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•LETTER TO THE EDITOR•

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Humoral response to inactivated SARS-CoV-2 vaccines in patients on sirolimus alone

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Dear Editor,

Sirolimus, a prototype of mammalian target of rapamycin (mTOR) inhibitor, was approved by the FDA as an immunosuppressant in combination with cyclosporine and corticosteroids for prophylaxis of organ rejection. Reduced immune response of SARS-CoV-2 vaccine has been observed in organ recipients on immunosuppressants containing sirolimus (Mazzola et al., 2022). Sirolimus has been widely used as a long-term monotherapy for lymphangioleiomyomatosis (LAM) (McCormack et al., 2011). However, the immune response of SARS-CoV-2 vaccines was unknown in patients on monotherapy of sirolimus. There are concerns whether (1) monotherapy of sirolimus would reduce the antibody response after SARS-CoV-2 vaccination and (2) patients should suspend sirolimus for vaccination.

We performed a single-center, prospective, observational cohort study. The flow chart of the studied subjects is shown as Figure 1A. The inclusion criteria were as follows: (1) diagnosed as LAM or probable LAM according to the guidelines (Gupta et al., 2017; Johnson et al., 2010); (2) in the time window of 28±7 days after administration of 2 doses of inactivated SARS-CoV-2 vaccine (regardless of manufacturers). The exclusion criteria were: (1) history of COVID-19 infection; (2) taking immunosuppressive medication such as glucocorticoids, cyclosporin, or mycophenolate sodium; (3) no access to blood samples on day 28±7 after the second dose of vaccine. The sirolimus group was defined as subjects who were taking sirolimus at least 2 weeks before the first dose of inactivated vaccine until the end of the study. The control group was defined as subjects who had never used sirolimus or other mTOR inhibitors from 2 weeks before the first inactivated dose to the end of the study. This study was approved by the Ethics Committee of Peking Union Medical College Hospital (JS-3061). All subjects provided written informed consent to participant in the study.

On day 28 (time window±7 days) after two doses of inactivated vaccine, the venous blood sample was collected. And the serum neutralizing antibody level was measured by SARS-CoV-2 Neutralization Antibody ELISA Assay (Dynamiker Biotechnology (Tianjin)), a competition ELISA assay. A neutralizing antibody level of ≥20 IU mL^{-1} was considered SARS-CoV-2 neutralization antibody positive

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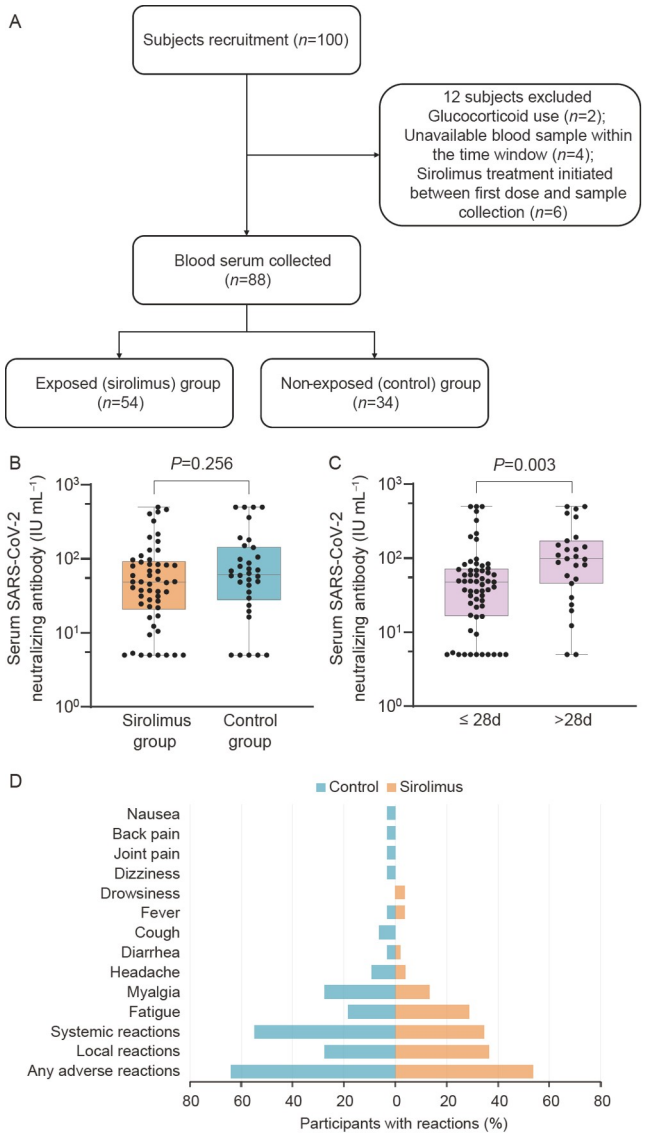

Figure 1 Serum SARS-CoV-2 antibody of subjects and adverse reactions of vaccines. A, flow chart of subjects. B, there was no significant difference between the sirolimus group and control group about the levels of SARS-CoV-2 neutralizing antibody (48.3(20.5-92.1) IU mL^{-1} for the sirolimus group vs. 61.9(28.0–144.3) IU mL^{-1} for the control group, P=0.256). C, serum neutralizing antibody level of patients with a two-dose interval of >28 days (98.8(45.6–172.2) IU mL^{-1}) was significantly higher than that of patients with an interval ≤28 days (47.7(16.7–71.9) IU mL^{-1}) (P=0.003). It suggested that the interval of two doses was a confounding factor for the neutralizing antibody level. D, adverse reactions within 7 days after each dose of vaccination. If the same adverse reaction occurs twice, it will be only counted once. Local adverse reactions including local pain, swelling, and pruritus were considered as one category. Solicited and unsolicited adverse reactions were combined in the analysis. No serious adverse reactions were found.

according to the manufacturer's recommendation.

The clinical characteristics of subjects were shown in Table S1 in Supporting Information. In the sirolimus group, 33 (61%) subjects were taking 1mg sirolimus daily, 13(24%) were taking 2 mg per day, 3(6%) were taking 1.5 mg per day, and 5(9%) were taking 0.5 mg per day. At least 89% of subjects had a sirolimus concentration between 3.5 and 9.0 ng mL^{-1}. All patients received two doses of inactivated COVID-19 vaccine from either Sinovac, or Sinopharm, or combination of them, and no significant difference was found in vaccine manufactures composition between the two groups. The median time of blood draw was 28 days after the second dose for the sirolimus group and 29 days for the control group (P=0.550). There were significant differences in the measurements of disease severity, such as pulmonary function, between the two groups. It was unclear, although it was unlikely, whether the severity of LAM affected the antibody response.

There was no significant difference between the sirolimus group and control group with regard to the levels of SARS-CoV-2 neutralizing antibody (48.3(20.5–92.1) IU mL^{-1} for the sirolimus group vs. 61.9(28.0–144.3) IU mL^{-1} for the control group, P=0.256, Figure 1B). The positive rate of neutralizing antibody in the sirolimus group was similar to that of the control group (75.9% vs. 79.4%, P=0.797). Compared with an interval of 3–4 weeks, a longer dosing interval was associated with higher neutralizing antibodies for both inactivated and non-inactivated vaccines (Skowronski et al, 2021; Zhang et al, 2021). Our subjects in the sirolimus group had shorter interval of two doses (24(21–28) days vs. 28(23–34) days, P=0.023). And serum neutralizing antibody level of patients with a two-dose interval of >28 days (98.8(45.6–172.2) IU mL^{-1}) was significantly higher than that of patients with an interval ≤28 days (47.7(16.7–71.9) IU mL^{-1}) (P=0.003, Figure 1C). It suggested that the interval of two doses was a confounding factor for the neutralizing antibody level. Taking the interval of two doses as a covariate, nonparametric analysis of covariance (Quade's test) was performed. There was still no significant effect of the sirolimus on the neutralizing antibody level on day 28 (F test, P=0.653).

The incidence of systemic adverse reactions in the sirolimus group was 35.2%, and the incidence of local adverse reactions was 33.3%, among which local adverse reactions included local pain, swelling, and pruritus. The most common systemic adverse reactions were fatigue and muscle pain (Figure 1D). No serious adverse events were observed. There was no significant difference in the incidence of systemic and local adverse reactions between the sirolimus group and the control group.

Our data demonstrated that monotherapy of sirolimus unlikely changed the antibody response of SARS-CoV-2 vaccine. Although sirolimus is labeled as an immunosuppressant, secondary infections in patients on monotherapy of sirolimus are rare. In placebo-controlled randomized clinical trial of sirolimus in LAM patients, pulmonary or upper respiratory infections or urinary infections were not increased in patients on mTOR inhibitors (McCormack et al., 2011). A meta-analysis demonstrated

that the incidence-rate ratio for respiratory infection among LAM patients treated with mTOR inhibitors was 0.71 (95% CI 0.50–1.02; P=0.06 compared to placebo subjects) (Courtwright et al, 2017), suggesting that there was no increased risk of pulmonary infection in LAM patients on mTOR inhibitor, and probably there was a protective role of mTOR inhibitors in reducing the risk of pulmonary infection. Interestingly, animal study (Keating et al., 2013) and two clinical trials (Mannick, et al., 2014; Mannick et al., 2018) have shown that mTOR inhibitors can improve immune responses to influenza vaccines. And no compromised humoral antibody response to SARS-CoV-2 vaccine was observed after sirolimus in our study. We can make a reasonable assumption that sirolimus alone does not adversely affect patients who have received inactivated vaccines such as COVID-19 or influenza vaccines. However, the role of sirolimus in other types of vaccines remains unclear.

One of the limitations of this study is that the blood samples of subjects were not collected before the first dose of vaccine. The baseline neutralizing antibody levels were unavailable. Owing to China′s strict COVID-19 screening policies, all infected patients would be identified. Therefore, we assumed that subjects without a history of COVID-19 should have no SARS-CoV-2 neutralizing antibodies before vaccination, and the level of neutralizing antibodies after vaccination could reflect the immune response of subjects to the vaccine. Another limitation was lack of evaluation of the changes of cellular immunity after vaccination in patients on sirolimus.

We conclude that the neutralizing antibody response of inactivated SARS-CoV-2 vaccine was unchanged in LAM patients on sirolimus. Monotherapy of sirolimus or other mTOR inhibitors unlikely hinders the antibody response to SARS-CoV-2 vaccines. We suggest that LAM patients on sirolimus should proceed to receive standard COVID-19 vaccination without adjustment of their sirolimus treatment.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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SUPPORTING INFORMATION

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