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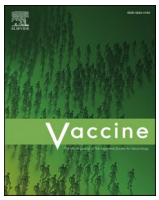
Vaccine 45 (2025) 126617

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Short communication

Timing of rejection events preceded by Covid-19 mRNA vaccination in recipients of solid organ transplants

Quentin Perrier [a], Johan Noble [b], Agnès Bonadona [c], Caroline Augier [d], Thomas Jouve [b], Aude Boignard [d], Loïc Falque [e], Salomé Gallet [f], Pierrick Bedouch [g], Lionel Rostaing [b], Olivier Epaulard [f,*], on behalf of INTEGRAL Study Group

[a] Univ. Grenoble Alpes, LBFA, INSERM, U1055, Pôle Pharmacie, Grenoble Alpes University Hospital, Grenoble, France
[b] Univ. Grenoble Alpes, Nephrology, Hemodialysis, Apheresis and Kidney Transplantation Department, Grenoble Alpes University Hospital Grenoble, France
[c] Univ. Grenoble Alpes, Hepatogastroenterology department, Grenoble Alpes University Hospital, Grenoble, France
[d] Univ. Grenoble Alpes, Cardiology department, Grenoble Alpes University Hospital, Grenoble, France
[e] Univ. Grenoble Alpes, Pneumology and Physiology department, Grenoble Alpes University Hospital, Grenoble, France
[f] Univ. Grenoble Alpes, Groupe de Recherche en Infectiologie Clinique, CIC-1406, INSERM, Infectious diseases department, Grenoble Alpes University Hospital, Grenoble, France
[g] Univ. Grenoble Alpes, TIMC, CNRS, UMR5525, Pôle Pharmacie, Grenoble Alpes University Hospital, Grenoble, France

ARTICLE INFO

Keywords:
SARS-CoV-2
Covid-19
Vaccin
Solid-organ transplantation
Rejection

ABSTRACT

Objectives: SARS-CoV-2 mRNA vaccine reactogenicity has raised concerns regarding the risk of rejection in solid organ transplant recipients. We explored whether SOT recipients diagnosed with acute rejection had previously received a vaccine injection within a timeframe consistent with a causal link.
Methods: We identified all SOT recipients with a diagnosis of acute rejection from 2020 to 2022 and who had previously received a SARS-CoV-2 vaccination, and analysed whether the delay between vaccination and rejection was constant.
Results: In the 45 identified patients, median delay between the last SARS-CoV-2 vaccination and the rejection was 102 days [IQR 48–178]; the continuous distribution of this delay, with no identifiable time pattern, is not in favor of a role of vaccination in rejection.
Conclusion: SARS-CoV-2 mRNA vaccination is unlikely to trigger rejection in SOT recipients.

1. Introduction

The aim of vaccination is to obtain an immune response toward a precise target; by the past, such an action had raised concern regarding the bystander risk of induction of transplant rejection in solid organ transplant (SOT) recipients. Indeed, it had been evoked that the activation of the immune system secondary to vaccination (rather than the mounting of the specific immune memory toward the vaccine antigen) could by non-specific pathways lead to the activation of allogeneic T lymphocytes, a parallel being made with the risk of rejection in SOT recipients experiencing a CMV infection [1]. However, numerous studies had explored this risk, and have produced reassuring data regarding various vaccines. E.g., in a recent meta-analysis [2], the administration of various unadjuvanted (influenza) or aluminum-adjuvanted (hepatitis B, pneumococcus, human papillomavirus) vaccines, and even live attenuated vaccines (varicella, and measles) to SOT recipients was not associated with an higher risk of post-vaccination rejection events. In addition, an inactivated AS01B-adjuvanted vaccine (herpes zoster vaccine) demonstrated a favorable safety profile as well [3].

SARS-CoV-2 vaccines, particularly mRNA vaccines, are associated with reactogenicity events (such as chills, fever, fatigue, and local pain) more frequently than most others vaccines [4]; post-vaccination myocarditis is an illustration of a unusual bystander [5] effect of aberrant immune activation triggered by these vaccines [6]. Therefore, concerns were emitted regarding the risk of rejection as another bystander effect of mRNA vaccines. A 2021 study [7] conducted in 127 SOT recipients observed no rejection episodes up to 6 weeks after a second dose. However, a 2022 review of literature [8] identified 56 rejection cases following SARS-CoV-2 vaccination, but 37 reports

* **Corresponding author at:** Olivier EPAULARD, infectiologie, CHU Grenoble Alpes, 38043 GRENOBLE, FRANCE.
E-mail address: oepaulard@chu-grenoble.fr (O. Epaulard).

https://doi.org/10.1016/j.vaccine.2024.126617
Received 31 July 2024; Received in revised form 7 December 2024; Accepted 10 December 2024
Available online 18 December 2024

concerned cornea transplantation, which suggests that either this organ is particularly sensible to vaccine-induced rejection, or that reporting has not been homogeneous across transplanted organs; the results of a more recent study [9] do not support the first. In addition, a 2022 report [10] detailed a case series involving five liver transplant recipients who manifested biopsy-proven acute cellular rejection 7 to 19 days following administration of a mRNA SARS-CoV-2 vaccination (first or second dose). We therefore aimed to assess our local cohort of solid organ transplant recipients to ascertain the potential correlation, if any, between SARS-CoV-2 vaccination and the occurrence of transplant rejection.

2. Methods

This was a retrospective, observational, monocentric study. All adults from our center (Grenoble-Alpes University Hospital, France) who had received a heart, kidney, liver, or lung transplantation, and that had experiment acute cellular or humoral rejection between January 2020 and September 2022 were included. Rejection was defined according to Banff classification for liver and kidney transplants, and ISHLT classification for heart and lung transplants. A patient with SARS-CoV-2 infection at the time of rejection has been excluded from the analysis. The date of the last injection of SARS-CoV-2 vaccine was collected to determine the delay between with the rejection, and to analyze whether it was constant, suggesting rejection trigger by the vaccination.

3. Results

A total of 95 SOT recipients with a diagnosis of rejection were included: 83.2 % with kidney transplantation, 12.6 % with liver transplantation, and 4.2 % with heart transplantation (no rejection in lung transplant recipients); 48 % of patients were male. Among all the patients, 61 (64.2 %) had a previous episode of an acute rejection (a median of 15.8 [10.5–31.0] months before the rejection episode included in this study). The median time elapsed since transplantation was 12.5 months (IQR 3.0–50.4). Median age at the time of rejection was 53.1 years (IQR 41.1–63.2). At the time of rejection, immunosuppression regimen featured calcineurin inhibitor (100 % of patients), steroids (83 %), mycophenolate acid (80 %), m-Tor inhibitor (11 %), and azathioprine (1 %). Fifty (52.7 %) had not received anti-SARS-CoV-2 vaccination before the rejection (mostly because the rejection occurred before the vaccines being available), and 45 (47.3 %) had received it (Table 1 shows the characteristics of patients whose rejection occurred after vaccination or not); the rejection occurred after the first, second, third and fourth dose of mRNA vaccine in 8, 9, 23 and 5 patients, respectively. The median time between SARS-CoV-2 vaccination and rejection was 102 days (IQR 48–178) (Fig. 1); no time pattern in favor of a causal link could be identified.

There was no influence of sex either ($p = 0.661$).

4. Discussion

When assessing the time between the last SARS-CoV-2 vaccine injection and the occurrence of rejection, we observed no distribution suggesting that rejection was triggered by vaccination. This is in line with virtually all previous reports in SOT recipient cohorts for other vaccines. Even if mRNA vaccines are particularly reactogenic, our study does not support the hypothesis that this reactogenicity leads to an aberrant, transplant-targeted immune response. This suggests new safety arguments to recommend universal vaccination of SOT recipients against SARS-CoV-2, in addition to those regarding the immunogenicity [11] and efficacy [12] of these vaccines in this population. This also suggests that future mRNA vaccines that may benefit SOT recipients would share the same safety profile.

Table 1
Characteristics of patients whose rejection occurred after vaccination or not.

		Rejection preceded by vaccination ($n = 45$)	Rejection not preceded by vaccination ($n = 50$)
Delay from transplantation (months) *median [IQR]*		4.3 [2.0–53.9]	24.5 [4.4–47.5]
Type of rejection	Humoral	29 (64.4 %)	30 (60.0 %)
	Cellular	14 (31.1 %)	17 (34.0 %)
	mixed	2 (4.5)	3 (6.0 %)

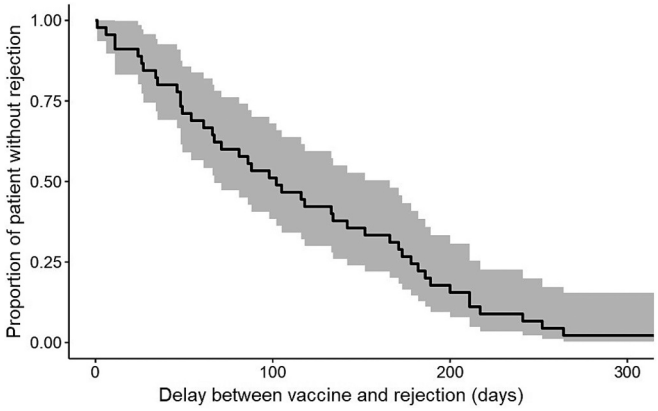


Fig. 1. Distribution of delay between the last vaccine dose and the rejection event (the grey area represents the 95 % confidence interval).

Transparency declaration

- Conflict of interest: none to disclose.
- Funding: no external funding was received for this study.
- Access to data: upon request.
- Contribution:

- *conception and design of the study*: OE, QP
- *acquisition of data*: QP, LF, JL, CA, ABon
- *analysis and interpretation of data*: QP, OE, JN, PB, ABoi, ABon, SG, LR
- *drafting the article*: QP, OE, JN
- *revising it critically for important intellectual content*: PB, LR, TJ, ABon, ABoi, CA, SG, LF
- *final approval of the version to be submitted*: all

CRediT authorship contribution statement

Quentin Perrier: Writing – review & editing, Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Johan Noble:** Writing – review & editing, Software, Formal analysis. **Agnès Bonadona:** Writing – review & editing, Validation. **Caroline Augier:** Writing – review & editing, Validation. **Thomas Jouve:** Writing – review & editing, Validation. **Aude Boignard:** Writing – review & editing, Validation. **Loïc Falque:** Writing – review & editing. **Salomé Gallet:** Writing – review & editing. **Pierrick Bedouch:** Writing – review & editing. **Lionel Rostaing:** Writing – review & editing. **Olivier Epaulard:** Writing – review & editing, Writing – original draft, Validation, Project administration, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

none

Data availability

Data will be made available on request.

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