Antibody response to the BNT162b2 SARS-CoV-2 vaccine in paediatric patients with inflammatory bowel disease treated with anti-TNF therapy

We read with interest the recent findings by Kennedy *et al*, which concluded that infliximab (IFX) impairs antibody responses to a single dose of the mRNA-BNT162b2 SARS-CoV-2 vaccine in adult patients with IBD.[1 2] Interestingly, another study showed that antibodies against SARS-CoV-2 diminish over time following infection in adult patients with IBD.[3] In general, more robust antibody responses have been observed in adolescents compared with adults in the BNT162b2 vaccine trial.[4] However, the true impact of immunosuppressant therapies on SARS-CoV-2 vaccine efficacy in paediatric IBD (PIBD) patients is unknown as they were excluded from the trials. Therefore, analysing vaccine responses directly in these patients is necessary to determine the best strategy.[5 6]

We undertook a study to evaluate immunogenicity of mRNA-based SARS-CoV-2 vaccines in PIBD patients treated with anti-TNF therapies. Given the urgent need for data, we herein present preliminary findings. The study prospectively enrolled PIBD patients 12–17 years, treated with anti-TNF agents either alone or in combination with an immunomodulator, who received the BNT162b2 vaccine. Serum antibody levels for (spike protein, receptor-binding domain (RBD) and nucleocapsid protein) were measured at baseline, 28 days and 3 months after the first vaccine dose. Antibody responses were assessed using the V-PLEX SARS-CoV-2 Panel 2 (IgG) assay (Meso Scale Diagnostics, catalogue number K15383U), where the data are reported as arbitrary units per mL. Kennedy *et al* used a different assay reported as units per mL. While both assays measured antibodies against portions of the spike antigen, differences in assays may affect the interpretation. Therefore, we also measured antibody viral neutralisation against the Wuhan 'wild-type' SARS-CoV-2/Canada/VIDO-01/2020 strain.[7]

In a preliminary analysis of 42 PIBD patients (PIBD A) on maintenance IFX monotherapy (baseline characteristics shown in table 1), spike and RBD antibody concentrations were comparable with uninfected healthy adults (n=20, median age: 36 years (IQR 29–40); 65% female) 28 days after first BNT162b2 dose (figure 1A). In contrast, in paediatric patients on IFX in combination with methotrexate or azathioprine, spike and RBD antibody concentrations were significantly lower than healthy controls (figure 1A). Nevertheless, after two doses of BNT162b2, there was no difference in antibody response 3 months after the first vaccine dose in a separate cohort of PIBD patients (PIBD B) on IFX alone or in combination with methotrexate or azathioprine, compared with healthy adults (n=12, median age:

Table 1 Demographics and clinical characteristics of PIBD cohorts

Baseline characteristics	PIBD cohort A (n=42)	PIBD cohort B (n=26)
Age, median (IQR)	14.5 (14–16)	15.0 (14–16)
Sex, n (%)		
Female	18 (42.8)	11 (42.3)
IBD subtype, n (%)		
CD	33 (78.6)	16 (61.5)
UC	9 (21.4)	10 (38.4)
Disease activity, n (%) *		
Remission		
Mild	4 (9.5)	3 (11.5)
Treatment, n (%)		
Infliximab monotherapy	18 (42.8)	11 (42.3)
Infliximab with methotrexate/azathioprine†	24 (57.1)	14 (53.8)
Adalimumab monotherapy	—	—
Adalimumab with methotrexate†	—	1 (3.8)
Doses of BNT162b2 SARS-CoV-2 vaccine received	1	2
Interval between 2 doses, median in days (range)	—	56 (22–105)

*Disease activity was assessed using PUCAI/PCDAI SCORES; REMISSION <10 and mild 10–30.
†Methotrexate (mean±SD, 14.4 mg±4.8), azathioprine (mean±SD, 83.8 mg±38.4).
CD, crohn's disease ; PCDAI, Pediatric Crohn's Disease Activity Index; PIBD, paediatric IBD; PUCAI, Pediatric Ulcerative Colitis Activity Index; UC, ulcerative colitis.

48 years (IQR 39–53), 21% female, median interval between doses 46 days (range 42–86)) (figure 1A).

When we assessed live viral neutralising capacity, we detected no significant difference at 3 months between PIBD patients receiving IFX monotherapy and health adults. Though most PIBD patients on combination therapy showed good antibody levels, their live virus neutralising capacity was statistically significantly lower than adults and paediatric patients on IFX monotherapy (figure 1B).

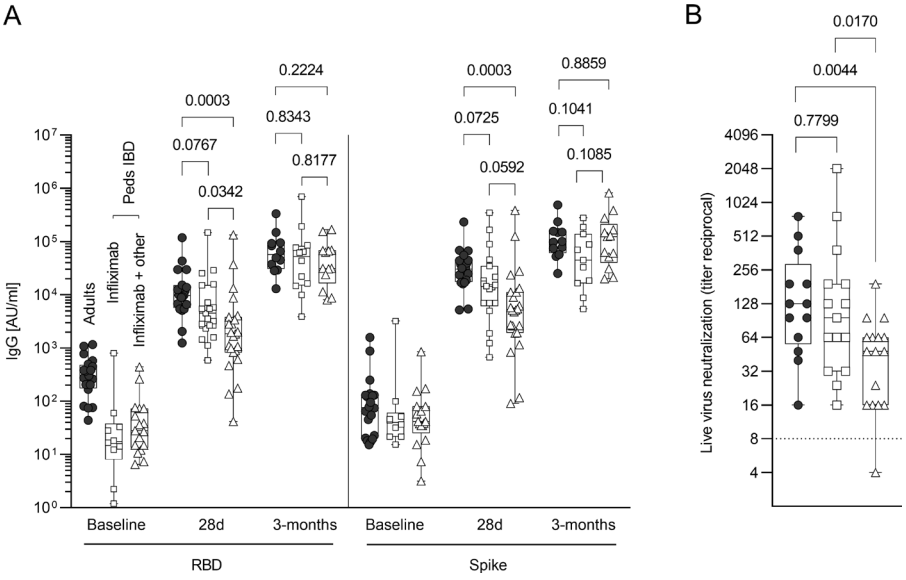

Figure 1 SARS-CoV-2 antibody outcomes in paediatric IBD patients compared with healthy adults before and after the BNT162b2 SARS-CoV-2 vaccine. (A) Serum IgG antibody levels against SARS-CoV-2 receptor-binding domain (RBD) and spike proteins in healthy adults (black circles), paediatric IBD patients (infliximab monotherapy (white squares) and infliximab therapy in combination with methotrexate or azathioprine (white triangles)) at baseline, 28 days after a single dose, and after two doses of BNT162b2 when measured 3 months after the first dose. (B) Reciprocal of the highest dilution where live virus neutralisation is detected in vitro in healthy adults (black circles), and paediatric IBD patients who received infliximab monotherapy (white squares), or in combination with methotrexate or azathioprine (white triangles). All data shown as boxes (25–75 percentiles) and whiskers with relevant p values (unpaired, two-sided t-tests on log-10 transformed antibody levels). AU, arbitrary units.

In conclusion, we provide preliminary evidence of attenuated antibody responses to BNT162b2 in children on IFX in combination with an immunomodulator. However, our data also show that most PIBD patients receiving IFX as monotherapy or combination therapy develop acceptable antibody responses compared with adults. Though these results are based on a small sample size, they provide reassuring data and contrast with the data reported by Kennedy *et al*.[1 2] These novel findings also highlight the importance of booster doses to achieve complete protection in these vulnerable patients.[4] Further investigations are warranted to determine the longevity of the immune responses and protection afforded by completed vaccine courses in PIBD patients receiving IFX combined with an immunomodulator. We are optimistic that the data generated from this study will provide real-time evidence informing guidelines for clinicians caring for this vulnerable group of patients.

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Contributors KJ has full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. KJ and PML conceived the study. KJ, PML, SL, ZJS and FR designed the study. ZJS and HS were responsible for clinical data. PML, FR, LG and AM were responsible for serological data. PNL was responsible for neutralisation data. KJ, PML, SL, ZJS and FR analysed the data. ZJS drafted the manuscript. All authors interpreted the data and provided critical revisions of the manuscript for important intellectual content. All authors approved the final draft of the manuscript.

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