Review Article

COVID -19 Vaccination in Patients with End Stage Kidney Disease. Early Results for an mRNA Vaccine in a Vulnerable Population

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Asian Journal of Complementary and Alternative Medicine. Volume 09 Issue 2

Published on: 17/06/2021

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Cite this article as: Yanay NB, Armaly Z. *COVID -19 Vaccination in Patients with End Stage Kidney Disease. Early Results for an mRNA Vaccine in a Vulnerable Population.* Asian Journal of Complementary and Alternative Medicine, Vol 9(2), 49-53:2021.

ABSTRACT

Patients with end stage kidney disease receiving dialysis treatment are at increased risk of COVID-19 infection. These patients have also higher rates of complications and mortality. The vulnerability may in part be explained by the profound changes in the immune system that are associated with impaired renal function. At the time of approval of the first vaccine for COVID-19, the BNT162b2 mRNA vaccine, there was no information on the efficacy and safety of the vaccine in dialysis patients. Preliminary reports on outcomes with the vaccine in the dialysis population have been published recently and the results are, in general, encouraging. However, these results indicate a lower response rate, a longer time to mount antibody response, lower antibody levels and possibly higher rate of COVID-19 breakthrough infection in the dialysis population. These results raise several questions that await further data to be reported. Meanwhile the dialysis patient's population may still need special attention. Lessons learnt in this special population may also be applicable for other vulnerable patient groups.

Keywords: Pfizer BioNTech COVID-19 vaccine, anti-spike antibody, end stage kidney disease, dialysis, immune-system

COVID-19 IN PATIENTS WITH ADVANCED KIDNEY DISEASE

Since the emergence of COVID-19 it was anticipated that patients with end stage kidney disease (ESKD) receiving dialysis treatment would be at high risk for contracting the disease, for complications and for mortality. These assumptions were based upon characteristics of this patient population: 1. End stage kidney disease is associated with alterations in the immune system. 2. Patients with ESKD often have complex comorbidities that are documented risk factors for adverse outcomes in patients with COVID-19. 3. In center dialysis treatment: patients must travel 3 times a week for dialysis treatment of an average 4-hours duration, and in many facilities, social distancing cannot be guaranteed [1]. Indeed, a higher rate of infection with COVID-19 was reported in the dialysis population when compared to the general population: The prevalence of infection reported from the French national REIN dialysis registry was between 1%-10% [2]. Another study from an urban center in the UK reported a prevalence of 19.6% infection in a large dialysis cohort [3]. Also, the mortality rate reported for these patients, in different countries was relatively high - between 16.2% to 31.7%- while at the same period the overall mortality rate from COVID -19 In Europe was 4% and in Japan 5.3% [4-9]. In the USA, excess mortality of 10.8-16.6 cases per 1000 people in the first 6 months of the pandemic was reported for the dialysis population [10]. The higher mortality rate persisted even after adjustment for demographic characteristics and comorbidities [4]. The most common risk factors for mortality are older age, frailty, and additional comorbidities.

Immune dysfunction in uremia

The immune system is profoundly affected in advanced kidney disease.

ESKD is associated with high susceptibility to infections and reduced response to vaccinations [9,11-15]. Infection is the second most common cause of mortality in dialysis patients after cardiovascular disease, and the annual rate of sepsis is 100-300-fold higher in dialysis patients when compared to the general population [16]. Immune system disturbances in dialysis patients are complex. They are caused by uremia per se; by chronic kidney disease associated comorbidities

and complications and by the dialysis treatment and other therapeutic interventions. Two connected but opposite aspects of the immune system are present in ESKD: activation-resulting in persistent systemic inflammation, and dysfunction-characterized by reduced function and immunosuppression. While an enhanced inflammatory state is predominately associated with cardiovascular morbidity and excess mortality, the immune dysfunction is associated with high susceptibility to infections and altered response to vaccination [15-17]. Immune defense against infections depends on integrity and cooperation of the innate and adaptive immune systems. The innate immune system response involves pathogen-associated molecular patterns that are non-pathogen-specific. These include: 1. Secreted opsonins that bind to the bacterial wall and lead to activation of the complement system. 2. Receptors on phagocytic cells, involved in pathogen clearance by endocytosis, in MHC-II associated antigen presentation and in the activation of T cells. 3. Activation of signal transduction pathways that enhance the inflammatory and immune response and activation of the adaptive immune response [12,14]. The adaptive immune system mounts an antigen and pathogen specific response through increased activation of specific T (killer and helper T cell populations) and B lymphocytes. The adaptive immune system is also responsible for immunological memory. These pathways are profoundly altered in ESKD. Some of these alterations include:

Decreased activity of monocytes that is associated with decreased activation of B and T lymphocytes [18]; Decreased phagocytic activity and killing capability of polymorphonuclear cells. This impairment is partially reversible after hemodialysis treatment [19]; Impaired terminal differentiation and maturation of monocyte derived dendritic cells, and reduced T cell proliferation in response to recall antigens. This impairment is independent on dialysis treatment [20]; Reduced CD4+/CD8+ T-lymphocyte ratio, reduced central memory T lymphocyte subpopulation and increased apopotosis [21] and B cell lymphopenia [22,23].

Because of the reduced response to vaccinations, there are specific recommended dose regimens for ESKD patients for some common vaccinations. An example is the Hepatitis B virus (HBV) vaccination regimen: Patients on hemodialysis have low response to HBV vaccine with a seroconversion rate between 50%-70% following the standard vaccination regimen. Therefore, the recommended regimen for this population consists of a double dose of each injection and an additional (fourth) injection [24].

Approval of mRNA COVID-19 vaccines

On December 2020, less than a year after the SARS-COV-2 pandemic was declared by the WHO, the first emergency use authorization for the COVID-19 vaccine was granted by the FDA first to the Pfizer BiONTech BNT162b2 and few days later to the Moderna mRNA 1273 vaccine [23-26]. The authorization was based on results of phase 3 clinical trial results. [27,28] The rollout of the vaccines and ongoing worldwide vaccination efforts represent a huge and possibly definitive step in the global battle against the pandemic. This was the first time mRNA vaccines had been approved. Both Pfizer BioNTech and the Moderna phase 3 pivotal clinical trials did not include some special populations such as children, pregnant women, people with severe clinical conditions like people with an organ transplant, people with malignancies or people with advanced/end stage kidney disease. In the Pfizer BioNTech phase 3 clinical trial patients with stable chronic conditions were included, among them 256 (0.7% of the trial population) patients with renal disease. Their chronic kidney disease stage was not mentioned. In the Moderna phase 3 clinical trial, there is no data on patients with kidney disease [27-29]. Clinical trials on the immunogenicity of COVID-19 vaccines in the dialysis population are ongoing and preliminary results are already available.

The response to the COVID-19 vaccine in the dialysis population; the experience with BNT162b2 mRNA vaccine

In a series of reports on nearly 500 dialysis patients who were vaccinated with the BNT162b2 mRNA vaccine, there were 3 main findings: 1. The response rate after completion of 2 doses of the BNT162b2 vaccine was found to be lower. 2.The development of the humoral response was slower and 3. The anti-spike antibody level was lower when compared to the general population. [30-35], (table 1.). In these clinical trials there were no reports of any safety signal for the dialysis population.

1. Response rate following vaccination: The reported anti-Spike antibody response rate in dialysis patients was between 80%-96%, as compared to a response rate of 100% in 227 people in control groups [32,35]. Studies in other patients' populations that are immunocompromised or immunosuppressed have yielded similar results the rate of response in patients with malignant conditions is between 60-95% [36]. The response rate reported in organ transplanted patients is between 22% - 54% [37-40].
2. The development of antibody response through the vaccination process may be slower in the dialysis population. In a study that evaluated the antibody response to vaccination in dialysis patients with and without previous COVID-19 infection, the response rate after the first dose of the BNT162b2 vaccine in patients with no previous infection was 18% [33]. Another study evaluated the initial response rate after the first vaccine

Table 1: summary of clinical trials on antibody response to the BNT162b2 vaccine in dialysis patients

Author (Reference)	Patient population & Control group	Vaccine type & number of doses	Outcome measure	Results
Jahn (31)	HD (72) Control (16)	BNT162b2 2 doses	Anti -S IgG level	HD-597AU/ml C-800AU/ml† For HD group antibody level negatively correlate with age†
Grupper (32)	HD (56) Control (95)	BNT162b2 2 doses	Anti -S IgG response rate Anti -S IgG level	HD-96% response HD-2900 AU/ml C-100% response† C-7401 AU/ml† Lower Ab levels in older patients HD & C
Agur (30)	HD (122) PD (23)	BNT162b2 2 doses	Anti -S IgG response rate	HD-93.4% response PD-95.6% response Lower Ab levels in older and in patients with low albumin level
Attias (31)	HD (64)	BNT162b2 1 & 2 doses	Anti -S IgG response rate	HD-18% response after first vaccine HD-80% response after second vaccine Lower Ab level in older patients: 75% response for>70 years
Berar Yanay (32)	HD (127) PD (33) Control (132)	BNT162b2 2 doses	Anti -S IgG response rate Anti-S IgG level % new COVID-19 infection	HD+PD- 90% response HD+PD Median antibody level 116AU/ml Lower Ab in older patients HD-3.75% COVID-19 infection post complete vaccination C-100% response† C- Median antibody level 176.5AU/ml† C-no cases of infection post vaccination†

HD- hemodialysis; PD- peritoneal dialysis; C control group; BNT162b2- Pfizer BioNTec 162b2 mRNA COVID-19 vaccine; anti-S IgG- anti-spike protein antibody; AU- arbitrary units.

†- $P<0.05$

dose in dialysis patients and reported a response rate of 35% [41], while in a study that evaluated the response rate to vaccination with the BNT162b2 vaccine in a cohort of health care workers, the response rate was 95.5% 14 days after the first dose [42]. Suggestions to delay or skip a second dose of the vaccine have been proposed [43,44], but this strategy may not be appropriate for dialysis patients and other patient groups with lower and/or slower antibody response to vaccination.

3. The level of anti-Spike antibodies is consistently and significantly lower in the dialysis population when compared with a control group [31,32,35] The most common factor associated with a low antibody titer was older age. Lower albumin level lower lymphocyte count and BMI above 30 Kg/m^{2}were also associated with lower antibody level [32,33]. The dialysis modality (hemodialysis versus peritoneal dialysis) and the dialysis vintage (time since the start of dialysis) were not associated with anti-spike antibody levels [33,34].Currently, there is no cut off level of anti-spike antibody that is defined as fully protective. It is possible that lower level could be associated with breakthrough infection. One study reported on 6 out of 160 (3.75%) dialysis patients who developed a breakthrough COVID-19 infection more than 7 days after the second vaccine dose, as compared to 0 cases in the control group (132 people). Patients who developed a new infection had an anti-spike antibody level in the lowest quartile in the dialysis group [35]. These results imply a possible association between a low antibody level and the risk for COVID-19 breakthrough infection. The impact of a booster dose or doses of the vaccine on anti-spike antibody levels is yet unknown. It is possible that for dialysis patients an extended vaccination regimen will be advised, like the recommendations for other vaccines in this unique population [24].

More data is needed to address some important remaining questions:

1. What is the response of dialysis patients to other COVID-19 vaccines?
2. Is there a need for monitoring antibody levels?
3. Should we give booster dose(s)to some or to all the patients?
4. If so, what would be the cut level for a booster dose?

CONCLUSION

As COVID-19 vaccination efforts are ongoing worldwide, preliminary reports on the efficacy and safety of the mRNA BNT162b2 vaccine in special vulnerable populations appear. For the dialysis population - results of these reports show overall high levels of efficacy and safety. However, this population does have a particular response pattern to vaccination; a lower response rate, a slower response, lower antibody titers post-vaccination and possibly further susceptibility for breakthrough COVID-19 infection. Some important questions regarding dosing regimen and need for antibody level surveillance await further clinical trial results. In the meantime, attention should be focused on maintaining some of the recommendations for social distancing and other precaution measures for further protection of dialysis patients even after vaccination is completed.

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