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Vaccinated kidney transplant recipients are yet not sufficiently protected against COVID-19

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OUTCOMES OF COVID-19 IN KIDNEY PATIENTS

The coronavirus 2019 (COVID-19) pandemic had a great impact on individuals and on society at large. Although this disease affected all people in the general population, there were some specific subpopulations that had a high risk for a more severe disease course. Williamson *et al.* [1] described in July 2020, in their article in *Nature*, the risk of mortality associated with COVID-19 in the general population in the UK. More than 17 million National Health Service–registered people were included, of whom 11 000 died due to COVID-19. As pointed out in an editorial based on these data [2], especially patients with severely impaired kidney function (CKD stages G4 and 5), those on dialysis and patients with an organ transplant were shown to be vulnerable. The COVID-19-associated mortality risk was reported to be ≈20% in kidney transplant patients and 25% in maintenance haemodialysis patients [3], which was 10- to 20-fold higher as compared with the general population and 3- to 4-fold higher in a model adjusting for other covariates [1, 2]. This risk of dying was considerably higher than the 1.5- to 2-fold increase that was described in previously established high-risk groups, such as patients with obesity, hypertension or diabetes [2]. Although the whole world was waiting for a vaccine to become available, these data make clear that an effective and safe vaccine was especially crucial for patients with kidney failure.

EFFICACY OF COVID-19 VACCINATION IN KIDNEY PATIENTS

The pivotal phase 3 registration trials with the messenger RNA (mRNA) vaccines reported an efficacy of 95% for the BNT162b2 (BioNTech/Pfizer) vaccine and 94% for the mRNA-1273 (Moderna) vaccine [4, 5]. Unfortunately, these studies excluded high-risk groups, including patients with severely impaired kidney function, patients on dialysis and kidney transplant recipients (KTRs). From studies with vaccinations against other pathogens, such as hepatitis B, influenza and *Streptococcus* pneumonia, it is known that the response to vaccination can be considerably lower in these patients due to uraemia or the use of specific immunosuppressive medications [6]. In a short period of time, several studies investigated the immunogenicity of COVID-19 vaccination in specific vulnerable patient groups. These studies revealed that, similar to vaccines against other pathogens, the response to the available COVID-19 vaccines was lower in these patients compared with the general population. That notwithstanding, in general the response was reasonable in patients with severely impaired kidney function and dialysis patients. When multiple vaccinations are used, vaccine response even reaches values near the normal population [7]. However, it was poor in KTRs, particularly in those using mycophenolate mofetil or mycophenolic acid (MMF/MPA) [8–10]. Consequently, these patients were invited to receive multiple repeat vaccinations [11] in an attempt to increase immunogenicity to reach a higher level of protection against COVID-19.

Despite such repeat vaccinations, the percentage of KTRs who remained unresponsive to vaccination was considerable, as measured by the formation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific antibodies. It ranged from 24 to 61% after a third vaccination [12–15]. Although this percentage decreased with a fourth and fifth vaccination [16], the patients who did show a response after vaccination often had much lower antibody levels compared with the general population [17]. These data suggest that vaccination remains less effective in these KTRs even after repeat vaccination.

EFFECTIVENESS OF COVID-19 VACCINATION IN KIDNEY TRANSPLANT PATIENTS—RESULTS FROM REAL-LIFE DATA

The effectiveness of COVID-19 vaccines in reducing the SARS-CoV-2 infection rate and in lowering COVID-19 severity and mortality has been uniformly demonstrated in the general population [18]. Results from registry data with respect to the effectiveness of COVID-19 vaccination in KTRs are conflicting. Hamm *et al.* [19] showed protective effects of COVID-19 vaccination in a national registry study from Denmark that included 1428 solid organ transplant recipients, of whom the majority were KTRs. COVID-19-related hospitalization rates were lower in vaccinated compared with unvaccinated patients (26.4% versus 48.5%; $P = .01$), as was COVID-19-related mortality (1.8% versus 9.1%; $P = .047$). However, Callaghan *et al.* [20] could not corroborate the clinical effectiveness of vaccination in solid organ transplant recipients in a study that included 43 481 subjects in England. Remarkably, the infection incidence was even significantly higher in vaccinated versus in unvaccinated solid organ transplant recipients {hazard ratio [HR] 1.28 [95% confidence interval (CI) 1.03–1.61]}. The authors argue that risk compensation with reduced adherence to restrictions in vaccinated patients may be the explanation for these remarkable results. Notwithstanding a higher

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infection risk, their data did indicate a reduced risk of death in vaccinated solid organ transplant recipients, although marginal and not reaching formal statistical significance [HR 0.80 (95% CI 0.63–1.00)] [20]. A registry study from Ontario, Canada that included 12 842 solid organ transplant recipients also showed very limited vaccine effectiveness after the first and second vaccination, although vaccine effectiveness improved after a third dose [21].

In this issue of *Nephrology, Dialysis and Transplantation*, Wijkström *et al.* present a nationwide observational study. In this impressive study they managed to link several Swedish national registries, resulting in a large dataset including detailed patient characteristics from 4097 dialysis patients and 5905 KTRs. These authors are, as far as we know, the first to report on COVID-19-related hospital and mortality rates of patients on kidney replacement therapy before and during the pandemic and during the pandemic before as well as after vaccination. They demonstrated that all-cause mortality rates increased by 10% and 22% in dialysis patients and KTRs during the first year of the pandemic and that rates decreased in dialysis patients after the national vaccination program started. However, this did not hold true for KTRs. In these patients, mortality rates remained increased despite the start of the vaccination program. Unfortunately, no individual vaccination data were available in this registry study, which prevented the authors from making firm conclusions on vaccine effectiveness. However, it can be assumed that >95% of patients on dialysis and living with a kidney transplant would have been vaccinated, as known from other studies.

Taken together, these data from registry studies indicate that the effectiveness of vaccination to protect against COVID-19 infection and mortality in KTRs is yet insufficient. This is probably related to their poor immune response after COVID-19 vaccination.

WHAT LESSONS ARE STILL TO BE LEARNED?

When the COVID-19 pandemic started, the medical community was totally overwhelmed and unprepared. Now that the number of hospital admissions for and mortality due to COVID-19 is declining, it is likely that interest in performing studies will also decline. This is not justified. Concerns remain that another, more pathogenic SARS-CoV-2 variant may become dominant or that another highly pathogenic virus such as bird flu will circulate in the near future. To be prepared for these eventualities, it is necessary that lessons are learned regarding how to increase vaccination efficacy in our patient groups.

As several studies have demonstrated that especially the use of the immunosuppressive agent MMF/MPA is associated with a poor immune response after vaccination, it is hypothesized that (temporary) discontinuation of MMF/MPA during vaccination will contribute to a higher antibody response. For this reason, we recently performed a randomized clinical trial, but found no beneficial effect on antibody response to vaccination after withdrawal of MMF/MPA 1 week before and 1 week after a repeated vaccination with mRNA-1273 [22]. Another study suggested a beneficial effect when MMF/MPA was withdrawn 5–7 days before and 3–4 weeks after vaccination [23]. However, this was a small-scale, single-centre, non-randomized study lacking a control group. Moreover, in this study seven patients that withdrew MMF/MPA showed resurgence of pre-existing donor-specific antibodies and one patient developed *de novo* donor-specific antibodies. These data indicate that there is a concern that a potential benefit of an increase in antibody levels after discontinuation of MMF/MPA may not outweigh the risk of eliciting an allograft-directed immune response.

Another option would be to replace MMF/MPA by another immunosuppressant. We recently showed that in a relatively small cohort of KTRs >65 years of age who were randomized as part of the OPTIMIZE study [24] to receive immediately after transplantation triple maintenance immunosuppressive therapy including everolimus or MMF/MPA, that significantly higher antibody levels after COVID-19 vaccination were achieved in the everolimus group when compared with the MMF/MPA group [25]. It remains to be established whether replacement of MMF/MPA by everolimus in KTRs who were previously treated with MMF/MPA also results in a higher immunogenicity after vaccination. To investigate this knowledge gap we plan to perform a randomized clinical trial to provide optimal evidence that this vaccination strategy will result in higher immunogenicity after vaccination. We will also investigate whether this is the case for COVID-19 as well as for herpes zoster vaccination. When we can demonstrate that this accounts for both vaccines, it will provide strong evidence that results of this study may be translated to any other vaccination strategy against (future) pathogens. In that case, the standard vaccination policy may be changed accordingly in patients using MMF/MPA, including KTRs, patients with other organ transplants or certain autoimmune diseases. We hope that (temporarily) changing MMF/MPA to everolimus around vaccination will result in improved protection against disease.

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AUTHORS' CONTRIBUTIONS

ALM wrote the first draft of the paper. RTG supervised and reviewed the paper after which a final version was submitted.

CONFLICT OF INTEREST STATEMENT

None declared.

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