Low Omicron BA.4 and BA.5 neutralising activity and breakthrough COVID-19 following pre-exposure prophylaxis with Tixagevimab plus Cilgavimab in vaccinated patients with autoimmune disease

Sirs,

Many immunosuppressed patients with autoimmune disease remain vulnerable to SARS-CoV-2 infection and potential poor COVID-19 outcomes owing to attenuated vaccine responses (1, 2). This prompted the authorisation of pre-exposure prophylaxis (PrEP) with the monoclonal antibody combination Tixagevimab and Cilgavimab (T+C) to complement vaccine-associated immunity and enhance protection versus SARS-CoV-2 (3). Initial efficacy data, however, was derived from an unvaccinated, immunocompetent cohort prior to the Omicron variant of concern (VOC) epoch (4), and protection afforded by T+C has been mitigated by the immune evasion exhibited by novel VOC (4, 5). There is a need for longitudinal evaluation of T+C safety and efficacy in vaccinated, immunosuppressed patients in the current VOC climate to optimise use, and to inform decision-making for future PrEP formulations. Thus, we sought to evaluate (i) binding antibody responses, (ii) serum neutralising capacity against VOC including Omicron sublineages, (iii) breakthrough COVID-19, and (iv) safety post-T+C in immunosuppressed patients with autoimmune disease.

Fully-vaccinated patients with autoimmune disease who received 300+300mg T+C (either single dose or two 150+150mg doses) within a prospective observational cohort submitted pre-and post-T+C blood samples (≤2 weeks before and 4-weeks post-T+C) between 1/2/2022-6/16/2022. Participants were enrolled and consented electronically as previously described (2). Binding antibody (anti-receptor binding domain [RBD], Roche approximately 1:1 with World Health Organisation binding antibody units [BAU]) and surrogate neutralisation (%ACE2 inhibition [0–100%]; Meso Scale Discovery) were measured against ancestral strain as well as variants including Omicron sublineages BA.1, BA.2, BA.2.12.1, BA.4 and BA.5. Based on prior work in solid organ transplant recipients utilising authentic live virus assays, ≥25% ACE2 inhibition was defined as "neutralising inhibition" given association with live virus neutralising antibody (6). Changes in antibody and neutralisation were assessed using Wilcoxon matched-pairs signed-rank test. Participants completed questionnaires detailing reactogenicity at day 7 and incident adverse events at day 30, 90 and 180 post-T+C respectively, as well as periodic surveys regarding breakthrough COVID-19 through 12/6/2022.

Among 11 participants, most (9/11) received a single 300+300mg T+C dose while 2/11 received two 150 mg+150 mg doses (interval of 15 and 25 days, respectively) (Supplementary Table S1). Most were white (10/11) and female (10/11). All had completed three-dose primary mRNA vaccination, while 4/11 received ≥4 vaccine doses pre-T+C. A diverse range of autoimmune diseases were reported. All participants were treated with at least one immunosuppressant medication, most commonly mycophenolate mofetil (MMF) (4/11).

The median (IQR) anti-RBD increased from 913.7 BAU/mL (IQR 137.1, 2523.3) to 6385.9 (IQR 4749.4, 8730.6) post T+C (p<0.0001) (Suppl. Fig. S1). Median ancestral variant neutralisation increased from 61.1% to 99.3% post-T+C (p=0.0001) (Fig. 1). Omicron BA.1 neutralisation was low and did not increase (2.81–0% post-T+C; p=0.9700). In contrast, BA.2 neutralization increased from 0% to 50.0% (p<0.0001)

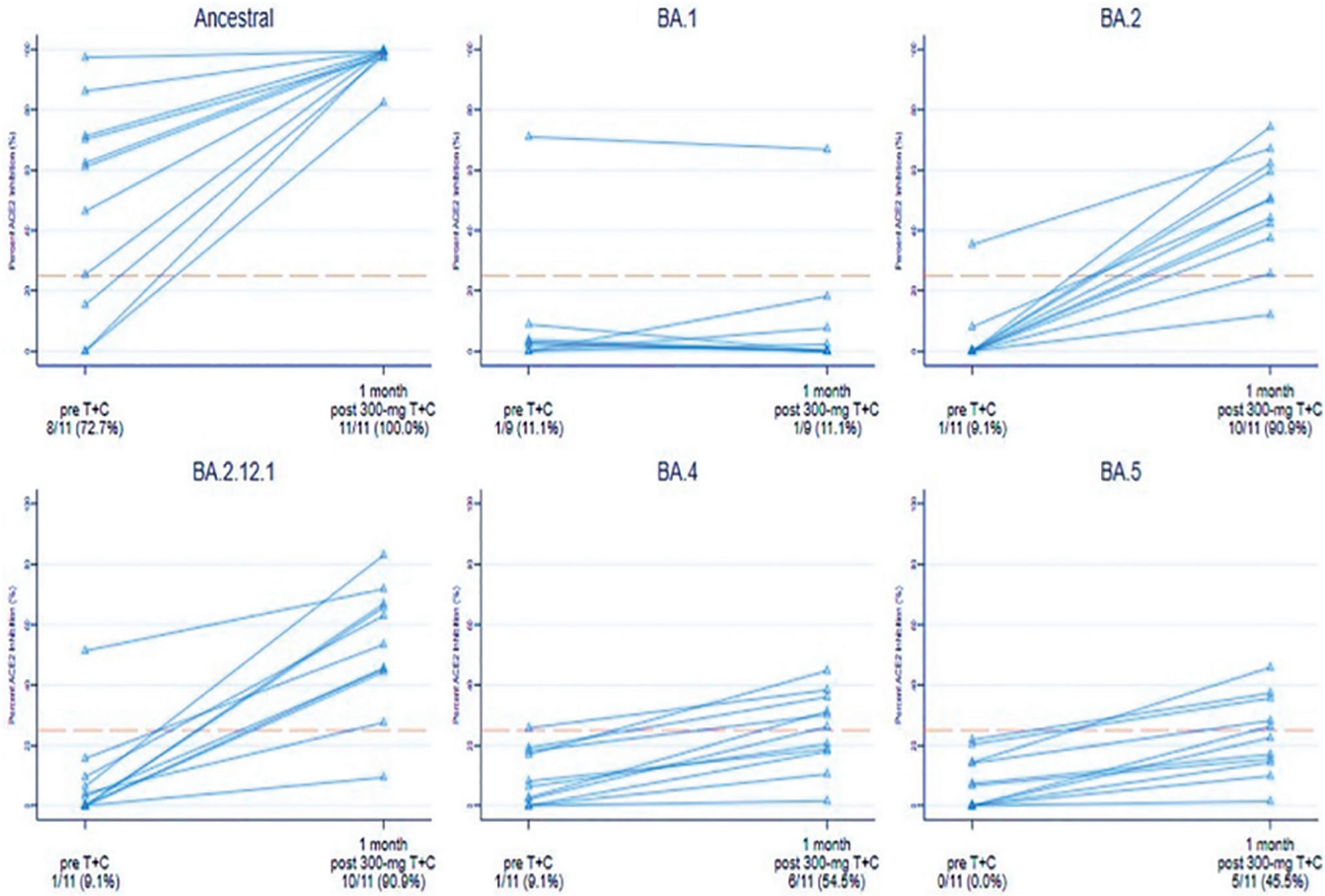

Fig. 1. Neutralising inhibition before and after Tixagevimab and Cilgavimab in 11 fully-vaccinated immunosuppressed patients with autoimmune diseases.

while BA.2.12.1 neutralisation increased from 2.98% to 53.4% (p<0·0001) post-T+C. Both BA.4 (6.27–26.14% [p=0.003]) and BA.5 (6.65–22.53% [p=0.004]) neutralisation increased post-T+C, though remained <25% for most.

One participant reported a reaction post-T+C, consisting of mild injection site pain and fatigue. There were no post-T+C anaphylactoid reactions or cardiovascular events. Two participants reported symptomatic breakthrough COVID-19 (both contemporary with BA.5 dominance in USA); one required hospital admission for intravenous antiviral therapy while the other received outpatient treatment with monoclonal antibody therapy.

Limitations of this study include small, diverse sample which limits associative analyses for neutralising responses.

These data demonstrate that T+C PrEP is well-tolerated and increases binding antibody responses against SARS-CoV-2 but confirms poor neutralising capacity against certain Omicron sublineages including BA.4 and BA.5. Our findings reaffirm that a multifaceted approach is required to enhance protection *versus* SARS-CoV-2 in vulnerable patients and highlights the need for the dynamic development of PrEP formulations that can effectively negate the evolving immune escape of SARS-CoV-2.

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Funding: this work was made possible by the generous support of the Ben-Dov and Trokhan Patterson families. This work was supported by the Jerome L. Greene Foundation Discovery Fund (C.M. Connolly, J.J. Paik) and grant number K23AR073927 (J.J. Paik) from National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), T32DK007713 (J.L. Alejo) from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), K24AI144954 (D.L. Segev), U01AI138897-S04, K08AI156021 (A.H. Karaba), and K23AI157893 (W.A. Werbel) from National Institute of Allergy and Infectious Diseases (NIAID). The analyses described here are the responsibility of the authors alone and do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organisations imply endorsement by the US Government.

Competing interests: D.L. Segev reports receiving honoraria from Sanofi (speaking), Novartis (speaking, consulting), Veloxis (consulting), Mallinckrodt (consulting), Jazz Pharmaceuticals (consulting), CSL Behring (consulting), Thermo Fisher Scientific (consulting), Caredx (speaking, consulting), Transmedics (consulting), Kamada (consulting), MediGO (consulting), Regeneron (consulting), AstraZeneca (speaking, consulting), Novavax (advisory board), Takeda (consulting), and Bridge to Life (speaking).
L. Christopher-Stine reports consultant fees from Janssen, Boehringer-Ingelheim, Mallinckrodt, EMD-Serono, Allogene, and ArgenX.
A.H. Karaba reports consultant fees from Roche.
W.A. Werbel reports speaking fees from AstraZeneca and honoraria from Novavax (advisory board).
J.J. Paik reports consultant fees from Alexion, ArgenX, EMD-Serono, Guidepoint, Kezar, and Pfizer.
The other authors have declared no competing interests.

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