Does allergen immunotherapy impact the susceptibility and severity of COVID-19?

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To the editor,

Allergic asthma (AA) and allergic rhinitis (AR) might be protective against SRAS-CoV-2 infection and progress to severe disease of coronavirus disease 2019 (COVID-19)¹. COVID-19 vaccination was safe and well tolerated in patients receiving allergen immunotherapy (AIT)²,³, and the adherence to subcutaneous immunotherapy (SCIT) was not affected during COVID-19 pandemic⁴. Whether AIT impacts the susceptibility and severity of COVID-19 is still unknown. In December 2022, China ended its “Zero-COVID” policy and more than 70% of the population got infected with SARS-CoV-2 within one month. We conducted an online WeChat questionnaire between 3rd Jan and 10th Jan 2023 to investigate the infection and hospitalization rates and symptom duration of COVID-19 in AR and/or AA patients receiving SCIT with house-dust mite (HDM) extract in China. The relatives of these SCIT patients, who did not receive SCIT, were also surveyed and divided into two groups: allergy group and non-allergy group. The study was approved by the Medical Ethic Committee of Tongji Hospital of Huazhong University of Science and Technology (Approval Number: TJ-IRB20230204). The informed consent was waived since the voluntary nature of responding to the questionnaire.

A total of 1246 SCIT patients and 1078 of their relatives (370 allergic and 708 non-allergic) responded to the questionnaire. SCIT patients were generally younger than allergy and non-allergy group. The proportion of male were higher in SCIT patients compared to allergy and non-allergy group. 82.4% of the SCIT patients were diagnosed with AR, only 5.3% were asthmatics, and the rest were AR with asthma (12.3%). The average duration of AIT was 1.4 ± 1.3 years. SCIT patients had a lower proportion of both at least one dose and completed three doses of COVID-19 vaccines when compared to allergy and non-allergy group (P = 0.000) (Table S1).

Most respondents had been infected with SARS-CoV-2. SCIT was associated with a lower infection rate (78.6%) compared to allergy (81.4%) and non-allergy group (81.5%) (P < 0.0001) (Table S2). The duration of COVID-19 symptoms was shorter in SCIT group (5.7 ± 4.0 days) compared to allergy group (7.0 ± 4.5 days, P = 0.000) and non-allergy group (7.7 ± 4.4 days, P = 0.000) (Table S2). The hospitalization rate was 0.4% in SCIT group, which was significantly lower than that in non-allergy group (1.73%) (P = 0.008).

We then performed a two-to-one matching of SCIT group with allergy and non-allergy group to adjust age and sex difference between the three groups. The infection rate was still slightly lower in SCIT group compared
to allergy and non-allergy group (78.3% vs. 81.9%, 81.4%). The duration of symptoms and hospitalization rate did not show much difference among three groups after adjusting (Table 1).

Moreover, we found that patients receiving 6-12 months SCIT had a shorter duration of symptoms caused by SARS-CoV-2 infection compared to those in SCIT course < 6 months and those receiving SCIT > 12 months, even though only one fourth of them completed three doses of COVID-19 vaccines (Table 2). short duration of symptoms. The duration of SCIT has no impacts on both infection and hospitalization rate (Table 2).

A lower expression of angiotensin converting enzyme 2 (ACE2) in airway epithelia may contribute to the protecting effect of type 2 inflammation against SARS-CoV-2 infection and severe COVID-19. This study revealed an almost same infection rates in allergic and non-allergic individuals after adjusting age and sex, suggesting ACE2 expression level had no effect on Omicron infection. More importantly, SCIT patients has a slightly lower infection rate compared to allergy and non-allergy groups, suggesting that repeated allergen stimulation during SCIT in HDM-sensitized individuals may elicit a strong T cell response with ability to cross-react with SARS-CoV-2, as demonstrated in silico analysis, which may protect SCIT individuals from infection. The proportion with three doses COVID-19 vaccines were significantly lower in SCIT patients, albeit SCIT was reported to dampen immune responses to SARS-CoV-2 vaccines, the infection rate of SARS-CoV-2 was still lower in SCIT patients. We also observed a shorter duration of symptoms due to SARS-CoV-2 infection in those receiving 6-12 months HDM-SCIT compared to those receiving < 6 months and > 12 months HDM-SCIT, consistent with previous studies showing the immune responses to SCIT reach a peak during 6-12 months. EAACI stated recently in a position paper that AIT and COVID-19 immune responses do not seem to interfere negatively, and AIT patients might even benefit from AIT. Thus, our results for the first time demonstrated that SCIT may have a protective effect against SARS-CoV-2 infection, especially immediately after completing the dose-escalation phase.

**KEYWORDS:** Allergic rhinitis; Allergen immunotherapy; SARS-CoV-2; Coronavirus disease 2019; Infection

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Table1, table 2.doc available at https://authorea.com/users/320601/articles/623908-does-allergen-immunotherapy-impact-the-susceptibility-and-severity-of-covid-19