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COVID-19 Vaccines in Pancreatic Transplant Recipients: A Single-Center Observative Study

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ABSTRACT

The SARS-CoV-2 pandemic was a real test of doctors' abilities to adapt and respond to patients' needs. The course of infection varied from influenza-like symptoms to severe infections with multi-organ failure and death. Therefore, the possibility of vaccination against the COVID-19 virus brought great hope.

Since 2004, 240 pancreas and pancreas with kidney (simultaneous pancreas and kidney transplantation, pancreas after kidney, pancreas transplants alone) transplants were performed in our center. Currently, 130 transplant patients are under the care of the transplant clinic. All patients were informed about the possibility of vaccination against SARS-CoV-2 with the mRNA vaccine.

The aim of the study was to evaluate the development of antibodies to SARS-CoV-2 in patients who had previously undergone transplantation. Fifty-three patients were vaccinated with the full double dose and 37 patients received an additional third dose.

The level of antibodies in the IgM and IgG classes was assessed in patients' serum. The level of antibodies was assessed before administration of the vaccine and then after administration of the first and second doses.

Most patients had no response to vaccination after 1 dose of the vaccine and 21 patients achieved therapeutic antibody levels after the full dose of vaccination. However, the highest titer of immunoglobulins was found in recipients who received the third dose.

The use of vaccinations is safe and can protect the group of patients after pancreas transplantation from serious complications of SARS-CoV-2 infection despite the use of immunosuppressive drugs.

A steady increase in the number of transplants, as well as an increase in the reporting of potential organ donors, was observed in Poland before the COVID-19 pandemic. In the course of the COVID-19 pandemic, many hospitals were converted into COVID hospitals and therefore could not carry out transplantation activities. Data from 2020 showed that the number of reported organ donors and the number of organ transplants significantly decreased (Table 1). In March 2020, the Polish Transplantation Society issued recommendations limiting the possibility of pancreatic transplantation due to the lack of urgent indications for this organ transplant the need to use depressive immunosuppression, which potentially causes a long-lasting reduction in immune immunity. In May 2021, the system of care for patients with COVID-19 changed in Poland, and COVID hospitals ceased to function and returned to the full range of activities. Despite this, the number of reported organ donors and organ transplants performed only slightly increased.

The Polish Society of Transplantation recommended administering COVID-19 vaccinations to patients after organ transplantation and to patients on dialysis awaiting transplantation. Chronic patients on dialysis with end-stage renal disease are known to have a lower response to vaccination than

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Table 1. Number of Organ Transplants in Poland, 2018-2021

Year	Donors	Actual Donors	No. of Organ Transplantations	No. of Kidney Transplantations	No. of Pancreas Transplantations
2018	638	498	1390	884	21
2019	639	502	1473	907	34
2020	529	393	1180	717	4
2021	546	396	1274	709	20

immunocompetent individuals, but this response is believed to be better in comparison to immunity after organ transplantation. After transplantation, antibodies produced after vaccination disappear faster, so patients awaiting transplantation should be vaccinated. Posttransplant vaccination should be performed about 4 weeks after surgery or after 3 to 6 months if depleting immunosuppression was used. Live vaccines are contraindicated after transplantation. The vaccines against SARS-CoV-2 infection currently available on the market are inactivated vaccines and can be used in patients after organ transplantation [1−10].

The aim of this study was to analyze the safety and efficiency of COVID-19 vaccination in a group of patients after pancreas transplantation.

MATERIAL AND METHODS

Prospective observation of all patients after pancreas transplantation was performed. Out of 240 patients, 53 were fully vaccinated. The choice of vaccination was done following guidelines of the Polish Ministry of Health. Patients after organ transplantation are recommended to receive an mRNA vaccine. Two recipients were excluded from the study because of adenovirus vaccination. One was vaccinated with a double dose (Vaxzevria, AstraZeneca) because of the patient's occupation (adenovirus vaccines were available sooner and recommended for teachers). One patient received a single dose of adenovirus vaccine (Jansen/JNJ) outside our center. At the beginning of the observation, there was no selection of vaccines due to limitations in delivery. Second and third doses were administrated according to the product used the first time.

An analysis of time from the transplant, age, and sex was performed. We also gathered information about SARS-CoV-2 infection before and after vaccination. The level of serum antibodies in the IgM and IgG classes was assessed in patients' serum (Anti-SARS-CoV-2 QuantiVac QuantiVac ELISA enzyme-linked immunosorbent assay IgG, BAU/mL). The level of antibodies was assessed before administration of the vaccine and then after administration of the first and second doses 3 weeks after vaccination.

We also collected data on side effects like fatigue, muscle pain, fever, and possible adverse events after each vaccine.

Surgical Technique

Our surgical technique was described in our previous articles [11−14]. We perform a double-layer duodenojejunal anastomosis, reconstruct the pancreas graft's arterial blood supply into a Y-graft from the iliac artery of the donor anastomosed to the supramesenteric and splenic arteries, and perform a single-layer continuous anastomosis to the common iliac artery. In most cases, we do not perform a portal vein reconstruction. Most often we use a left kidney and a retroperitoneal approach.

Observation and Comprehensive Management

In our clinic, we prefer regular patient visits including clinical examination and laboratory tests every 2 to 3 weeks in the first quarter after transplantation. We use a 3-drug immunosuppression scheme with induction with polyclonal antibodies thymoglobulin in a total dose of 1.5 mg/kg. We start with a low-molecular-weight heparin in a single or double dose. Three months after transplant, hospitalization with computed tomography and laboratory tests is planned. Low-molecular-weight heparin is changed to 75 mg of acetylsalicylic acid daily. In the next quarter, visits are made approximately every 6 to 8 weeks on an outpatient basis. Another hospitalization occurs 1 year after the transplant, and in subsequent years, outpatient visits occur every 3 months.

During outpatient examinations, we always measure peripheral blood counts, electrolytes, creatinine levels, estimated glomerular filtration rate, pancreatic enzymes, urinalysis, C-peptide levels, HBA1, and the concentration of immunosuppressants. Depending on the patient's condition or test results, we can additionally perform imaging tests; for example, ultrasound. Once a year we measure the level of tumor markers [carcinoembryonic antigen (CEA), prostate-specific antigen (PSA), The cancer antigen 125 (CA 125), CA 19-9] and cytomegalovirus deoxyribonucleic acid (CMV DNA).

A dermatologic evaluation is required at least once a year because of the increased risk of skin cancer after organ transplantation.

During hospitalization, after 3 months, after 1 year, or, if necessary, we perform imaging tests, including computed tomography, to assess the transplanted organs' functions, morphology, presence of pathologic reservoirs, connections, pseudoaneurysms, aneurysms, etc.

Each transplant consultation is associated with a decision about the possible modification of immunosuppression or other drugs taken chronically, setting the date of the next visit, and planning imaging tests and possible hospitalization.

In 2020, due to the COVID pandemic, patients at the Transplant Outpatient Clinic were informed about the benefits of vaccinating against this disease. They had the opportunity to get vaccinated at a hospital vaccination point, and during laboratory tests they had antibodies against COVID-19.

RESULTS

Fifty-one patients were fully vaccinated by September 2021. The mean age of the group was 46 years (range, 29-69; SD = 9.23). There were 23 females in the group. There were 46 patients after simultaneous pancreas and kidney transplantation, 4 pancreas transplants alone, and 1 pancreas after kidney.

Forty-seven patients received a double dose of BNT162b2 (BioNTech, Pfizer, Germany), 4 received a double dose of mRNA-1273 (Moderna, NIAD, Rockville, MD, United States). The mean time from pancreas transplant to vaccination was 6.37 years (range, 1-16; SD = 3.829) (Fig 1). Thirty-seven patients received an additional dose. The mean time from the first to the third dose was 6 months (range, 2.5-9.5; SD = 1.3). In 3 cases it was mRNA-1273 and in 34 it was BNT162b2 (Fig 2).

The mean IgG before the vaccination was 420.62 BAU/mL (range, 1.9-1700; SD = 673). IgM was positive (>1) in 7 cases. Fourteen patients had a history of SARS-CoV-2 infection before the vaccination. The mean IgG after I dose of

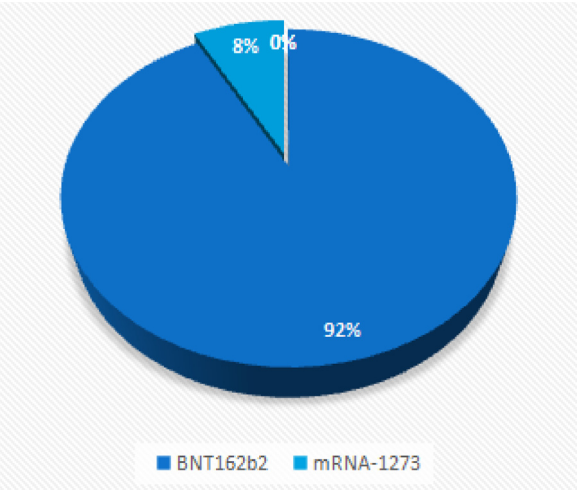

Fig 1. Distribution of the type of vaccination, doses 1 and/or 2.

vaccination was 53.67 BAU/mL (range, 4.8-55.2; SD = 48) and 383.76 BAU/mL (range, 4.8-2080; SD = 669) after the second dose (Fig 3 and Fig 4).

The mean IgG after the third dose was 219 BAU/mL (range, 4.8-1370; SD = 355). We did not observe any difference in the levels of IgG between the vaccination types. Five patients had SARS-CoV-2 infection after full vaccination.

Patients who had lower IgG after the second dose more often developed SARS-CoV-2 infection ($P < .001$; Fig 5). A third vaccination prevented infection ($P < .005$). Forty-three percent of patients without a third dose were ill compared to only 21% after the third dose.

No severe side effects were observed. The most common complaint was fatigue and influenza-like disorders that were transient and lasted up to 3 days.

DISCUSSION

Patients after pancreatic transplantation are a very small group of patients undergoing vascularized organ transplantation.

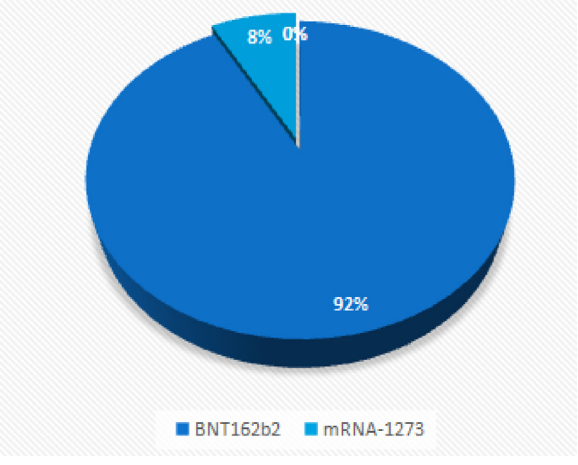

Fig 2. Distribution of the type of vaccination, dose 3.

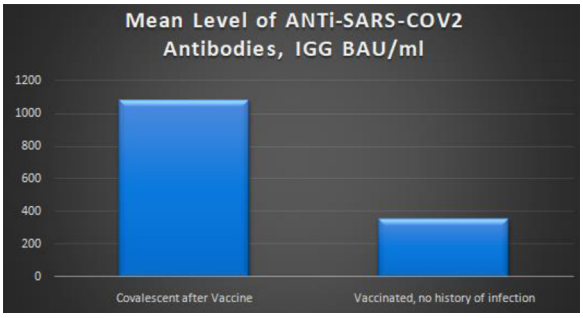

Fig 3. Level of antibodies in 2 groups of pancreas transplantation recipients: those who recovered from COVID-19 and those with no history of infection.

Annually in Poland they comprise about 1.5% to 2.0% of transplants. Therefore, posttransplant care must be carried out in specialized centers.

To our knowledge, this is one of the first observative studies of pancreas recipients vaccinated with a third dose. An Italian group reported an analysis of 25 pancreas transplants alone and simultaneous pancreas and kidney transplant recipients who received 2 doses of COVID-19 vaccine. They did not find significant differences in the analyzed parameters: graft function, inflammation, or autoimmune reactivation. Seven patients had elevated D-dimer and 12 had an increase in C3 factor [15].

Though the risk of lethal complications from COVID-19 among pancreas transplant recipients was well known, the availability of the vaccine was limited and the onset of vaccination was delayed. Such a trend was not only observed in our cohort. Only 2 of our patients were vaccinated in January 2021 when the governmental program started and vaccination was available for health care providers and the elderly. Also, patients' hesitation was an important cause of delay in immunization. In a retrospective study, Tsapepas et al analyzed solid organs recipients (kidney or pancreas) who were willing to be vaccinated and reported that 110 out of 320 patients were not interested in vaccination. Recipients willing to get the vaccine were older ($P < .001$) [16].

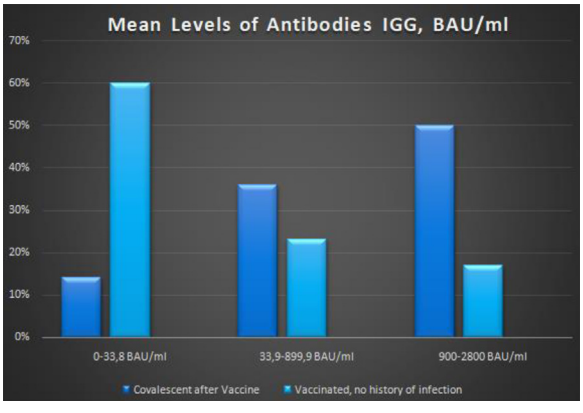

Fig 4. Levels of IgG antibodies in serum of pancreas recipients.

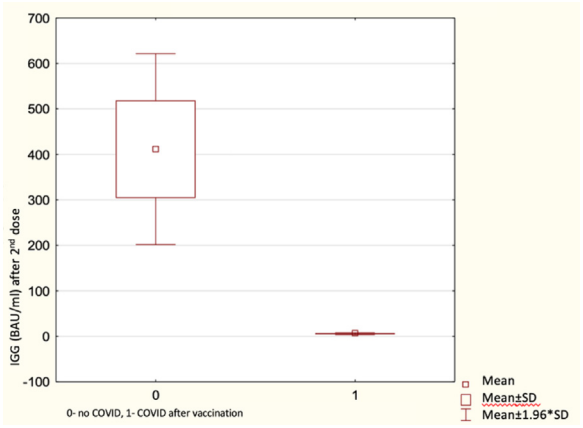

Fig 5. Box plot presenting the level of anti–COVID-19 IgG depending on infection after vaccination.

Data regarding pancreas recipients are limited. There are, however, several studies that prove safety among kidney recipients. One adverse event, manifested with the development of donor-specific antibodies, was reported by Massa et al after the second dose [17]. No cases of graft loss or clinical signs of rejection were observed [17]. We did not observe any serious adverse events, and those reported did not differ from side effects reported by healthy vaccinated individuals.

COVID vaccines were designed to develop effective immunity, both humoral based on the production of antibodies against SARS-CoV-2 and cellular immunity formed by T lymphocytes. The humoral response, despite being only one part of the immunity, is the easiest to detect and evaluate because of the widespread use and standardization of tests. IgM antibodies are the first to be detectable in human blood and prove the initial stages of infection. They usually appear in the blood between 3 and 6 days after the beginning of the infection. Around day 8, IgG antibodies that persist after infection and vaccination against COVID-19 can be detected [18]. In our center, antibodies were determined by chemiluminescence, which is based on the measurement of chemiluminescence in the collected blood. It also uses spike protein (S), which in its structure contains a receptor-binding protein. This domain guarantees that the virus gets into the host cell. Antibodies directed against this protein neutralize the virus. The purpose of vaccination is to produce antibodies directed against protein S. Accurate measurement of the postvaccination humoral response allows to predict whether people are protected from infection. However, it should be remembered that the development of the postvaccination response is influenced by many individual factors, and it also depends on the type of vaccine used. Antibody values above 33.8 BAU/mL were considered positive, and values below 33.8 BAU/mL were considered negative [18].

Vaccination does not prevent SARS-CoV-2 infection among healthy volunteers, and patients on immunosuppression seem to be at a higher risk. There are data suggesting that solid graft recipients did not develop sufficient humoral immunization after 2 doses of the BNT162b2 vaccine and still remained at risk of infection [19,20]. Up to 75% of kidney recipients did not have an optimal response [21]. The suboptimal response might be due to immunosuppressive agents [22]. Mycophenolate mofetil decreases the proliferation of helper CD+T lymphocytes and interferes with antibody production by B lymphocytes [22], and the exact response of specific SARS-CoV-2 T cells after vaccination is still not fully proven [23]. Long-term care for patients after organ transplantation involves the need to respond to various population situations, such as pandemics and changes in the availability of immunosuppressive drugs, but also individual needs such as planning procreation and the need to modify and change immunosuppressive drugs. Based on preliminary results, Caillard and Thaunat debated the effect of lowering the dose of mycophenolate mofetil or replacement with belatacept [22]. The findings of Cucchiari et al showed that half of patients with negative antibodies after vaccine developed a humoral response and the absence of antibodies does not mean lack of immunity [24]. Dialysis might be responsible for impairment of cellular and humoral responses in the course of SARS-CoV-2 infection [25]. Data showed that the third dose of vaccination provides sufficient immunization among pancreas and kidney recipients [26,27]. In our cohort, after the third dose, patients were less likely to have COVID-19 infection.

We excluded patients after adenovirus vaccinations from the study group, because there were no recommendations from the Polish Health Ministry and patients were vaccinated outside our clinic. Moreover, some data showed that adenovirus vaccines (Jansen) provide a worse humoral immunity than mRNA vaccines [21].

Meshram et al reported 2 cases of serious COVID-19 in kidney recipients after 2 doses of the Oxford-Astra Zeneca vaccine and 2 after BBV152 (Covaxin, India) [28]. We have previously described the course of COVID-19 in kidney recipients [29]. In our cohort, after 2 or 3 doses, recipients had a mild course of the infection.

CONCLUSIONS

mRNA vaccines are safe and should be recommended to patients after pancreas transplantation. We observed no severe side effects after vaccination. A third dose should also be considered, because our data as well as other observations prove that immunization gained after an additional dose is sufficient to prevent infection.

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