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Title: Combination therapy of infliximab and thiopurines, but not monotherapy with infliximab or vedolizumab, is associated with attenuated IgA and neutralisation responses to SARS-CoV-2 in inflammatory bowel disease.

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Text:
The effect of immunomodulator and biological therapy for inflammatory bowel disease (IBD) on the immune response to SARS-CoV-2 is of substantial interest to patients and clinicians worldwide. The CLARITY IBD study recently reported attenuated serological responses in IBD patients treated with infliximab in comparison to vedolizumab1, with the effect greatest in those on infliximab/thiopurine combination therapy. Independently, the global SECURE-IBD registry highlighted that infliximab/thiopurine
combination therapy, but not infliximab or vedolizumab monotherapies, was associated with more severe clinical outcomes upon SARS-CoV-2 infection\textsuperscript{2,3}.

However, these studies have not addressed treatment effects on neutralising antibody responses, which are associated with protection to SARS-CoV-2; nor have they analysed the range of serological signatures that may influence clinical outcomes\textsuperscript{4,5}.

To answer these questions, we performed an extended analysis of serological responses to SARS-CoV-2 infection in seropositive IBD patients treated with either infliximab or vedolizumab monotherapy, or infliximab/thiopurine combination therapy (Figures 1&2). Blood samples were collected from consenting patients attending infusion centres in Oxford and London between May and December 2020. Sera were initially screened by Abbott assay for SARS-CoV-2 antibody responses\textsuperscript{6}. Serological reactivity profiles in positive samples were compared with those from healthy adult controls seropositive in the same assay\textsuperscript{7} (Supplementary information table 1).

Antibody reactivity to the receptor-binding domain (RBD) of the SARS-CoV-2 spike, full-length spike (S), and the nucleocapsid (N) was assayed by IgG/IgA standard enzyme-linked immunosorbent assays (ELISA) and IgG high-throughput MSD V-PLEX assay. An ACE2-SARS-CoV-2 RBD inhibition assay was used to detect neutralising antibodies\textsuperscript{5,8}.

All treatments were associated with significantly reduced IgG antibody responses compared to healthy controls for all SARS-CoV-2 antigens, using an MSD V-PLEX assay (Figure 1). The greatest reduction in IgG response by ELISA was observed in individuals treated with infliximab/thiopurine combination therapy (Figure 2a; p=0.00019). Furthermore, IgA responses were significantly reduced in individuals treated with infliximab/thiopurine combination therapy compared to healthy controls (Figure 2b; p=0.009), but not in IBD patients treated with infliximab or vedolizumab monotherapy.

Next, we utilized an ELISA-based inhibition assay to determine the ability of serum to neutralize the binding of SARS-CoV-2 RBD-ACE2 interaction (Figure 2c). Individuals treated with vedolizumab or infliximab monotherapy did not show a significant difference in neutralising antibody responses compared to healthy individuals (Figure 2c). However, individuals treated with infliximab/thiopurine combination therapy showed a significantly reduced response compared to either monotherapy groups, and to the healthy control group (Figure 2c, p=0.0054, 0.0022 and p= 0.0092).
Our data are novel, firstly in demonstrating that infliximab/thiopurine combination therapy is associated with significantly lower IgA as well as a range of IgG responses, and most importantly, with impaired functional neutralising antibody responses, compared to responses in healthy individuals. Secondly, we show that whilst IgG responses were significantly reduced in individuals with IBD treated with infliximab or vedolizumab monotherapy compared to healthy controls, this was not the case for IgA and neutralising antibody responses. As neutralising antibody responses are associated with protection\textsuperscript{9,10}, this observation may provide the mechanistic explanation for the observation reported by the SECURE-IBD study that individuals with combination therapy were at greater risk of severe COVID-19 outcomes than patients on monotherapy\textsuperscript{9,10}.

The interpretation of these data requires circumspection in view of the relatively modest size of the study, notwithstanding the significant differences between treatment groups. In this context we present these data as an important basis to direct further research in this field rather than to alter clinical practice.

In demonstrating that these therapeutic interventions are selectively associated with a pattern of attenuated antibody responses to SARS-CoV-2 infection compared to healthy controls, we believe these data extend current understanding in this important area, and have potentially important implications for patient care and vaccination strategies.

References:


Figure legends

**Figure 1. IgG responses to whole spike, receptor binding domain and nucleocapsid following SARS-CoV2 detection in IBD patients and healthy controls.** A. IgG SARS-CoV-2 spike responses measured by high throughput V-PLEX MSD ELISA. B. IgG SARS-CoV-2 receptor binding domain (RBD) of the spike responses measured by VPLEX MSD. C. IgG SARS-CoV-2 nucleocapsid responses measured by VPLEX MSD. Ifx = infliximab monotherapy, ifx+thiopurines = infliximab/thiopurine combination therapy vdz = vedolimamab monotherapy. P-values are derived from a Wilcoxon (rank-sum) test for unpaired populations, not adjusted for multiple comparisons.

**Figure 2. Neutralisation and IgA/IgG response following SARS-CoV2 detection in IBD patients and healthy controls.** A. IgG SARS-CoV-2 spike responses measured by indirect ELISA. B IgA SARS-CoV-2 spike responses measured by indirect ELISA. C. Neutralising antibody responses measured by ACE2-RBD inhibition ELISA. Ifx = infliximab monotherapy, ifx+thiopurines = infliximab/thiopurine combination therapy vdz = vedolimamab monotherapy. P-values are derived from a Wilcoxon (rank-sum) test for unpaired populations, not adjusted for multiple comparisons.