A Review of Humoral and Cellular Immune Responses to SARS-CoV-2 Vaccination Following Solid Organ Transplantation

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The introduction of vaccines preventing a severe course of COVID-19 disease is particularly important in immunocompromised patients, among whom organ recipients and patients awaiting transplantation constitute a large group. The article is a critical review of 68 recent publications on the impact of the SARS-CoV-2 pandemic on transplantology worldwide. The study discusses research results concerning various aspects of SARS-CoV-2 vaccination in transplant patients; it also lists important factors influencing vaccination effectiveness. A suboptimal immune response to 2 doses of vaccine in this group of patients is a major challenge prompting further research. Therefore, this review aims to provide an update on the humoral and cellular immune responses to SARS-CoV-2 vaccination following solid organ transplantation.

Keywords: COVID-19 • COVID-19 Vaccine • Transplant Recipients • Immunocompromised Host • mRNA-1273 vaccine • mRNA Vaccine

Abbreviations: COVID-19 – coronavirus disease 2019; DSA – donor-specific antibodies; KTx – kidney transplants; LTx – liver transplants; SARS-CoV-2 – severe acute respiratory syndrome-related coronavirus 2

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Background

The first year of the COVID-19 pandemic resulted in a sharp decrease in the number of transplantations performed, both from deceased and living consenting donors. When comparing the number of transplantations carried out in the world year-on-year, the year 2020 saw a 17.5% decrease in the number of transplantations. This mostly involved kidney transplants (KTx) (decreased by 20.9%), pancreas transplants (decreased by 16.2%), lung transplants (decreased by 12.7%), liver transplants (LTx) (decreased by 11.3%), and heart transplants (decreased by 8%) [1]. In the United States, this resulted in an increase in patient mortality of up to 170% in patients awaiting transplantation, especially of the kidneys and lungs [2,3]. In Spain, the world leader in organ transplantation, the daily number of organ donations in the pandemic decreased from 7.2 to 1.2, and the number of transplantations performed decreased from 16.1 to 2.1 [4]. In Poland, in the beginning of the pandemic, the number of potential organ donors decreased by 43%, which resulted in a 60% reduction in the number of kidney and liver transplants performed [5]. The substantial decline in the number of transplantations was due to several factors. Firstly, there was concern about the life and health of patients from transplant waiting lists, as well as organ and bone marrow recipients, when exposed to SARS-CoV-2 infection. Transplantation centers in many countries recorded high mortality rates (up to 30%) caused by COVID-19 in this group of patients [6-11]. Secondly, limited access to intensive care units, where transplant patients would stay postoperatively and organ donors would be hospitalized. Moreover, for logistical reasons, constant testing for COVID-19 of both recipients and donors to monitor their infectious status was much more difficult [4,12-14]. To counter these very unfavorable tendencies, international transplant societies and transplantation centers developed guidelines to enable the continuation of organ transplantation. These activities, along with vaccinations against COVID-19 that began at the end of 2020, and gradually improved the situation [13-21]. The currently approved SARS-CoV-2 vaccines are BNT162b2 (Pfizer BioNTech) and mRNA-1273 (Moderna) containing mRNA encoding the S-glycoprotein (spike) of the virus [22,23] and 2 vector vaccines (ChAdOx1 nCoV-19 vaccine (AZD1222) AstraZeneca and Ad26.COV2.S Janssen) containing replication-defective adenovirus (vector) with an integrated fragment of SARS-CoV-2 genetic material encoding the S-glycoprotein [24,25]. Although transplant recipients can safely receive any type of inactivated anti-SARS-CoV-2 vaccine, mRNA preparations are preferred for vaccination against COVID-19 in people with severe or moderate immunodeficiency [26]. Introduced at in 2021, COVID-19 mRNA vaccines BNT162b2 (Pfizer BioNTech) and mRNA-1273 (Moderna) offer 90-100% humoral and cellular immunity, preventing the acute form of the disease [22,23]. However, this does not apply to immunocompromised patients, including transplant recipients on immunosuppression. Therefore, this review aims to provide an update on the humoral and cellular immune responses to SARS-CoV-2 vaccination following solid organ transplantation.

Vaccinations in Solid Organ Transplant Recipients

In 2 consecutive papers published in March and May 2021 in JAMA, Boyarsky demonstrated that on day 20 after the first dose of COVID-19 vaccination, antibodies were found in 17% of the examined transplant recipients, and on day 29 after the second dose of vaccination, antibodies were present in 54% of transplant recipients (48% of kidney transplants, 80% of liver transplants, 56% of heart transplants, 39% of lung transplants, and 20% of pancreas transplants). Thus, 46% of transplant recipients did not produce antibodies after 2 doses of mRNA vaccines [27,28]. Other researchers have also confirmed a worse response to vaccination in transplant patients, both in terms of humoral and cellular response. Immune response to 2 doses of vaccination was insufficient [21,29-32]; no immunity to infection was found in more than 40% of transplant recipients [21,29-32], especially in patients over 60 years of age, in whom the humoral response was only in 4.8% of the study participants [31]. In a study by Hall, involving 127 examined transplant patients, antibodies were found only in 5% of patients after the first dose and in 34.5% of patients after the second dose of mRNA-1273 (28.5% of kidney transplants, 72.7% of liver transplants, 12.5% of heart transplants, 41.4% of lung transplants, and 38.9% of pancreas with kidney transplants). Cellular response was found in 47.9% of patients [32]. In the author’s opinion, it may be the case that despite receiving 2 doses of vaccination, a significant proportion of transplant recipients will not produce a level of antibodies sufficient to protect themselves against infection, and in this group of patients an alternative treatment should be considered [32].

Vaccinations in Patients Awaiting Transplantation

A reduced response rate to vaccination was observed not only in organ recipients but also in patients awaiting transplantation: those receiving dialysis for renal failure and those with cirrhosis [33-36]. The dialysis patients and cirrhotic patients had a much weaker response to vaccination compared to the healthy general population, but better than those after KTx and LTx. As Crespo et al reported, positive response was obtained in 96.6% of healthy patients, 89.3% of patients on peritoneal dialysis, 77.6% of patients on haemodialysis, and 61.3% of KTx patients. The combined humoral and cellular immune response was 100% in healthy patients, 95.4% in dialysis patients, and...
78.8% in kidney transplant patients [34]. As Bertrand noted, SARS-CoV-2 vaccination is more efficient in patients on dialysis therapy than KTx recipients, indicating that vaccination should be first recommended for those registered on a waiting list for kidney transplant [37]. In yet another study, a similarly positive response was found among patients awaiting liver transplant: 100% for healthy patients, 65.4% for cirrhotic patients, and 36.6% for LTx patients [33]. Thuluvath and colleagues found that 24% of those with chronic liver diseases had undetectable or suboptimal antibody responses, and 61.3% of liver transplant recipients had a poor response. Antibody levels were completely undetectable in 17.8% of liver transplant recipients, in 3.8% of those with cirrhosis, and in 4.3% of those with chronic liver diseases without cirrhosis [38] (Table 1).

The humoral immune response after 2 doses of the COVID-19 vaccine in 30-50% of KTx patients and 80-95% of dialysis patients was insufficient [28,33,39], and, according to French authors, it is an indication for the administration of a third dose of the vaccine [36]. De Belo presented the results of a study on 396 transplant patients in whom the administration of the third dose increased the humoral response rate from 46.3% to 67.9%. In addition, in more than 40% of patients in whom there was no seroconversion despite the second dose, the third dose resulted in a humoral response [40]. Numerous authors have reported an improvement in the humoral response in organ recipients after the third dose of the vaccine [41–45], but it was also reported to be ineffective by others [32,33,46]. In view of this, Hall’s proposal of alternative treatment in patients without established seroconversion, despite vaccination, may be legitimate [32]. Possibly, the introduction of the fourth and fifth doses of vaccination in these patients might also be a solution [47,48].

Factors Influencing Response to Vaccination

Status Post-COVID-19 Infection

It has been observed that after the first dose of the vaccine, post-transplant patients who recovered from COVID-19 had antibody levels similar to the healthy, immunocompetent population [31,49–51]. This pattern was noted in both renal and hepatic transplant patients as well as in dialysis patients awaiting transplantation [31,49–52]. The humoral immune response was better in patients after a full-blown symptomatic course of infection and was found in 68.4% of patients, whereas seropositive results after a mild or asymptomatic course of infection were found in 9.4% and 4.6% of patients, respectively [31]. Despite the increase in immunity among organ recipients who recovered from COVID-19, most researchers agree that for the level of humoral response to be sufficient, 2 doses of the SARS-CoV-2 vaccine are required [49–51].

Type of Vaccine Used and Patient Age

The available recommended COVID-19 vaccines – BNT162b2 (Pfizer BioNTech) and mRNA-1273 (Moderna) – are highly

| Author of the study | Kidney transplant recipients (%) | Liver transplant recipients (%) | Heart transplant recipients (%) | Lung transplant recipients (%) | Pancreas ± kidney transplant recipients (%) | Haemodialysis patients (%) | Cirrhotic patients (%) |
|---------------------|----------------------------------|---------------------------------|---------------------------------|---------------------------------|------------------------------------------|--------------------------|----------------------|
| Marinaki [21]       | 20                               | –                               | 75                              |                                 |                                          |                          |                      |
| Boyarski [28]       | 48                               | 80                              | 56                              | 39                              | 20                                       |                          |                      |
| Grupper [29]        | 37.5                             |                                 |                                 |                                 |                                          |                          |                      |
| Shostak [30]        |                                  |                                 | 60                              |                                 |                                          |                          |                      |
| Hall [32]           | 28.5                             | 72.7                            | 12.5                            | 41.4                            | 38.9                                     |                          |                      |
| Ruether [33]        | 36.6                             |                                 |                                 |                                 | 65.4                                     |                          |                      |
| Crespo [34]         |                                  |                                 |                                 |                                 | 77.6                                     |                          |                      |
| Bertrand [37]       | 17.8                             |                                 |                                 |                                 | 88.9                                     |                          |                      |
| Thuluvath [38]      | 38.7                             |                                 |                                 |                                 | 76                                       |                          |                      |
| Narasimhan [55]     |                                  |                                 |                                 |                                 | 25                                       |                          |                      |
| Nazaruk [57]        | 88.9                             |                                 |                                 |                                 |                                          |                          |                      |
| Rabinowich [59]     | 47.5                             |                                 |                                 |                                 |                                          |                          |                      |

Table 1. Seropositive immune response for 2 doses of mRNA SARS-CoV-2 vaccine (%).
logical response to vaccination. There have been attempts to
administration of steroids [61] significantly reduce the sero-
high doses in triple immunosuppressive regimens [46,63], or
in the first year after transplantation [58], administration of
response was as high as 50% [36,46,62]. In addition, vaccination
recipients who were not administered this medication, the re-
non-suppressants has had the greatest impact on the recorded
The vast majority of researchers claim that the use of immu-
transplanted organ [45], a white blood cell count lower than
ogies reducing vaccine effectiveness of vaccines in patients
[31-33,46,57], research shows the importance of other pathol-
immunocompromised patients, among whom organ recipients and
study, Hall's proposal of alternative treatment in pa-
tation worldwide. The introduction of vaccines preventing a

Post-Vaccination Adverse Events

There is no information available on severe post-COVID-19
vaccination-associated complications in transplant patients
[40,44,46,47,58,60,61,65,66]. There have been no cases of the
presence of donor-specific antibodies (DSA) that could damage the
transplanted organ [58,60,67,68]. In a literature review on the
efficacy and safety of the administration of the third dose of
the vaccine based on data from 835 organ recipients, Efros
did not report any cases of anaphylactic shock or other life-
threatening complications. Typical adverse effects were mild
or moderate pain at the injection site, headache, and short-
term general weakness. In 1 case, mild rejection symptoms,
not requiring intensification of immunosuppression, were ob-
served on day 7 after the third dose of vaccine. According to
the researchers, the relationship between this incident and
vaccination is only hypothetical [44,46].

It is widely known that patient immunity after the second
dose of vaccine is insufficient [28,33,39]; hence, the introduc-
tion of the third dose, also not always effective [32,33,46]. In
view of this, Hall's proposal of alternative treatment in pa-
tients without established seroconversion, despite vaccina-
tion, may be legitimate [32]. Possibly, the introduction of the
fourth and fifth doses of vaccine in these patients might also
be a solution [47,48].

Conclusions

The aim of the above is to review the available literature on
the impact of the SARS-CoV-2 pandemic on organ transplan-
tation worldwide. The introduction of vaccines preventing a
severe course of COVID-19 is particularly important in immu-
nocompromised patients, among whom organ recipients and
patients awaiting transplantation constitute a large group. The
fact that there appeared so many scientific papers based on
post-transplant research in such a short period of time con-
tributed to transplantation safety. However, the suboptimal
response to vaccinations in this group of patients is a ma-
Jor challenge for both doctors and the patients themselves.
Further prospective studies assessing the response to vacci-
nation, antibodies levels, or COVID-19 incidence despite vac-
cination will certainly bring new data and provide answers to
many questions.
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