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Serologic status according SARS-CoV-2 in patients after orthotopic heart transplantation (HTx)

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Title: Serologic status according SARS-CoV-2 in patients after orthotopic heart transplantation (HTx)

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Abstract

Serologic status according SARS-CoV-2 in patients after orthotopic heart transplantation (HTx)
Background: pandemic SARS-CoV-2 is still ongoing. In this context, patients after organ transplantation are especially endangered due to their increased susceptibility to infections. Real effectiveness of vaccinations against SARS-CoV-2 and exposition to the virus in population after organ recipients is still being assessed.

Methods: We investigated 371 adult pts (17.3% women), aged 54 ±14 years, median time from transplantation 1296, IQR: 473-400 days after orthotopic heart transplantation consecutively admitted to Transplant Centre in the timeframe between February and September 2021. SARS-CoV-2 spike protein antibodies were assessed quantitatively by Elecsys® Anti SARS-CoV-2 S, Cobas – Roche. Data according past COVID-19 infection and vaccination were compared with the test results.

Among the whole group, 59 pts were unvaccinated and had no past COVID-19 infection, full course of vaccination (two doses) with mRNA vaccine had 200 pts, one patient received viral vector vaccine, after single dose of two-doses vaccine were 11 pts, after the infection were 99 pts. Median time from vaccination to antibodies’ assessment was 54 days, IQR: 30-76 days.

Aim: Determination of exposure to the virus among patients after HTx before the vaccination and humoral response to the vaccination. Assessment of the role of anti-spike antibodies in the prevention of infection.

Results After vaccination 22.3% (45 pts) had no antibodies, 47.3% (95 pts) had titer between 0.8 U/ml (0.82 BAU/ml) and 250 U/ml (257.25 BAU/ml), 30.2% (61 pts) had titer above 250 U/ml (257.25 BAU/ml). After single dose of two-doses vaccine 63% pts had no antibodies. In the group of unvaccinated patients, 3 pts (5.1%) had the titer above 250 U/ml (257.25 BAU/ml), 12 pts (20.3%) had the titer up to 250 U/ml (257.25 BAU/ml).

In the patients after COVID-19 only 2% did not show anti-spike antibodies, in 61.4% their titer was above 250 U/ml (257.25 BAU/ml).

In the group of patients infected after the full course of vaccination (4 pts after single dose of two dose vaccine, 2 after two doses), none of the patients developed antibodies after the vaccination. Up to end of September 2021, none of the patients with antibodies against SARS-CoV-2 developed COVID-19.
Conclusion: we suppose, that presence of spike protein antibodies may be relevant marker of effective vaccination. In the HTx group exposition to SARS-CoV-2 is high.

Keywords: COVID-19 vaccinations, SARS-CoV-2 infection, heart transplantation
Background
Due to wide spectrum of symptoms or even asymptomatic course [1] of SARS-CoV-2 infection in patients after orthotopic heart transplantation (HTx) the real exposition to the virus is not known. Both, the vaccination against the virus and the infection itself elicit anti-spike antibodies, known of its neutralizing potential to the virus [2]. Parallely, both the vaccination and the infection may induce cellular response, that may be present also in the absence of humoral response [3]. Efforts are made to assess the effectiveness of vaccinations against COVID-19 in patients after solid organ transplantation.

Aim of the study:
Determination of antibody response to anti SARS-CoV-2 vaccination in cohort of patients after HTx. Determination of exposure to the virus among patients after HTx before the vaccination. Assessment of the role of anti-spike antibodies in the prevention of infection.

Materials and methods:
Single center prospective observational study. Included were consecutive adult patients admitted to transplantation ward or transplantation ambulance between February 2021 and September 2021. The whole analyzed group consisted of 371 patients (17.3% women) after HTx. Mean age of investigated patients was 54 ±14 years, median 58, IQR: 44.8-65.6 years.

Median time from transplantation was 1296 (IQR: 473-4001) days.
Data according current and previous COVID-19 infection were compared with the test results. Among the whole group 59 pts were unvaccinated and had no known past COVID-19 infection, 201 patients after full course of vaccination (two doses) with mRNA vaccine, one patient received viral vector vaccine. Among the investigated group were 11 patients after single dose of two-doses vaccine (partially vaccinated) and 99 pts after the infection. Median of the time from vaccination to antibodies’ assessment was 54 days, IQR: 30-76 days.
Assessed were anti SARS-CoV-2 antibodies determined by quantitative method: Elecsys® Anti SARS-CoV-2 S, produced by Cobas – Roche. The sensitivity and specificity of the test are 84% and 100% accordingly [4]. The positive cut-off was at least 0.8 U/mL.

The study was performed in accordance with the Declaration of Helsinki. The Bioethics Committee of the Medical University of Silesia gave permission to keep the study (decision No. PCN/CMN/0022/KB1/30/21.

Statistical analysis

Categorical variables were presented as counts and percentages. Continuous variables were presented as the mean and standard deviation or median with lower and upper quartiles.

Results

Among the fully vaccinated patients 45 (22.3%) did not produce antibodies. Among the seropositive patients 61(30.2%) have titer above 250 U/ml (257.25 BAU/ml). Among partially vaccinated patients (after single dose of two-doses vaccine), 63% of pts did not produced antibodies. In the group of unvaccinated patients in 3 pts (5.1%) titer above 250 U/ml (257.25 BAU/ml) was observed, in 12 pts (20.3%) the titer was up to 250 U/ml (257.25 BAU/ml).

In patients after COVID-19 infection only 2% did not show anti-spike antibodies, in 61.6% the titer was above 250 U/ml (257.25 BAU/ml).

In the group of patients who were infected after the full course of vaccination (4 pts after single dose of two doses vaccine, 2 after two doses), none of the patients had developed antibodies after the vaccination. Up to end of September 2021 none of the patients with presence of antibodies against SARS-CoV-2 spike protein did not developed COVID-19. Detailed clinical characteristics is presented in Tab. 1

Discussion

Patients receiving immunosuppression are especially vulnerable group and in the context of pandemic, achieving adequate response to the vaccination against SARS-CoV-2 is pivotal. General population studies showed high efficacy of vaccines against SARS-CoV-2 infection [5], but in case of immunocompromised patients the response is impaired. Among patients after renal transplantation the
antibody response was low – only 36.4% showed antibody response to the vaccination [6]. In small group of patients after heart transplantation (26pts) the rate of seroconversion was only 34.8% [7]. Authors like Boyarsky et al. [8] in inhomogeneous group of solid organ transplant recipients showed lowered seroconversion rate after single dose (17%) and two doses (54%) of mRNA vaccine [9]. In this context, our group showed surprisingly high seroconversion rate. The observation is particularly interesting, because our group was vaccinated by mRNA- vaccine (the same as in previously cited studies) and for the antibody assessment we used one of the two assays applied in their studies. The main difference was, that our group comprised only patients after heart transplantation.

It is worth of mentioning that some patients in unvaccinated group, defining themselves as patients with no previous COVID-19 had positive antibodies. Having in mind 100% specificity of the used assay we suggest, that they were convalescents from asymptomatic infection. Furthermore, none of the patients who developed antibodies after the vaccination presented SARS-CoV-2 infection. However, the observation was made during waning of the virus in our population. The long-term observations are needed.

Simultaneously, it is suggested that level of anti-spike (neutralizing) antibodies, that we assessed is connected with degree of protection against the infection [10, 11]. The protective level is still to be estimated, but it is suggested, that antibody titer higher than 100 BAU/ml may be protective [12]. Other authors suggest that the protective value against severe form of exceeds 265 BAU/ml.

There is also a possibility of existence of cell-mediated (T Cells and NK T Cells) response to the vaccine even in the absence of humoral response [10]. Additionally, important role against the infection may play innate immunity independent from vaccinations.

Up to now, the routine estimation of antibody titer is not recommended by the Food and Drug Agency and other organizations [10].

Due to weakened response to the vaccination many strategies to improve vaccination efficacy are proposed: the third dose of the vaccine [13], lowering of the immunosuppression prior to vaccination, especially cessation of antimetabolites, immunization with different types of the vaccine [14], immunizations based on antibody response [15].
Due to impaired access to medical resources in the pandemic we suggest rather as the safest option the double strength vaccination of SOT recipients rather than modification of immunosuppressive regimen, which may potentially lead to graft rejection. Assessment of antibodies may be beneficial option, but is connected with additional medical visits. We feel that investigations in these two directions should be performed.

Limitation of the study:

Observation was made before fourth wave of pandemic. During the observation period number of infections in the general population was low. Furthermore, we did not assess response of B and T lymphocytes.

Conclusion

Exposition to SARS-CoV-2 virus in the population of patients after HTx is high. Probably some of the infections were asymptomatic. The reaction to vaccination is surprisingly high (when compared to other SOT recipients), but the titers are low. It is not certain if high titers of anti-spike antibodies prevent from infection or severe course of COVID-19 in this group of patients, but the lack of the antibodies should prompt higher infectious vigilance in case of exposition.

Literature:

1. Kolonko A, Kuczaj A, Musialik J et al. Clinical insights into the role of immunosuppression and its disturbances in solid organ transplant recipients with coronavirus disease 2019. PAMW. 2021; doi:10.20452/pamw.16139.
2. Calllard S, Thaunat O. COVID-19 vaccination in kidney transplant recipients. Nature Reviews. Nephrology. 2021; https://doi.org/10.1038/s41581-021-00491-7.
3. Schmidt T, Klemis V, Schub D et al. Cellular immunity predominates over humoral immunity after homologous and heterologous mRNA and vector-based COVID-19 vaccine regimens in solid organ transplant recipients. Am J Transplant. 2021; 00:1–13.
4. Liu Q, Qin C, Liu M et al. Effectiveness and safety of SARS-CoV-2 vaccine in real-world studies: a systematic review and meta-analysis. Infectious Diseases of Poverty. 2021; 10:132. Available from: https://doi.org/10.1186/s40249-021-00915-3 Accessed 02.12.2021.

5. Higgins V, Fabros A, Kulasingam V. Quantitative measurement of anti-SARS-CoV-2 antibodies: analytical and clinical evaluation. J Clin Microbiol. 2021; 2021 Mar 19;59(4):e03149-20. doi: 10.1128/JCM.03149-20.

6. Rozen-Zwi B, Yahav D, Agur T et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. Clinical Microbiology and Infection 2021; 27:1173.e11173.e4.

7. Mazzola A, Todesco E, Drouin S et al. Poor Antibody Response After Two Doses of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine in Transplant Recipients. Clinical Infectious Diseases. 2021; XX(XX):1–4

8. Boyarsky BJ, Werbel WA, Avery RK et al. Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients. JAMA.2021; 325(17):1784-1786.

9. Boyarsky BJ, Werbel WA, Avery RK et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA. 2021 Jun 1;325(21):2204-2206. doi: 10.1001/jama.2021.7489.

10. Joint Statement about Vaccine Efficacy in Organ Transplant Recipients. ISHLT-AST. Available from: www.ishlt.org. Accessed 02.12.2021.

11. Harvey RA, Rassen JA, Kabelac CA. Association of SARS-CoV-2 seropositive antibody test with risk of future infection. JAMA Intern Med. 2021; Available from: https://doi.org/10.1001/jamainternmed.2021.0366. Published online 24th February. Accessed 02. December 2021.

12. Bozkurt B, Fedson SE. Cardiac Transplant Patients Should Receive a Booster For COVID-19 Vaccination. https://www.acc.org/latest-in-cardiology/articles/2021/08/13/16/21/cardiac-transplant-patients-should-receive-a-booster-for-covid-19-vaccination. Accessed: 01.12.2021.
13. Pfizer. Pfizer and Biontech initiate a study as part of broad development plan to evaluate Covid-19 booster and new vaccine variants. 2021 Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-study-part-broad-development. Accessed 02. December 2021.

14. Ledford H. Could mixing COVID vaccines boost immune response? Nature. 2021; 590:375e6.

15. Manisty C, Otter AD, Treibel TA et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2- infected individuals. Lancet. 2021;. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00501-8/abstract. Accessed 02. December 2021.
|                                | Unvaccinated/ no past COVID-19 | Vaccinated (2 doses) | Vaccinated partially (1 dose) | Past COVID-19 infection | Total No. (%) |
|--------------------------------|--------------------------------|----------------------|-------------------------------|-------------------------|---------------|
| **No. of pts**                 | 59                             | 202                  | 11                            | 99                      | 371           |
| **Age, median (IQR)**          | 52.5 (38.9-63)                 | 61.2 (48.1-66.4)     | 57.1 (48.6-62.7)              | 55.8 (43.1-64.6)        | 54 (44.8-65.6) |
| **Gender, female, n (%)**      | 8 (13.6%)                      | 36 (17.8%)           | 1 (9.1%)                      | 19 (19.2%)              | 64 (17.3%)    |
| **Time post transplant, median (IQR)** | 1951 (925-3733)              | 1620 (591-4766)      | 927 (144-1506)                | 1443 (369-4367)         | 1296 (473-4001) |
| **Oryginal cardiovascular disease (cardiomyopathy, No. (%)** |                                      |                       |                               |                         |               |
| Ischemic                       | 17 (28.8%)                     | 77 (38.1%)           | 7 (63.6%)                     | 33 (33.3%)              | 134 (36.1%)   |
| Hypertrophic                   | 4 (6.8%)                       | 9 (4.5%)             | 0 (0%)                        | 3 (3%)                  | 16 (4.3%)     |
| Dilated                        | 33 (55.9%)                     | 80 (44.6%)           | 8 (27.3%)                     | 48 (48.5%)              | 174 (46.9%)   |
| Valvular                       | 1 (1.7%)                       | 4 (2.5%)             | 0 (0%)                        | 2 (2%)                  | 7 (1.9%)      |
| Arrhythmic                      | 0 (0%)                         | 3 (1.5%)             | 0 (0%)                        | 2 (2%)                  | 5 (1.3%)      |
| Restrictive                    | 0 (0%)                         | 7 (3.5%)             | 1 (9.1%)                      | 4 (4%)                  | 12 (3.2%)     |
| Congenital heart disease       | 0 (0%)                         | 5 (2.5%)             | 0 (0%)                        | 2 (2%)                  | 7 (1.9%)      |
| Other                           | 4 (6.8%)                       | 7 (2.5%)             | 0 (0%)                        | 5 (5.1%)                | 16 (4.3%)     |
| **Antibody status, No. (%)**   |                                |                      |                               |                         |               |
| <0.8U/mL                       | 44 (74.6%)                     | 45 (22.3%)           | 7 (63.6%)                     | 2 (2%)                  | 98 (26.4%)    |
| 0.8-250 U/mL                   | 13 (20.3%)                     | 96 (47.5%)           | 4 (36.4%)                     | 36 (36.4%)              | 148 (39.9%)   |
| >250U/ml                       | 3 (5.1%)                       | 61 (30.2%)           | 0 (0%)                        | 61 (61.6%)              | 125 (33.7%)   |