SARS-CoV-2 Infection and Anti-SARS-CoV-2 Vaccination in CKD Patients

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Chronic kidney disease (CKD) is associated with phenotypic and functional changes in the immune system, followed by detrimental clinical consequences, such as severe infections and defective response to vaccination.

Keywords: renal transplantation ; immune system ; COVID-19 ; vaccination

1. Impact of CKD-Associated Immunological Changes to COVID-19 Manifestations

As anticipated, with a combination of immunological deficits and abnormalities being present, patients with CKD are more prone to severe COVID-19 manifestations.

The presence of end-stage kidney disease, especially when patients are on dialysis, has been recognized as one of the most vicious factors, predisposing to worse outcomes. A wide range of disease severity and complications has been manifested, such as severe pneumonia, liver failure, gastrointestinal symptoms, such as diarrhea and gastrointestinal bleeding, cardiovascular events, including atrial fibrillation and QTc interval prolongation, and acute respiratory distress syndrome (ARDS). Age, comorbidity, for instance, ischemic heart disease, and severe symptomatology at diagnosis are factors associated with worse outcomes, ARDS, and increased mortality [1][2][3]. Immunological alterations in these patients also seem to play a substantial role in the outcome of infection. The repository of TCRs in naïve T-cell populations is reduced, and T-cell-mediated intracellular signaling is less effective, thus rendering their function impaired. Additionally, plasmacytoid DCs (pDCs), the major source of type I interferon (IFN) [4], a chemokine of main importance in the combat against COVID-19, are decreased. All the previous changes are responsible for delayed virus clearance and prolonged stimulation of SARS-CoV-2-reactive memory T-cells. As Tregs are also defective and the numbers of naïve T-cells are low, the ability of the immune system to control this large-scale expansion of highly reactive T-cells and the consequent cytokine storm is restricted, with the collateral damage caused being significant. Interestingly, in the case of COVID-19, the intensity of the immune response is possibly much worse at the tissue level compared to peripheral blood, as the expansion of reactive effector T-cells seems to be more extended in the lung parenchyma [5].

2. CKD-Associated Immune Changes and Response to Vaccination against COVID-19

Although the determination of anti-SARS-CoV-2 Ab titters is a quick way of assessing the patient's response to immunization, cellular immunity assays are also necessary in order to form a more comprehensive image regarding their condition. Cellular immunity activation is of great importance in the defense against SARS-CoV-2 since it can significantly reduce the risk of infection, with cytotoxic CD8+ T-cells being a potential asset in terms of viral clearance [6]. According to the results of recent trials, both mRNA and viral vector vaccines have the potential to induce sufficiently strong humoral and cellular responses in the general population. More specifically, it has been proven that IM administration of two mRNA vaccine doses can mediate a robust S protein-specific Ab production and a satisfactory CD4+ and CD8+ T-cell activation, while the viral-vectored ChAdOx1 nCoV-19 can cause sufficient NAb development and T-cell mobilization in the great majority of vaccines [6][7]. On the contrary, protein subunit and inactivated viral vaccines are poor inducers of CD8+ T-cells and mainly promote CD4+ Th responses and Ab formation [8]. Interestingly, based on phase 3 trial results, Windpessl et al. stated that, since mRNA vaccines had prevented COVID-19 in a larger proportion of participants compared to ChAdOx nCoV-19 [8][9][10], they could possibly be a more suitable solution for immunocompromised individuals [6].

In their review, Carr et al. support that a significant proportion of dialysis patients display Ab development after two vaccine doses; nevertheless, humoral immunity activation among them is still deficient in comparison to that of the general population, rendering them more dependent on the administration of booster doses in order to maintain protective

concentrations [11]. Indeed, according to the meta-analysis of Ma et al., dialysis patients had an 18% lesser possibility of producing anti-SARS-CoV-2 Abs, while no statistically significant difference was observed between peritoneal dialysis (PD) patients and healthy individuals [12]. Other investigators, however, described a similar humoral response, estimated by the anti-spike IgG levels, between PD and HD patients, with almost 50% of both groups developing detectable levels after the first dose and increasing to 90% following the second dose of vaccination [13].

It is, however, important to underline that, as their Ab-producing ability is markedly superior to that of renal transplant recipients (RTRs), completion of the vaccination scheme against SARS-CoV-2 prior to renal transplantation (RT) should be seriously considered in persons planning to receive a graft [11].

Cellular immunity activation has also been evaluated in various studies. In the research of Bertrand et al., almost all HD participants had developed a detectable spike-reactive T-cell response after the completion of the two-dose BNT162b2 series at levels comparable to those recorded in the general population [14]. The findings described above were consistent with those of Sattler et al., according to whom most individuals in HD have the potential to mount cellular and humoral anti-SARS-CoV-2 response after the administration of an mRNA vaccine [15]. However, Van Praet et al. stated that, in dialysis patients in their study, after vaccination with the mRNA-1273, both the mean IFN-γ release by circulating CD4+ and CD8+ T-cells induced by SARS-CoV-2 glycoprotein stimulation and the percentage of individuals having IFN-γ production above the cut-off value, was significantly lower than those of healthy controls. The same authors also observed that anti-SARS-CoV-2 response was even more compromised in the subgroup of hepatitis B virus (HBV) vaccination non-responders and supported that mRNA-1273 is more immunogenic than BNT162b2 in HD patients, possibly due to the presence of a higher mRNA dose in it [16]. Interestingly, a German team of researchers noticed that after two doses of BNT162b2, people in dialysis tend to display increased levels of proinflammatory cytokines (such as chemokine C-C motif ligand 2 (CCL-2) and IL-8), which reflects a more profound innate immune response activation (with the participation of monocytes, neutrophils, and endothelial cells), accompanied by an impaired SARS-CoV-2-specific T-cell response [17].

Nevertheless, even though vaccination against SARS-CoV-2 in individuals with ESKD or in HD mediates weakened and defective immune responses compared to the general population, it still offers remarkable clinical results, as it reduces the infection, hospitalization, and death rates in that group of patients [18].

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