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LETTER

Third dose corrects waning immunity to SARS-CoV-2 mRNA vaccines in immunocompromised patients with immune-mediated inflammatory diseases

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Immunocompromised patients treated with immunosuppressive drugs are at increased risk of adverse outcomes following SARS-CoV-2 infection.[1] There is limited information on the effect of immunomodulatory therapies on the quality of SARS-CoV-2 vaccine-induced immunity in these populations.[2] In a cohort of patients with immune-mediated inflammatory diseases (IMIDs) not treated with B-cell depleting agents or corticosteroids, we recently demonstrated that antibody levels and T cell responses showed greater waning by 3 months following the second dose of SARS-CoV-2 mRNA vaccine compared with healthy controls, emphasising the need for third doses of the vaccine.[3] Here, we investigated immune responses in uninfected patients with IMID following a third dose of the Pfizer/BioNTech BNT162b2 or Moderna mRNA-1273 mRNA vaccine.

We collected blood samples 2–4 weeks after the third dose of vaccine from 62 patients (median (range) age 40 (22–70) years, 34 females) enrolled in our ongoing study (figure 1A) and diagnosed with one or more of the following IMIDs: inflammatory bowel disease (37 patients), psoriasis (11), psoriatic arthritis (10), ankylosing spondylitis (2), rheumatoid arthritis (2) or hidradenitis suppurativa (1). The patients analysed included 6 healthy controls, 5 patients with IMID not on treatment, 18 patients on anti-TNF, 9 on anti-TNF with methotrexate/azathioprine (MTX/AZA), 6 on anti-IL-17, 10 on anti-IL-12/23, 6 on anti-IL-23 and 2 on MTX/AZA. IgG responses against coronavirus S protein (spike) and receptor binding domain (RBD) were measured by automated ELISA.[3] PBMCs were stimulated for 48 hours with SARS-CoV-2 Wild-type or Omicron B.1.1.529 spike peptide pools. T cell responses were analysed by measuring the release of IL-2 and IL-4 in cell culture supernatants using a bead-based immunoassay (see reference Dayam *et al* for details).[3]

Anti-spike and anti-RBD antibody levels increased following the third dose (T5, figure 1A), with 92% of patients showing relative ratios greater than the medians of the convalescents for spike and RBD (figure 1B). T cell responses showed significant variation in IL-2 and IL-4 production (figure 1C). We previously reported significant waning of IL-2 and IL-4 responses by 3 months postdose 2 (T4, figure 1A).[3] Pooled analysis of all study subjects revealed that the third dose of vaccination (T5) corrects the waning immunity, significantly boosting IL-2 and IL-4 responses (figure 1C; median IL-2 sqrt(Δpg/mL) at T4: 4.65 vs T5: 13.73 *p<0.0001; median IL-4 sqrt(Δpg/ml) at T4: 0.05 vs T5: 1.65 *p<0.0001). IL-2 responses were stronger after a third dose of vaccination compared with after the second dose (figure 1C; median IL-2 sqrt(Δpg/ml) at T3: 6.40 vs T5: 13.73 *p<0.0001) while IL-4 responses were similar after the second and third dose of vaccination (figure 1C; median IL-4 sqrt(Δpg/ml) at T3: 1.32 vs T5: 1.65 p=0.42). We additionally

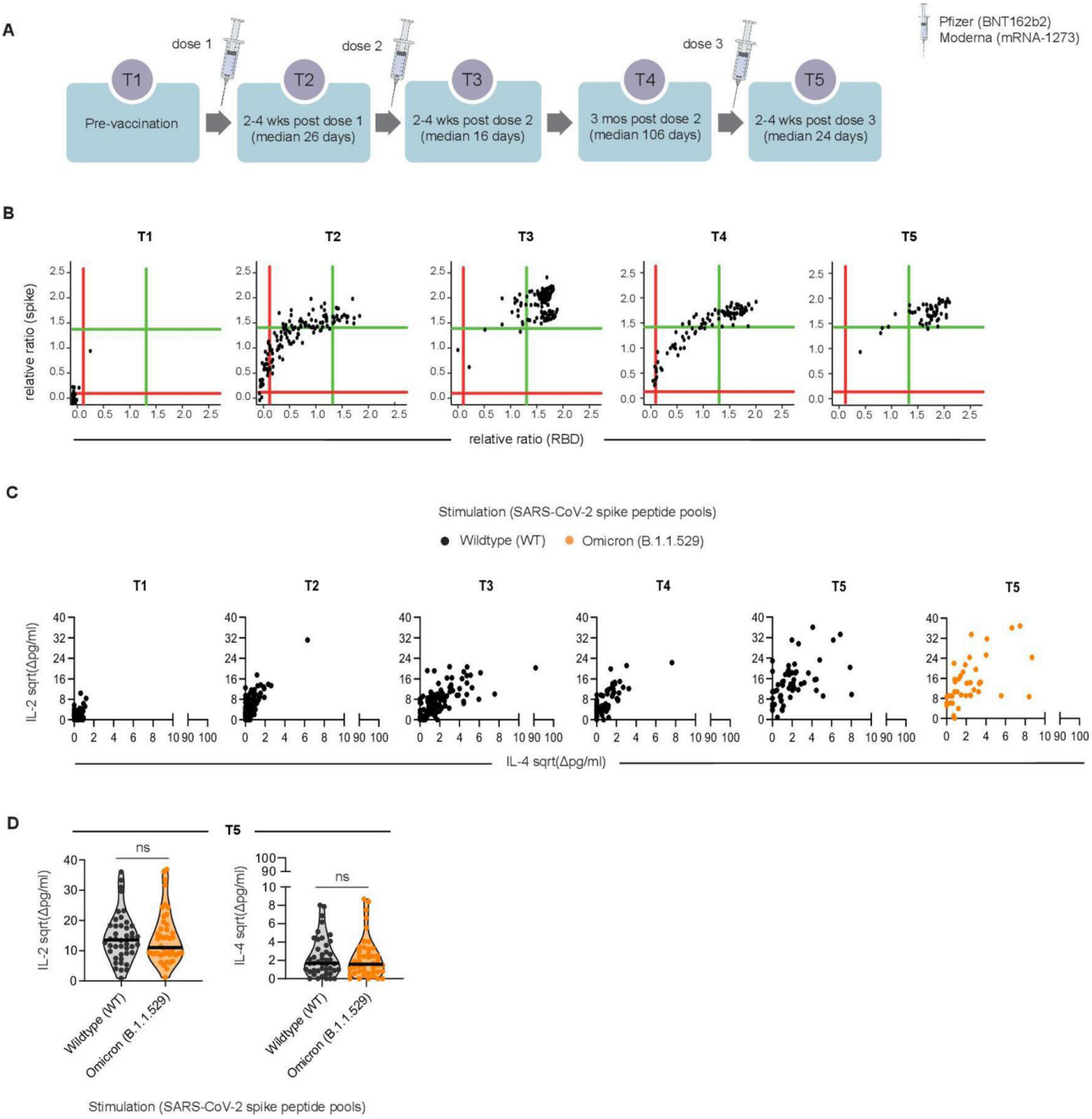

Figure 1 Antibody and T cell responses after three doses of mRNA vaccine. (A) Schematic diagram of the sampling scheduling spanning pre and post one, two and three doses of mRNA vaccine. (B) IgG response to vaccination across all participants at time points T1–T5, as defined in A. Anti-spike (y-axis) and anti-RBD (x-axis) IgG levels (relative ratio to synthetic standard—see ref [3]) at indicated time points. The green line is the median ratio in convalescent patients (340 samples collected 21–115 days after symptom onset). The red line is the seropositivity threshold, set to pass both a 1% FPR and greater than or equal to 3 SDs from the log10 means of the negative controls. (C) The release of IL-2 and IL-4 in cell culture supernatants after 48 hours stimulation of PBMCs with SARS-CoV-2 wild-type (black dots) or Omicron B.1.1.529 (orange dots) spike peptide pools were analysed by LEGENDplex bead-based immunoassay. Depicted are IL-2 and IL-4 responses across all participants at time points T1–T5, as defined in a: T1, n=102; T2, n=117; T3, n=126; T4, n=88; T5 (Wuhan), n=58; T5 (Omicron), n=46. Values are reported in pg/mL after subtracting background signal from wells containing PBMCs cultured with DMSO alone, as indicated by 'Δ'. SQRT refers to square root transformation of the data for visualisation purposes. (D) Violin plots showing the release of IL-2 and IL-4 in cell culture supernatants after 48 hours stimulation of PBMCs with SARS-CoV-2 wildtype or Omicron B.1.1.529 spike peptide pools. Depicted are IL-2 and IL-4 responses across all participants (n=46) pooled at time point T5, as defined in A. Values are reported in pg/mL after subtracting background signal from wells containing PBMCs cultured with DMSO alone, as indicated by 'Δ'. SQRT refers to square root transformation of the data for visualisation purposes. The median is indicated by the black line. Pairwise comparisons were made by Mann-Whitney U test after excluding subjects with a nucleocapsid (NP) IgG response and/or previously diagnosed with COVID-19. NS, non-significant; RBD, receptor binding domain; FPR, false positive rate; PBMC, peripheral blood mononuclear cells; DMSO, dimethyl sulfoxide; SQRT, square root.

assessed T cell responses against Omicron B.1.1.529, and observed no difference in IL-2 and IL-4 responses compared with wild-type (figure 1C,D) in agreement with similar studies in healthy individuals.[4 5]

Thus, we observed robust serological and cellular responses in patients with IMID following the third dose of SARS-CoV-2 mRNA vaccine. Importantly, the third dose rescues waning of T cell-mediated and antibody-mediated immunity in patients with IMID observed by 3 months after the second dose. Additionally, patients with IMID retain T cell immunity to Omicron B.1.1.529. Our results agree with a recent systematic review and meta-analysis.[6] Future studies will analyse additional cellular and humoral readouts, durability of the responses and effect of additional doses in this cohort.

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Contributors MWC conducted T cell assays, analysed data and edited manuscript. RMD analysed antibody data, conducted statistical analysis, prepared figures and edited the manuscript. JCL designed and assisted with T cell assays. RLG contributed to study conception and design. GYCC provided overall project management including patient recruitment and validation of data records. JMS and DP contributed to project management and patient recruitment. NF, DC, LA, SR, JDL and DG contributed to patient recruitment. RL assisted with PBMC preparation. MD-B and GM handled samples and conducted ELISA assays. A-CG and THW contributed to study design, supervised the laboratory assays, analyzed data, acquired funding and edited the manuscript. VP and MSS contributed to study design, acquisition of funding, supervised clinical coordinators, contributed to data interpretation and manuscript editing. VC contributed to study design, acquisition of funding, supervision of patient recruitment, data analysis and wrote the manuscript.

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Competing interests VP has no personal financial ties with any pharmaceutical company but has received honoraria for speaker and/or advisory board member roles from AbbVie, Almirall, Celgene, Janssen, Kyowa Kirin, LEO Pharma, Novartis, Pfizer, Sanofi, UCB and Union Therapeutics. In his role as Department Division Director of Dermatology at the University of Toronto, VP has received departmental support in the form of unrestricted educational grants from AbbVie, Bausch Health, Celgene, Janssen, LEO Pharma, Eli Lilly, L'Oréal, NAOS, Novartis, Pfizer, Pierre-Fabre, Sandoz and Sanofi in the past 36 months. MSS has received research support, consulting fees and speaker honoraria from AbbVie, Janssen, Takeda, Pfizer, Gilead, and Amgen. VC has received research grants from AbbVie, Amgen and Eli Lilly and has received honoraria for advisory board member roles from AbbVie, Amgen, BMS, Eli Lilly, Janssen, Novartis, Pfizer and UCB. His spouse is an employee of AstraZeneca. None of the other authors have any conflicts of interest.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study was approved by the ethics boards of the University of Toronto (REB 7673), Sinai Health System (REB 21-0022-E), University Health Network (REB 21-5096) and Women's College Hospital (REB 2021-0023-E). Participants gave informed consent to participate in the study before taking part.

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