 infections among hospital employees and the general population [44–46], indicating that 'trained immunity' may play a role in one's individual susceptibility to contract COVID-19. Other vaccines that are not deemed urgent should be postponed and should not be administered within 2 weeks prior to/after receipt of the COVID-19 vaccine. Urgent vaccinations include vaccinations against meningococcal/pneumococcal strains when eculizumab or ravulizumab is used in the management of immune-mediated kidney diseases.

Does the formation of antibodies reflect antiviral immunity?

This is unclear at the moment. The formation of antibodies is perceived as a surrogate biomarker for antiviral protection, but whether the detected antibodies are of a neutralizing type or whether protective immunity is present even at low or absent antibody levels remains unclear. Therefore antibody testing has not generally been recommended.

Most individuals exhibit a strong antibody response following COVID-19 vaccine administration. Eight weeks after receiving a second dose of mRNA-1273 or BNT162b2, high levels of Spike protein and receptor binding domain (RBD)-neutralizing antibodies were detected [47]. Notably, Spike1-specific and virus neutralization antibody titres were higher in participants receiving BNT162b2 compared with samples from participants following a SARS-CoV-2 infection. Antibody levels peaked around Day 29 (1 week after the booster dose) and decreased over time but remained above the level of sera from convalescent patients 63 days after the booster dose [48]. A small subset of patients receiving Gam-COVID-Vac had a measurement of RBD and neutralizing antibodies by Day 42. The seroconversion rate was close to 100% and the results indicated that antibody response was comparable among different age groups [8]. The published trials did not provide antibody measurements of participants who contracted COVID-19 following vaccination. Thus there is no information if antibody formation elicits protection against COVID-19 or if specific antibody levels are indicative of protection. Further research in this field is necessary, but we can expect that patients with ongoing immunosuppression will have lower antibody levels compared with healthy subjects.

CONCLUSION

Even with the approval of several COVID-19 vaccine candidates 'the pandemic will not end overnight'. A shortage of vaccine supply limits the 'roll-out' to vulnerable patient groups (i.e. those with immune-mediated kidney diseases). The vast majority of our patients are keen to receive a COVID-19 vaccine, but for others an in-depth discussion about safety and efficacy is necessary to reduce vaccine hesitancy. This is particularly important, as many unscientific sources raise irrational safety issues, which have not been reported in one of the recent Phase 3 trials. Interpretation of data and comparison of different vaccine platforms are difficult, as different efficacy endpoints were used in landmark trials.

In this position article, we addressed 13 important questions and addressed specific issues that need to be considered in patients with immune-mediated kidney diseases. More pressing questions will be answered during the coming months of the pandemic, including the potential of transmission of SARS-CoV-2 once an individual has received a vaccine. We advise that all individuals living in the same household should be vaccinated in a timely manner, as this is likely beneficial if somebody is not mounting an adequate vaccine response.

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CONFLICT OF INTEREST STATEMENT

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Benefits and risks of frequent or longer haemodialysis: weighing the evidence

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ABSTRACT

Although the ability of individuals with end-stage renal disease to maintain body homoeostasis is equally impaired during all weekdays, conventional haemodialysis (HD) treatment is scheduled thrice weekly, containing two short and one long interdialytic interval. This intermittent nature of HD and the consequent fluctuations in volume, metabolic parameters and electrolytes have long been hypothesized to predispose to complications. Large observational studies link the first weekday with an increased risk of cardiovascular morbidity and mortality. Several schemes of frequent and/or longer, home or in-centre HD have been introduced, aiming to alleviate the above risks by both increasing total dialysis duration and reducing the duration of interdialytic intervals. Observational studies in this field have non-uniform results, showing that enhanced frequency in home (but not in-centre) HD is associated with reduced mortality. Evidence from the randomized Daily and Nocturnal Trials of the Frequent HD Network suggest the opposite, showing mortality benefits with in-centre daily but not with home nocturnal dialysis. Secondary analyses of these trials indicate that daily and nocturnal schedules do not have equal effects on intermediate outcomes. Alternative schemes, such as thrice weekly in-centre nocturnal HD or every-other-day HD, seem to also offer improvements in several intermediate endpoints, but need further testing with randomized trials. This review summarizes the effects of frequent and/or longer HD