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Rapid Waning of Immune Memory Against SARS-CoV-2 in Maintenance Hemodialysis Patients After mRNA Vaccination and Impact of a Booster Dose



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INTRODUCTION

Patients on maintenance hemodialysis (MHD) are at high risk of both infection by SARS-CoV-2 and death from COVID-19,¹ justifying the early prioritization of this vulnerable population for vaccination. It is widely accepted that the protection induced by vaccination against symptomatic COVID-19, in both the general population² and immunocompromised patients,³ is due to neutralizing antibodies. Cellular immunity, which is able to limit the risk of severe COVID-19 in the absence of neutralizing antibodies, appears to be a second step of immune protection.²

In the general population, the high level of neutralizing antibodies induced by mRNA vaccine wanes after 6 months, whereas cellular immunity persists.⁴ This explains why symptomatic COVID-19 can recur after 6 months postvaccination, whereas the protection against severe COVID-19 persists.^{51–52}

Our group and others have reported that, if the amount of immune effectors generated by MHD patients after 2 doses of mRNA vaccine is insufficient,^{5,53–57} a previous contact with the live virus (hybrid immunity) or a third vaccine injection allows the restoration of a level of protection close to that of healthy volunteers (HV).^{6,58–511} However, in contrast to these reassuring data, a recent epidemiologic study reported that being

on dialysis increases the risk of severe breakthrough COVID-19 infection in fully vaccinated individuals by a magnitude of 60 when compared with the general population.⁷ This observation raises the question of the persistence of immune effectors responsible for protection after vaccination in MHD patients over time. Furthermore, additional doses of mRNA vaccine are currently recommended for MHD patients in many countries; however, there is no consensus regarding the timing or on how a previous encounter with the virus should be taken into account. Finally, the impact of this boost on the immune response of MHD patients remains ill-defined.

RESULTS

Study Design and Population

The 71 patients on MHD of the study were distributed in 2 groups on the basis of the way they generated anti-SARS-CoV-2 immunity (Figure 1a). The first group included patients who only received vaccinations (vaccinated MHD, $n = 62$, red open circles). Most of them ($n = 57$ of 62, 92%) received the 3 recommended doses of BNT162b2. Patients from the second group (hybrid MHD, $n = 9$, red dots) all had a previous infection with SARS-CoV-2 before receiving BNT162b2 mRNA vaccine injections (6 of 9, 66% received only

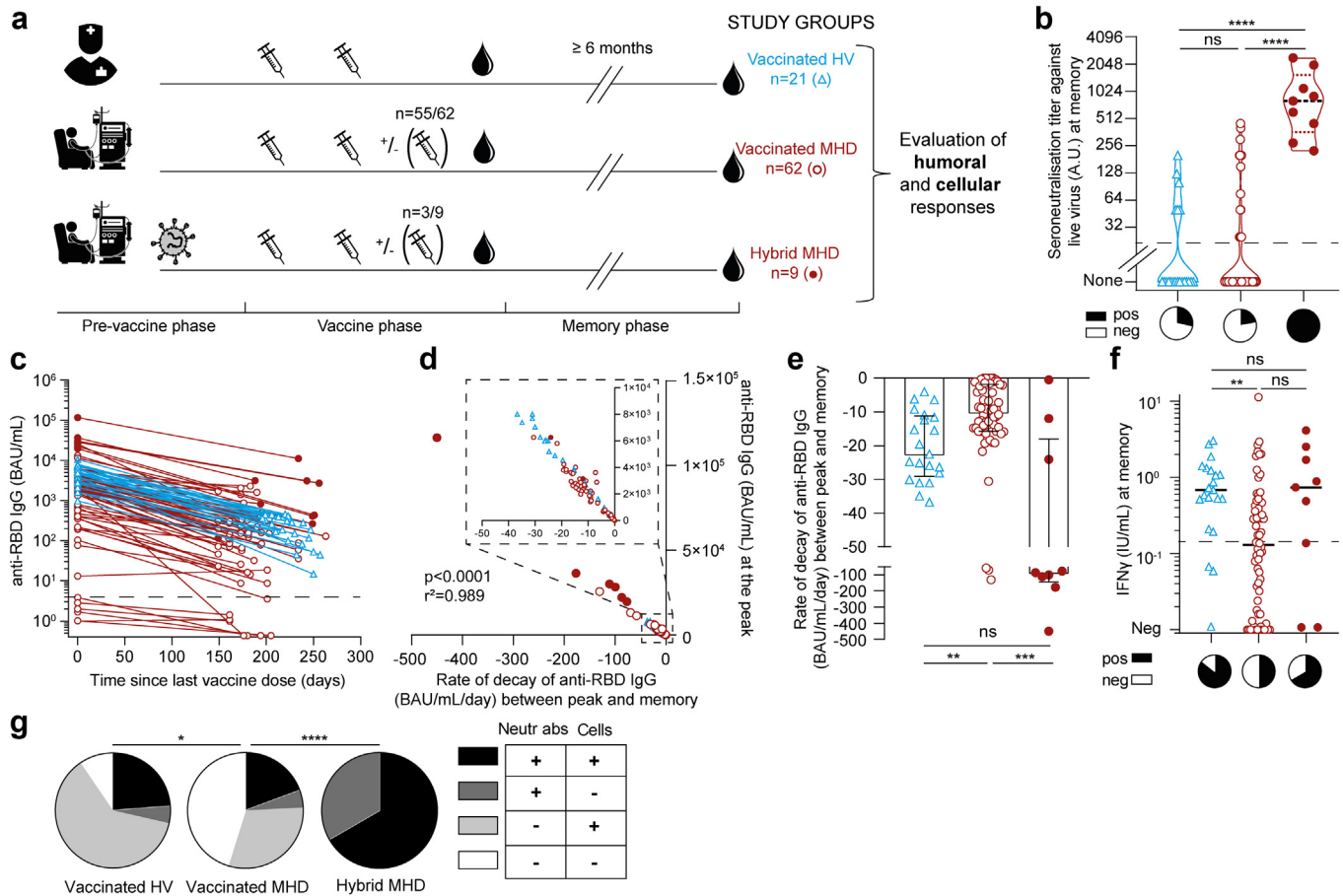


Figure 1. Assessment of humoral and cellular immune responses directed against SARS-CoV-2 at memory phase. (a) Graphical representation of the study. Each symbol is an individual. The color code is, blue open triangles: vaccinated healthy volunteers; red open circle: vaccinated MHD patients; red dot: hybrid MHD patients. (b) Violin plots showing the individual values of the capacity of the sera collected at memory phase to neutralize the cytotoxicity of SARS-CoV-2 *in vitro*. The dotted line represents the limit of positivity of the test. Pie charts represent the proportion of positive patients in each group. Kruskal-Wallis test. (c) Evolution of anti-RBD IgG titers (BAU/ml) between the peak of the vaccine phase and the memory phase. (d) Correlation between the rate of decay of anti-RBD IgG at the peak of vaccine phase and the value of anti-RBD IgG at the peak of vaccine phase. Spearman correlation coefficient. (e) Rate of decay of anti-RBD IgG titers (BAU/ml) between the peak of the vaccine phase and the memory phase. Median ± interquartile ranges. Kruskal-Wallis test. (f) Dot plots showing individual values of interferon-gamma releasing assay (IU/ml) at memory phase. Filled line represents the median of each group, and dotted line represents the threshold of positivity of the test. (g) Pie chart showing the distribution of patients according to the presence of the various immune effectors at memory phase in each groups. HV, healthy volunteers; MHD, maintenance hemodialysis; RBD, receptor-binding domain.

2 doses of BNT162b2, which were sufficient to obtain high levels of neutralizing antibodies). The 2 groups of patients on MHD were compared with a group of vaccinated HVs (vaccinated HV, $n = 21$, blue open triangles) with no previous history of COVID-19, and who received the standard 2 doses of BNT162b2. Patients who were diagnosed with COVID-19, received a perfusion of monoclonal antibodies or an additional vaccine dose during the vaccine or the memory phase were excluded (Supplementary Methods).

Immune responses were evaluated at the peak of the vaccine phase (10–14 days after the last dose of vaccine) and at memory phase (at least 6 months after the last vaccine injection). Of note, vaccinated patients on MHD were sampled significantly earlier than

vaccinated HV and hybrid patients on MHD (181 days [161–195] vs. 223 [208–238] and 243 [191–250] days, $P < 0.0001$), owing to the third vaccine injection they received. The clinical characteristics of the 3 groups are described in Supplementary Table S1.

Waning of Immune Memory in Vaccinated Patients on MHD 6 Months After the Last Dose

The ability of patient’s serum to neutralize the *in vitro* cytotoxicity of a live SARS-CoV-2 virus (ancestral strain), was evaluated as previously described⁶ (Supplementary Methods). At memory phase, only 13 of 62 (21%) vaccinated MHD patients exhibited serum neutralization capacity. This proportion was similar to that observed in vaccinated HV (29%); however, it was

drastically lower than the 100% observed in the hybrid MHD group ($P < 0.0001$; Figure 1b). As expected, this loss of neutralization capacity correlated with a decrease in anti-RBD IgG titers between the peak of the vaccine phase and the memory phase (Figure 1c). The rate of decay of anti-RBD IgG titers, which perfectly correlated with the peak value of anti-RBD IgG ($r^2 = 0.989$, $P < 0.0001$; Figure 1d), was the lowest for vaccinated MHD patients (Figure 1e).

We next evaluated the cellular immune memory, using an interferon-gamma releasing assay, as previously described⁸ (Supplementary Methods). At memory phase, only 31 of 62 (50%) vaccinated patients on MHD still had detectable anti-SARS-CoV-2 cellular immunity, than 18 of 21 (85.7%) vaccinated HV ($P = 0.005$) and 6 of 9 (66%) hybrid MHD patients ($P = 0.34$, Figure 1f).

Overall, at 6 months postvaccination, 28 of 62 (45%) vaccinated patients on MHD had neither neutralizing antibodies nor cellular immunity, suggesting high vulnerability to COVID-19 (Figure 1g). In contrast, patients devoid of protective immunity at memory phase represented only 2 of 21 (9.5%) vaccinated HV (mainly conserving cellular immunity, Figure 1g) and none of the hybrid patients on MHD (all with neutralizing antibodies, Figure 1b and g).

Booster Dose of Vaccine Restores Serum Neutralization Capacity in MHD Patients

A booster dose of mRNA vaccine was administered to 33 (53%) patients of the vaccinated MHD group which developed an immune response after the initial vaccination. Among these 33 patients, 15 of 33 (45.5%) received a full dose (30 µg) of BNT162b2 vaccine, and 18 of 33 (54.5%) received half a dose (50 µg) of mRNA-1273 (Figure 2a). No severe adverse events were reported. Sera were sampled 21 to 28 days after the injection. Clinical characteristics of these patients are described in Supplementary Table S2.

Vaccine rechallenge induced a strong increase in anti-RBD IgG titers in all patients (Figure 2b). The magnitude of the antibody response was similar with the full dose of BNT162b2 (from 115.4 [71.9–300.6] to 3490 [1794–4889] BAU/ml, $P < 0.0001$) and the half dose of mRNA-1273 (from 223.8 [25.9–454.4] to 6989 [3693–23919] BAU/ml, $P < 0.0001$). More importantly, the booster dose of vaccine restored the capacity of patients' sera to neutralize the *in vitro* cytotoxicity of SARS-CoV-2 in all (33 of 33, 100%) revaccinated MHD patients (Figure 2c), regardless of the mRNA vaccine type used for the boost.

DISCUSSION

Our study demonstrates that, in contrast to vaccinated HV that also experienced the waning of serologic

memory but exhibited persistent cellular memory, almost half of vaccinated MHD patients had neither serologic nor cellular immune memory 6 months after the last vaccine dose. These findings, also reported by others^{S12} suggest a very high vulnerability of vaccinated patients on MHD to COVID-19 after 6 months. This is even more true if we consider that the viral neutralization capacity of the serum was assessed against the initial strain of SARS-CoV-2 in our study, which overestimates the protection against variants of concern (especially, the Omicron strain).^{S13–S14}

Although it is tempting to attribute the defective immune response of MHD patients to end-stage renal disease condition, it shall be noted that a significant proportion of vaccinated MHD patients from our cohort were also on therapeutic immunosuppression (Supplementary Table S1), which could also have played a role. In fact, among the 6 patients on MHD who failed to develop both anti-RBD IgG and a cellular response after vaccination, 3 were on immunosuppressive drugs for a (nonkidney) graft, 2 recently received chemotherapy for malignancy, and the last patient was on a high dose of corticosteroid for cryoglobulinemia (Supplementary Table S1).

The loss of serum neutralizing capacity against SARS-CoV-2 in vaccinated patients on MHD correlated with the decrease in anti-RBD IgG titers, a phenomenon already reported by others,^{S12} which was indeed shown to be associated with the risk of developing a symptomatic breakthrough COVID-19.⁹

Recent studies have reported that a booster dose of vaccine failed to improve the anti-SARS-CoV2 cellular response of immunocompromised patients.^{S15–S16} Although we did not evaluate this aspect in our study, we did observe that a booster dose of mRNA vaccine was very well tolerated and allowed a prompt restoration of the viral neutralization capacity in 100% of the patients on MHD, regardless of the type of mRNA vaccine used, like in the general population.^{S17–S18}

Our data, therefore, strongly suggest that vaccinated patients on MHD should receive a vaccine boost before 6 months after their last vaccine injection. The determination of the optimal timing of the vaccine boost for each patients on MHD requires larger studies to identify the clinical variables associated with the kinetics of waning of the serologic memory. In this regard, the observation that all hybrid MHD patients showed persistence of neutralizing antibodies at memory phase is interesting. This finding is coherent with data from the general population, in whom hybrid immunity was shown to generate higher and more persistent levels of neutralizing antibodies than vaccine induced immunity.^{S19} In our study, this was not because of a

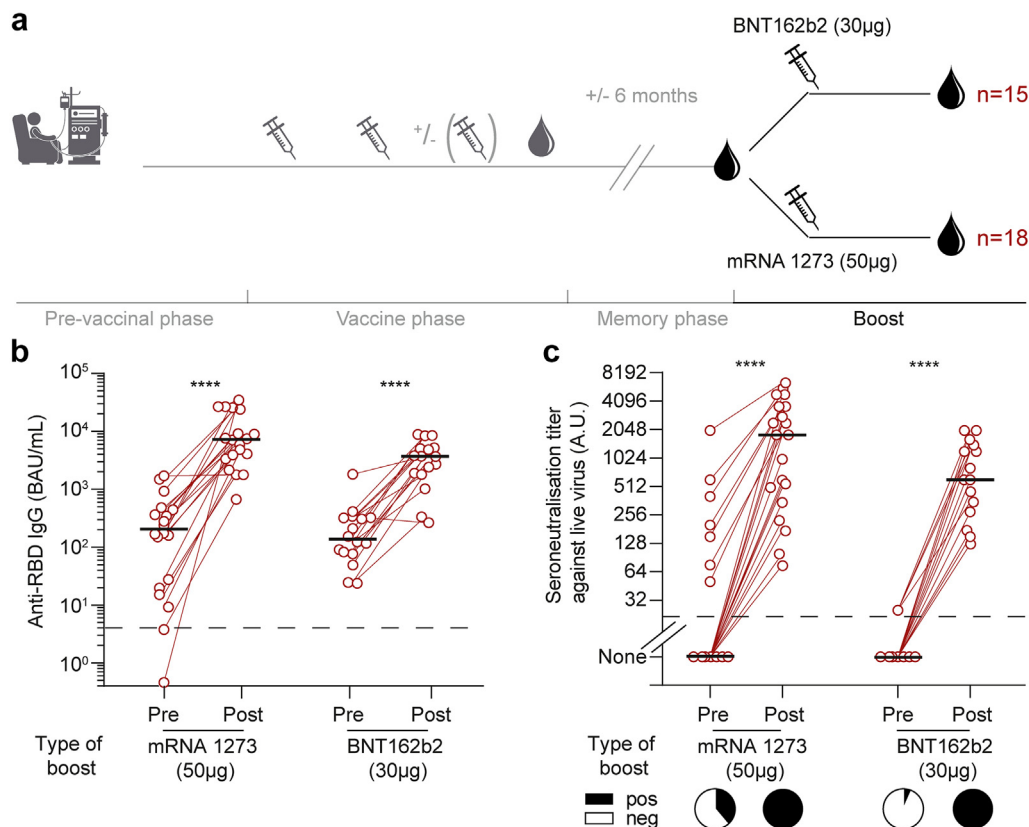


Figure 2. Immunogenicity of mRNA vaccine boost in MHD patients. (a) Graphical representation of the study. (b) Dot plots showing the individual values of anti-RBD IgG (BAU/ml) before and after the vaccine boost by half a dose (50 µg) of mRNA-1273 (left) or a full dose (30 µg) of BNT162b2 (right). Wilcoxon matched-pairs test. (c) Dot plots showing the neutralization titers before and after the vaccine boost by half a dose of mRNA-1273 (50 µg, left) or a full dose of BNT162b2 (30 µg, right). Wilcoxon matched-pairs test. Pie charts represents the proportion of positive patients. MHD, maintenance hemodialysis; RBD, receptor-binding domain.

slower rate of decay of anti-RBD IgG titers (which was on the contrary the highest in this group), but rather to the generation of higher levels of neutralizing antibodies at the peak of the vaccine response.

Patients on MHD with vaccine induced immunity experience a rapid waning of immune memory and should therefore receive a booster dose of vaccine in the 6 months following the last injection. This vaccine boost is well tolerated and highly effective to restore protective levels of neutralizing antibodies.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary Files (PDF)

Supplementary Methods.

Supplementary References.

Table S1. Clinical characteristics of the different study groups.

Table S2. Clinical characteristics of patients receiving a boost.

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