

COVID-19 VACCINATION IN RENAL TRANSPLANT PATIENT AND DIALYSIS PATIENTS

Cristina Popa^{1,2,*}, Cristina Ipate^{1,*}, Simona Hogas^{1,2} and Adrian Covic^{1,2}

¹Nephrology Clinic, Dialysis and Renal Transplant Center – “C.I. Parhon” University Hospital, 700503.
²“Grigore T. Popa” University of Medicine, Iasi, Romania

Corresponding authors: cristina-adriana_cg_rusu@d.umfiasi.ro, cristinaalexandraipate@gmail.com,
simona.hogas@umfiasi.ro, adrian.covic@umfiasi.ro

Accepted March 19, 2021

Among patients evaluated by various medical specialties, renal patients have the most comorbidities, the highest number of drugs prescribed and the highest mortality. Chronic kidney disease patients have higher mortality than the general population. Renal patients with stage 4–5 chronic kidney disease, dialysis and renal transplant occupy the first 3 places in terms of COVID-19 mortality. In this context, these categories of patients would have the greatest benefits from COVID-19 vaccination. Current studies of COVID-19 vaccines have included not enough or no renal patients. There are uncertainties about the safety and efficacy of vaccines in this category of patients, which is why further studies are needed.

Key words: COVID-19, chronic kidney disease, renal transplant, dialysis.

INTRODUCTION

A new coronavirus was identified in Wuhan, China in 2019 and in February 2020, the World Health Organization (WHO) designated the disease COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

In the first months of pandemic, the most frequent comorbidities of patients hospitalized with COVID-19 were considered diabetes mellitus (DM), hypertension and cardiovascular disease (CVD).¹ Regarding hospitalizations for COVID-19, a meta-analysis of 76993 patients, revealed hypertension, CVD, DM, chronic kidney disease (CKD), smoking and chronic obstructive pulmonary disease (COPD) as the most prevalent comorbidities.²

CKD patients have higher mortality than the general population. Among patients evaluated by various medical specialties, renal patients have the most comorbidities, the highest number of drugs prescribed and the highest mortality.³ According to the United States Renal Data System Report (USRDS) from 2020, mortality for dialysis patients in pre-pandemic era was 2 times higher than that of

patients with a history of myocardial infarction and 2.5 times higher than that of patients with cancer. Patients receiving renal transplant have longer survival than dialysis patients, but lower than patients without end stage renal disease (ESRD).⁴

Although CKD was only briefly mentioned initially, a recent analysis of risk factors for developing a severe form of COVID-19 using OpenSAFELY, a health analytics platform developed in England, including more than 17 million adults, showed that CKD (eGFR<30ml/min/1.73m²), dialysis and transplant patients were top three risk factors of mortality.⁵ Mortality among dialysis patients was two times higher and in transplant patients mortality can be six times higher than in patients of similar age with COVID-19. This may be due to the multitude of comorbidities found in this category of patients. Also, mortality risk in kidney transplant recipients with COVID-19 was 28% higher compared with a matched group dialysis patient.⁶

The previous studies have shown the need for to prioritize vaccination in renal patients.

There are several vaccines that have been developed and are now approved for adult patients in Europe, including Romania: two mRNA vaccines – BNT162b2 (Pfizer BioNTech COVID-19 vaccine), mRNA 1273 (Moderna COVID-19 vaccine) – and a replication-defective adenoviral

* These authors contributed equally.

vector vaccine, AZD1222 (AstraZeneca COVID-19 vaccine). We can note some differences between their immunogenicity, efficacy, and safety profiles, but they all have a thing in common: they have not been tested on CKD patients.

COVID VACCINE IN RENAL TRANSPLANT PATIENTS

The ERACODA study shows higher mortality in SARS-CoV2 renal transplant recipients (21%) and in dialysis patients (25%).⁶

SAFETY CONCERNS

mRNA vaccines are not likely to produce novel or more side effects in kidney transplant recipients, including rejection episodes.⁷ It was evaluated the safety of the first dose of SARS-CoV2 vaccination in 187 SOTRs (solid organ transplant recipients), many of whom activated as front-line healthcare workers (64%). 31% were male and the median age was 48 years (37–59), with a median of years since transplantation of 6 (3–13). The majority were kidney transplant recipients (52%), but the study also included patients with a liver (19%), heart (14%), lung (9%), kidney/pancreas (3%) and multiorgan (3%) transplant. Half of the participants received the Pfizer BioNTech mRNA vaccine, while the other half was vaccinated with Moderna mRNA vaccine. During early follow up, there were not reported cases of acute rejection, allergic reactions that required adrenaline or neurological diagnoses (Guillain-Barré syndrome, neuropathy, Bell's palsy). The adverse effects were similar to those encountered in the randomized trials of the vaccines and included local site reactions (mild pain, mild redness, mild swelling) and systemic reactions (fatigue, headache, myalgias, fever, chills).⁸ Although further randomized studies are necessary to assess the safety issues, these results are encouraging for both SOTRs.

EFFICACY CONCERNS

In immunocompetent adults the mRNA vaccines showed around 95% efficacy in preventing the infection with SARS-CoV2; in patients diagnosed with COVID-19 after vaccination, the symptoms were milder, suggesting that vaccines prevent severe forms of the disease. However, regarding SOTRs it has been

hypothesized that transplant patients may have a lower antibody response than the general population.⁷

Kidney transplant recipients develop serological responses to SARS-CoV2,⁹ but data concerning the amplitude of the response and the lifespan of the antibodies was lacking. Chavarot et al evaluated the presence of IgG anti-SARS-CoV2 antibodies at 2 and 6 months after symptomatic COVID-19. At month 2, 71% of the 42 patients were seropositive, whilst at month 6, only 36% presented antibodies.¹⁰ Keeping in mind this rapid decrease of antibody levels, after COVID 19 infection, the need for vaccination becomes more prominent.

COVID 19 VACCINE IN DIALYSIS

The COVID-19 vaccine should be administered to vulnerable populations. Dialysis patients represent, in the context of increased mortality, one of the most vulnerable categories of patients. Thus, in this category of patients the benefits would be higher than among the general population.¹¹

In the current pandemic context, international nephrology societies (National Kidney Foundation and ERA-EDTA) recommend COVID-19 vaccine prioritization in dialysis patients, having as main arguments:

- Higher exposure: The hemodialysis patient performs 3 hemodialysis sessions per week, respectively 156 hemodialysis sessions per year. During the pandemic, measures were taken to prevent SARS-CoV2 infection: social distance, wearing protective equipment, triage of patients by telephone and in the dialysis center, PCR testing. Because patients with end-stage renal disease (ESRD) cannot survive without dialysis, they need to travel to dialysis centers, maintaining an increased risk of infection, despite all measures.
- Higher risk of Intensive Care Unit admission (ICU) and mortality

The ERA-CODA study that included dialysis and kidney transplant patients showed a higher rate of ICU admission (12% for dialysis patients) and a higher mortality rate at 28 days (21.3%) for dialysis patients.⁶

SAFETY CONCERNS

A systematic review that included 123 trials of various types of COVID-19 vaccines found that

16% of them excluded patients with kidney disease regardless of severity, 33% – excluded those with severe kidney disease, and 46% left investigators to decide on kidney function. Regarding phase 3 trials, 39.4% of them included patients with moderate CKD. The Pfizer BNT162b2 trial included patients with stable chronic disease, but only 0.7% of patients had CKD, an insufficient proportion of renal patients compared to the general population. The Moderna mRNA-1273 trial included patients with chronic diseases, but did not publish additional data. The Novavax NVX-CoV2373 phase 3 study vaccine will not rule out patients with CKD.¹²

Currently, there are no published data on the safety of COVID-19 vaccines in dialysis patients. However, dialysis patients, those with stage 4-5 CKD, and those with kidney transplants were included in a trial: The REnal Patients COVID-19 VACcination Immune Response (RECOVAC-IR) Study (NCT04741386). This study aimed to evaluate the safety and efficacy of COVID-19 in renal patients. The completion date of the study is December 2022. Also, there is a French study COVADIAL (NCT04728828), that included only hemodialysis patients, but also the study completion date is in 2023. Until then, given the indisputable data on increased mortality in the dialysis patients, many nephrologists wonder if the benefit of vaccination does not outweigh the risk and maybe they already vaccinate their patients.

EFFICACY CONCERNS

Infectious pathology remains an important source of mortality and morbidity in patients, so prevention by vaccination plays a very important role. Although, due to a degree of immunosuppression caused by uremia, dialysis patients produce a lower titer of antibodies than the general population, hepatitis B, Influenza and pneumococcal vaccines are used with a good safety-efficacy profile.

The efficacy of COVID-19 vaccines in immunocompromised patients is unknown. Compared to attenuated vaccines, mRNA-based and viral-vectored vaccines induce better humoral immunity and a better immune response from T cells.. (Jeyanathan M., 2020) Despite the progress made in the last year, the immunity induced by COVID-19 vaccines and especially its duration are not fully understood.¹³

After SARS-Cov2 infection, in dialysis patients, seroconversion is close to 100%, but, as in the general population, the duration of the post-infection immune response is not known. A study that included dialysis patients in Belgium reveals that the titer of IgG anti-SARS-Cov2 antibodies decreases after 3 months from infection.¹⁴ Thus, in immunocompromised patients, in whom the vaccine does not induce a satisfactory level of seroconversion, there may be several options: administration of an additional booster dose or respiratory mucosal vaccination. Respiratory mucosal vaccination, in contrast to intramuscular, can produce immunological memory mediated by the mucosa's own cells. Such an approach can provide protection in the early stages of SARS-Cov2 infection, thus providing an advantage to immunosuppressed patients.¹⁵

Immunogenicity of COVID-19 Vaccine in Hemodialysis Patients Trial (COVADIAL) that included only hemodialysis patients, propose as secondary outcomes: defining lack of seroconversion evaluation and longevity of the antibody synthesis induced after Covid-19 vaccination.

VACCINE CHOICE FOR DIALYSIS PATIENTS

In renal patients replication-defective viral-vectored vaccines such as ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and the mRNA vaccines (Pfizer-BioNTech and Moderna) are safe to use.¹⁵

Pfizer-BioNTech,¹⁶ Moderna,¹⁷ (Baden L.R., 2020) and Astra-Zeneca¹⁸ prevented COVID-19 in 95%, 94,1%, respectively 70.4%. Considering that dialysis patient is at risk of producing a lower titer of antibodies (as in the case of the Influenza vaccine), until further studies, it is preferable to use vaccines that produce a greater protective response.

CONCLUSION

Regarding that kidney transplant patients and dialysis patients associate the highest COVID-19 mortality of all patients with chronic diseases, they should be a priority in the vaccination process.

DISCUSSION

Chronic kidney disease or kidney transplantation present in a COVID-19 patient is a negative prognostic factor. No other comorbidity causes

such high mortality among COVID-19 patients; but kidney patients have many other diseases. Thus, for this category of patients, in the absence of an effective treatment for COVID-19, the benefit is much greater than the general population.

COVID-19 vaccines are safe for kidney transplant or dialysis patients, and are recommended by international nephrology societies. No additional or more frequent adverse reactions were observed in transplant patients than in the general population and also – no episodes of acute rejection. However, additional studies are needed.

There are concerns about the effectiveness of COVID-19 vaccines in patients with kidney transplantation or dialysis. Given that these patients have an immunocompromised status, it can be assumed that the vaccines cause lower immunogenicity and would be less effective than in the general population. Further studies are needed to determine the effectiveness of vaccines in this category of patients.

Regarding vaccine options for transplant patients, mRNA vaccines are safe.⁸ (Boyarsky BJ, 2021). In dialysis patients, mRNA vaccines are currently recommended because they have better efficacy.¹⁵

REFERENCES

- Huang C; Wang Y.; Li X.; *et al.* *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet*, **2020**; 395, 497-506.
- Emami A.; Javanmardi F.; Pirbonyeh N.; Akbari A., *Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. Arch Acad Emerg Med*, **2020**; 24; 8(1):e35.
- Tonelli M.; Wiebe N.; Manns B.J.; *et al.*, *Comparison of the Complexity of Patients Seen by Different Medical Subspecialists in a Universal Health Care System. JAMA Netw Open*. **2018**; 1(7):e184852. doi:10.1001/jamanetworkopen.2018.485
- United States Renal Data System Report (USRDS) (2020)* doi:https://adr.usrds.org/2020
- Williamson E.J.; Walker A.J.; Bhaskaran K.; *et al.*, *Factors associated with COVID-19-related death using OpenSAFELY, Nature*, **2020**, 584(7821),430-436.
- Hilbrands L.B.; Duivenvoorden R.; Vart P.; *et al.*, ERACODA Collaborators, *COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. Nephrol Dial Transplant*. **2020**, 35(11), 1973-1983.
- American Society of Transplantation. (2021, March 2)*. Retrieved from COVID-19 Vaccine FAQ Sheet: <https://www.myast.org/covid-19-vaccine-faq-sheet>
- Boyarsky B.J.; Ou M.T.; Greenberg R.S.; Teles A.T.; *et al.*, *Safety of the First Dose of SARS-CoV-2 Vaccination in Solid Organ Transplant Recipients, Transplantation*, **2021 Feb 4**. doi: 10.1097/TP.0000000000003654.
- Predecki M.; Clarke C.; Gleeson S.; *et al.*, *Detection of SARS-CoV-2 Antibodies in Kidney Transplant Recipients. J Am Soc Nephrol*, **2020**, 31(12), 2753-2756.
- Chavarot N.; Leruez-Ville M.; Scemla A.; Burger C.; *et al.*, *Decline and loss of anti-SARS-CoV-2 antibodies in kidney transplant recipients in the 6 months following SARS-CoV-2 infection. Kidney Int*. **2021**,99(2), 486-488.
- Combe C.; Kirsch AH.; Alfano G.; *et al.*, EUDIAL Working Group of the ERA-EDTA; Board Members of the EUDIAL Working Group. *At least 156 reasons to prioritise COVID-19 vaccination in patients receiving in-centre haemodialysis. Nephrol Dial Transplant*, **2021 Jan 20** doi: 10.1093/ndt/gfab007
- Glenn D.A.; Hegde A.; Kotzen E.; *et al.*, *Systematic review of safety and efficacy of COVID-19 vaccines in patients with kidney disease, Kidney Int Rep*. **2021 Feb 9**. doi: 10.1016/j.ekir.2021.02.011.
- Poland G.A.; Ovsyannikova I.G.; Kennedy R.B., *SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates, Lancet*, **2020**, 396(10262):1595-1606.
- Labriola L.; Scohy A.; Seghers F.; *et al.*, *A Longitudinal, 3-Month Serologic Assessment of SARS-CoV-2 Infections in a Belgian Hemodialysis Facility, Clin J Am Soc Nephrol*, **2020** doi: 10.2215/CJN.12490720
- Windpessl M.; Bruchfeld A.; Anders H.J.; *et al.*, *COVID-19 vaccines and kidney disease, Nat Rev Nephrol*. **2021 Feb 8**. doi: 10.1038/s41581-021-00406-6.
- Polack F.P.; Thomas S.J.; Kitchin N.; *et al.*, C4591001 Clinical Trial Group, *Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine, N Engl J Med*, **2020**, 383(27), 2603-2615.
- Baden L.R.; El Sahly H.M.; Essink B.; *et al.*, COVE Study Group. *Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine, N Engl J Med*, **2021**, 384(5), 403-416.
- Voysey M.; Clemens S.A.C.; Madhi S.A.; *et al.* Oxford COVID Vaccine Trial Group, *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*, **2021**, 397(10269), 99-111.