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Allergen Immunotherapy Reverses Immune Response to SARS-CoV-2 Vaccine in Patients with Allergic Rhinitis: A Prospective Observational Trial

To the Editor:

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have shown high efficacy in the prevention of coronavirus disease (COVID-19) (1). Allergic diseases, including allergic rhinitis (AR), asthma, and atopic dermatitis, are characterized by skewed type 2 immune responses and are estimated to affect 30–50% of the population globally (2). Recently, we have reported that after two doses, patients with AR displayed an enhanced humoral immune response to inactivated SARS-CoV-2 vaccines compared with healthy control samples, which was associated with an increase in type 2 follicular helper T ($T_{FH}2$) cells in patients with AR (3). Allergen immunotherapy (AIT) is an effective disease-modifying treatment for allergic diseases by inducing immune tolerance and correcting or antagonizing skewed type 2 responses (4). A significant reduction of $T_{FH}2$ cells and an increase of follicular regulatory T cells (T_{FR}) are noted in patients with AR after AIT (5, 6). Thus, it is critical and interesting to understand whether AIT will influence the efficacy of SARS-CoV-2 vaccination in allergic patients.

A prospective observational trial (ClinicalTrials: NCT05009134) was conducted to compare the immunological response to inactivated

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Author Contributions: Y.Y. planned and performed most experiments with major support from A.H. and Y.-K.D. Z.-Z.W., N.W., Y.L., and H.-Y.Z. collected and processed blood samples. Z.-Z.W. and R.-F.Z. collected clinical data. Z.L., D.Y., and Y.Y. designed the study and supervised the project.

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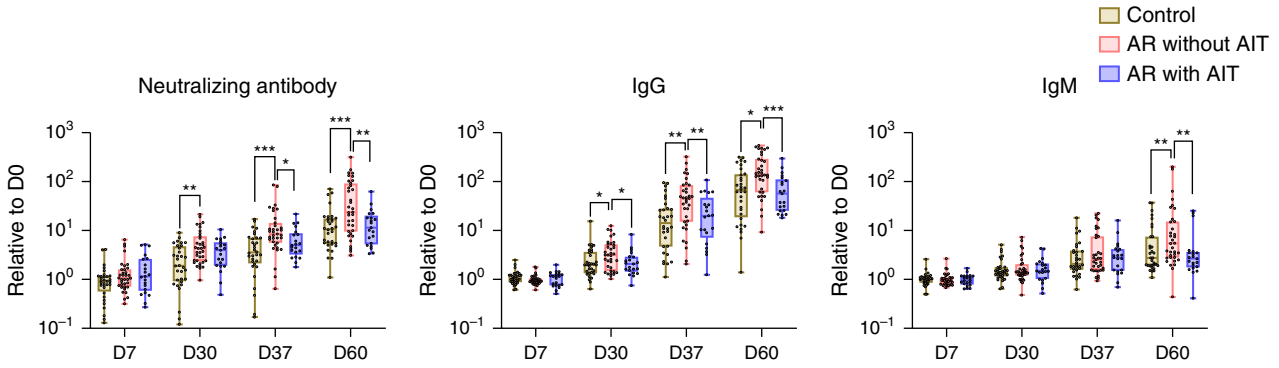

Figure 1. Reversed protective antibody responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine in patients with allergic rhinitis (AR) receiving allergen immunotherapy (AIT). Healthy subjects ($n = 32$), patients with AR without AIT ($n = 35$), and patients with AR receiving AIT for more than 1 year ($n = 21$) were enrolled and given inactivated SARS-CoV-2 vaccine on Days 0 and 30. Peripheral blood was collected on Days 0 (baseline), 7, 30, 37, and 60. Plasma-neutralizing antibodies against the receptor-binding domain of the SARS-CoV-2 S1 protein and IgG and IgM against the SARS-CoV-2 S and N proteins were measured by chemiluminescent immunoassay. Each dot represents one individual. Changes in antibody concentrations at the indicated time points are displayed as fold changes by normalizing to the baseline concentrations. Data are presented as median and interquartile range and analyzed by Mann-Whitney *U* test. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. D0 = Day 0; D7 = Day 7; D30 = Day 30; D37 = Day 37; D60 = Day 60.

SARS-CoV-2 vaccine in patients with AR with and without AIT. Thirty-three healthy subjects, 35 patients with AR without AIT, and 23 patients with AR receiving AIT for more than 1 year were enrolled from June 10, 2021, to December 15, 2021, at Tongji Hospital. Three groups of subjects were recruited simultaneously. All subjects had never been infected with SARS-CoV-2. All patients with AR had positive skin prick tests for *Dermatophagoides pteronyssinus* or *D. farina*. AIT was performed subcutaneously with semidepot house dust mite allergen extracts (Allergopharma GmbH) (5). All subjects received inactivated SARS-CoV-2 vaccine (WIBP-CorV, Sinopharm) on Days 0 and 30. Peripheral blood was taken on Days 0, 7, 30, 37, and 60 to analyze humoral immune responses to vaccination. One participant in the control group and two participants in the AR with AIT group were excluded because of loss to follow-up. Chemiluminescent immunoassay was performed to detect neutralizing antibodies against the receptor-binding domain (RBD) of the SARS-CoV-2 spike (S)1 protein (iFlash-2019-nCoV neutralization assay kit, YHLO Biotech Co), and IgG and IgM against the SARS-CoV-2 S and nucleocapsid (N) proteins (iFlash-SARS-CoV-2 IgM/IgG antibody test kit, YHLO Biotech Co) in plasma. B- and T-cell responses in peripheral blood were assessed by flow cytometry. This study was approved by the Ethics Committee of Tongji Hospital (TJ-IRB20210610), and written informed consent was obtained from each participant.

Control, AR without AIT, and AR with AIT groups were comparable in baseline demographic characteristics, including age (median and interquartile ranges, 26 years [24–38] for the control group, 27 years [23–38] for AR without AIT group, and 29 years [25–36] for AR with AIT group) and sex (female/male, 21/11 in control group, 22/13 in AR without AIT group, and 12/9 in AR with AIT group). SARS-CoV-2 vaccination elicited robust serological responses, showing markedly increased neutralizing antibody, IgG, and IgM after vaccination in all three groups (Figure 1) (3). Patients with AR without AIT displayed higher fold changes of neutralizing antibody on Days 30, 37, and 60, IgG on Days 30, 37, and 60, and IgM on Day 60 relative to the baseline concentrations at Day 0 than those in healthy control samples (Figure 1). However, interestingly, AIT reversed serological response to the SARS-CoV-2 vaccine in patients with AR, as reflected by the comparable changes of antibodies between patients with AR with AIT and healthy control samples (all $P > 0.05$) (Figure 1).

We next assessed antigen-specific B-cell immune response to SARS-CoV-2 after vaccination (Figure 2). Higher frequencies of circulating RBD-specific memory B cells were found in patients with AR without AIT compared with those in patients with AR receiving AIT at Day 60, in which the RBD-specific memory B-cell frequencies were comparable to those in healthy control samples ($P > 0.05$) (Figure 2). T_{FH} cells are critical for the generation of protective antibodies and long-lived humoral immunity after vaccination (7). We found that SARS-CoV-2 vaccination induced a robust expansion of circulating $CXCR5^{+}ICOS^{high}PD\text{-}1^{high}$ T_{FH} cells at Day 37 (7 days after the second dose of vaccination) in all three groups. Notably, the increase of T_{FH} cells in patients with AR without AIT as compared with healthy control samples was, again, reversed in AR with AIT group on Days 7, 37, and 60 (Figure 2), as reflected by no significant difference in changes of T_{FH} and follicular regulatory T (T_{FR}) cells between control and AR with AIT groups at all time points (all $P > 0.05$) (Figure 2).

On the basis of the expression of chemokine receptors CXCR3 and CCR6, human circulating T_{FH} cells can be divided into $T_{FH}1$, $T_{FH}2$, and $T_{FH}17$ cells (7). Marked expansion of $T_{FH}1$ and $T_{FH}2$ cells, but not $T_{FH}17$ cells, was noted on Day 37 in all three groups (Figure 2). We have recently reported that increased $T_{FH}2$ cells were associated with an enhanced humoral immune response to SARS-CoV-2 vaccines in patients with AR (3). Here, we observed a significant decrease in changes of $T_{FH}2$ cells in patients with AR with AIT compared with those without AIT on Days 37 and 60 relative to the baseline concentrations at Day 0, and there was no difference in the changes of $T_{FH}2$ cells between control and AR with AIT group (all $P > 0.05$) (Figure 2). We also noted a temporary increase of change of $T_{FH}1$ cells on Day 7 in patients with AR without AIT compared with patients with AR with AIT and control samples (Figure 2). Fold

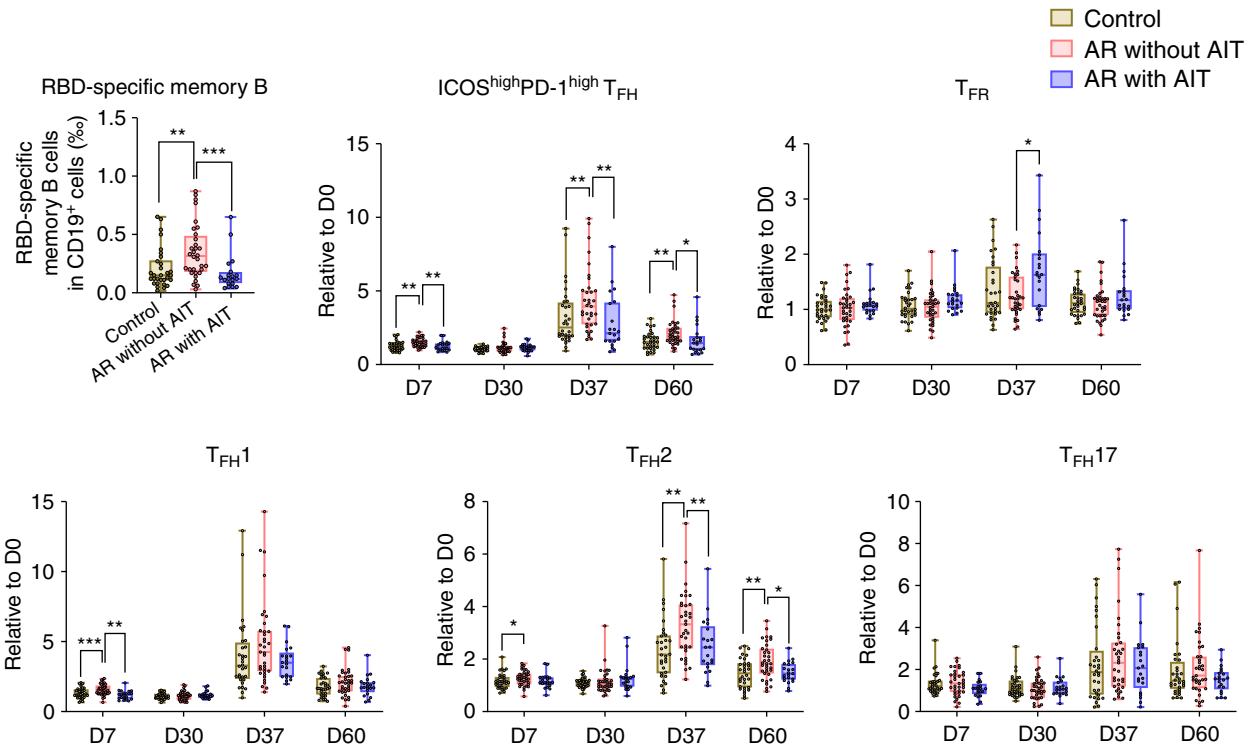

Figure 2. Reversed B- and T-cell responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine in patients with allergic rhinitis (AR) receiving allergen immunotherapy (AIT). Frequencies of circulating RBD-specific $CD3^-CD19^+CD20^+CD27^+$ memory B cells in healthy subjects ($n = 32$), patients with AR without AIT ($n = 35$), and patients with AR receiving AIT for more than 1 year ($n = 21$) on Day 60 were analyzed by flow cytometry. Frequencies of circulating $CD4^+CD45RA^{low}CXCR5^+ICOS^{high}PD\text{-}1^{high}CD25^{-/low}$ T_{FH} cells, $CD4^+CD45RA^{low}CXCR5^+CD25^{high}CD127^{low}$ T_{FR} cells, and circulating $ICOS^{high}PD\text{-}1^{high}$ T_{FH} subsets ($CXCR3^+CCR6^-$ $T_{FH}1$, $CXCR3^-CCR6^+$ $T_{FH}17$, and $CXCR3^-CCR6^-$ $T_{FH}2$) before and after vaccination were analyzed by flow cytometry. Each dot represents one individual. The changes of T cells in the indicated time points are displayed as fold changes by normalizing to the baseline amounts. Data are presented as median and interquartile range and analyzed by Mann-Whitney *U* test. $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. D0 = Day 0; D7 = Day 7; D30 = Day 30; D37 = Day 37; D60 = Day 60; RBD = receptor-binding domain; T_{FH} = follicular helper T; $T_{FH}1$ = type 1 T_{FH}; $T_{FH}17$ = type 17 T_{FH}; $T_{FH}2$ = type 2 T_{FH}; T_{FR} = follicular regulatory T.

changes of $T_{FH}1$ and $T_{FH}17$ cells were comparable between control and AR with AIT group at all the time points (all $P > 0.05$) (Figure 2). Collectively, these results indicate that AIT may reduce the humoral immune responses to inactive SARS-CoV-2 vaccine in patients with AR; however, the humoral immune responses in patients with AR undergoing AIT are not compromised in comparison to healthy control samples. The prospective design in this study allowed us to measure serological and cellular response to SARS-CoV-2 simultaneously, both supporting the above conclusion. Several previous studies have evaluated the effect of biologic therapies targeting type 2 responses on antibody response to SARS-CoV-2 infection or vaccination. Ungar and colleagues reported lower antibody concentrations after COVID-19 infection in patients with atopic dermatitis treated with dupilumab compared with those receiving systemic or limited/no therapies (8). Similarly, Bhalla and colleagues described in a case report that a dupilumab-treated patient with asthma had blunted IgG and IgM antibodies to SARS-CoV-2 S protein and RBD after SARS-CoV-2 infection in comparison with two patients with asthma without dupilumab treatment (9). Recently, Runnstrom and colleagues have observed lower antibody concentrations after SARS-CoV-2 mRNA vaccination in patients with severe asthma or atopic dermatitis on biologics targeting type 2 responses than those in healthy adults (10). Their data, together with ours, suggest that type 2 response-modifying treatments may decrease the immune response to SARS-CoV-2 vaccination.

In summary, by extending our previous findings (3), we revealed that AIT may reverse the enhanced humoral response to SARS-CoV-2 vaccination in patients with AR to degrees comparable to healthy control samples. The change of $T_{FH}2$ cells may underline these phenomena. Nevertheless, our study is limited by small sample size, and further studies with longer follow-up are required to confirm our findings. In addition, whether AIT can change immune responses to other SARS-CoV-2 vaccines, such as mRNA vaccines, deserves further investigation. ■

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Effect of a Transitional Care Intervention on Rehospitalization and Mortality after Sepsis: A 12-Month Follow-up of a Randomized Clinical Trial

To the Editor:

In the United States, nearly 2 million adults are hospitalized with sepsis each year (1). Although more than 80% of patients with sepsis survive the acute hospitalization, sepsis survivors are vulnerable to new and worsening health problems for years after leaving the hospital —leading to high rates of rehospitalization and mortality (2, 3). We recently completed a randomized clinical trial demonstrating that proactive and sepsis-specific multicomponent transitional support improved 30-day outcomes after sepsis hospitalization (4). In this study, we compared 12-month outcomes to determine if 30-day transitional support program benefits were sustained beyond participation.

The current study presents 12-month follow-up from the IMPACTS (Improving Morbidity during Post-Acute Care Transitions for Sepsis) trial conducted at three hospitals in North Carolina from January 2019 to March 2020 (NCT 03865602). Trial methods and intervention characteristics have been described (4, 5). Briefly, adults hospitalized for suspected sepsis and deemed to be high risk for 30-day rehospitalization and mortality were randomized to receive usual care alone (UC; $n = 342$) or Sepsis Transition and Recovery (STAR; $n = 349$) program support for 30 days. The intervention was a multicomponent transition program led by a nurse navigator through telephone and electronic health record communication to facilitate best-practice postsepsis care strategies during and after hospitalization. Core intervention components included post-discharge medication review, evaluation for new impairments or symptoms, monitoring comorbidities, and palliative care consultation when appropriate. Clinical oversight and care escalation, as needed, was provided by a Hospital Medicine Transition Services team. The primary outcome was all-cause mortality or rehospitalization within 12 months after index hospital discharge, assessed using national death records and the health system's data warehouse. Logistic regression models were constructed to compare the primary outcome composite between treatment arms. As in the primary trial, we calculated conditional (i.e., adjusted) odds ratios (ORs) with 95% confidence intervals (CIs) to measure patient-level effects adjusting for baseline characteristics known to be associated with mortality and rehospitalization after sepsis (age, comorbidity burden, count of failed organs). We used the same approach to evaluate rehospitalization and mortality outcomes separately. We also fit a proportional subdistribution hazards model examining STAR effects on rehospitalization, accounting for death as a competing risk. Finally, to explore coronavirus disease (COVID-19) pandemic–related temporal changes, we estimated treatment effects

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