

Risk of adverse events and reported clinical relapse after COVID-19 vaccination in patients with IBD

We have read with interest the recent papers of Kennedy *et al*^{1,2} regarding the attenuated anti-SARS-CoV-2 antibody response in patients with IBD and the crucial role of the COVID-19 vaccine in this cohort. The COVID-19 vaccine has been recommended especially for the vulnerable population, including immune-mediated inflammatory diseases.³⁻⁵ Therefore, we explored the rate of adverse events (AEs) and the onset of GI symptoms after vaccination

Table 1 Patients' demographics and characteristics

| Characteristics | Total (N=488) |
|---------------------------------------|---------------|
| Age (years), mean (SD) | 55.3 (14.4) |
| Gender (male), n (%) | 218 (44.9) |
| Type of disease, n (%) | |
| UC | 246 (50.4) |
| CD | 233 (47.8) |
| IBD-U | 9 (1.8) |
| Disease duration (years), mean (SD) | 18.4 (10.3) |
| Therapy, n (%) | |
| No treatment | 132 (27.1) |
| Mesalamine | 227 (46.5) |
| Corticosteroids | 13 (2.7) |
| Azathioprine | 32 (6.6) |
| Anti-tumour necrosis factor- α | 75 (15.4) |
| Infliximab | 21 (4.3) |
| Adalimumab | 49 (10.0) |
| Golimumab | 5 (1.0) |
| Vedolizumab | 28 (5.7) |
| Ustekinumab | 21 (4.3) |
| Tofacitinib | 2 (0.4) |
| Previous COVID-19, n (%) | 42 (8.6) |
| COVID-19 vaccine, n (%) | |
| Only one dose | 55 (11.3) |
| Two doses | 433 (88.7) |
| COVID-19 vaccine type, n (%) | |
| BNT162b2 (Pfizer) | 320 (65.6) |
| mRNA-1273 (Moderna) | 150 (30.7) |
| Vaxzevria (AstraZeneca) | 18 (3.7) |
| Remission of disease, n (%) | 397 (81.4) |
| State of mind before vaccine, n (%) | |
| Unconcerned | 118 (24.2) |
| Afraid | 23 (4.7) |
| Anxious | 89 (18.2) |
| Wishful | 246 (50.4) |
| Glad | 12 (2.5) |

CD, Crohn's disease; IBD-U, undetermined IBD; UC, Ulcerative Colitis.

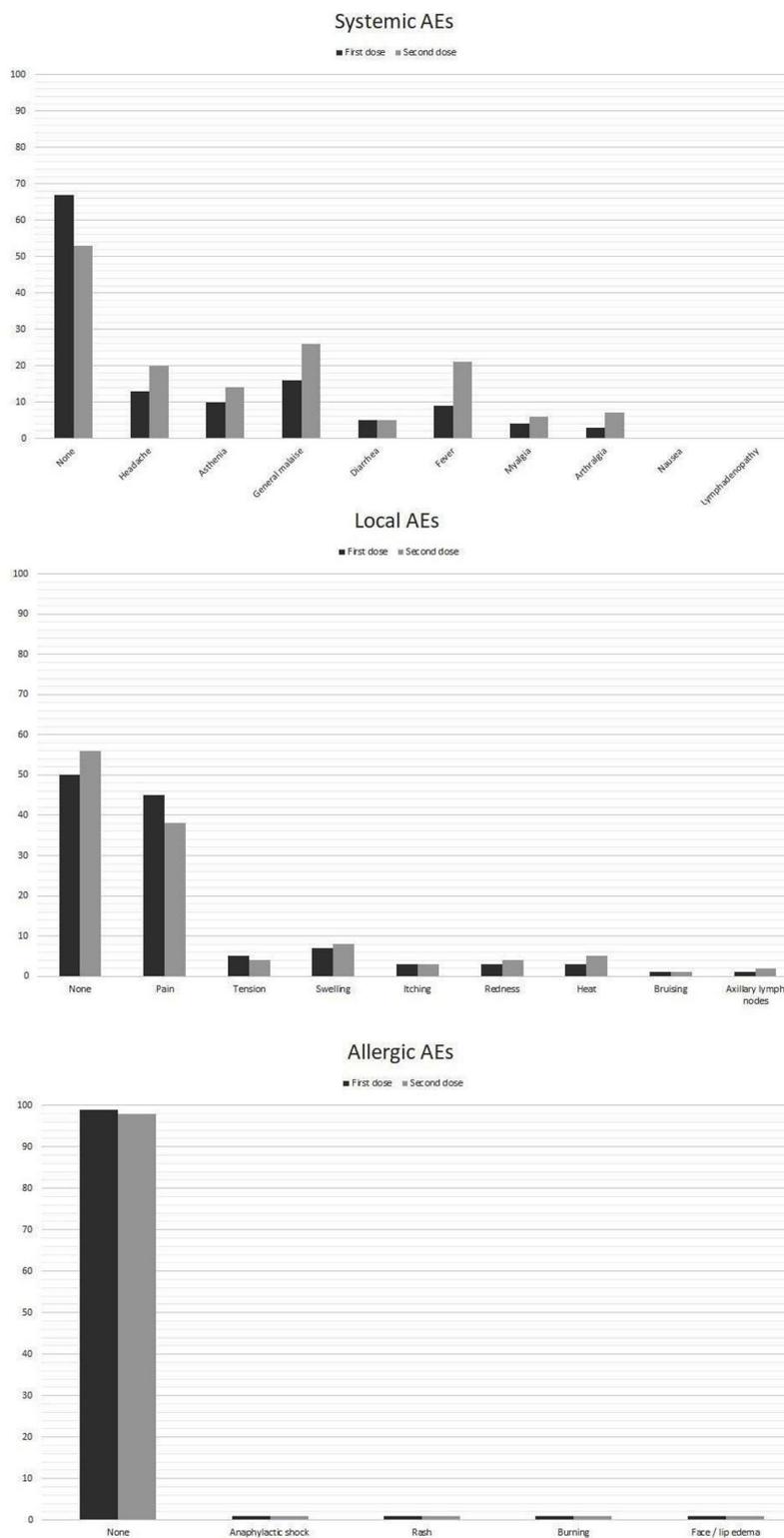


Figure 1 Systemic, local and allergic adverse events (AEs) in our IBD cohort. Data are expressed in %.

with different COVID-19 vaccines in a large cohort of patients with IBD.

In this prospective study, we collected data (demographic and clinical variables, COVID-19 vaccine type, local, systemic or allergic AEs, and GI symptoms) from 488 (mean

age \pm SD 55.3 \pm 14.4 years, 44.9% male) patients with IBD (UC 50.4%, Crohn's disease 47.8% and undetermined IBD 1.8%) on regular follow-up at our IBD unit who had been administered COVID-19 vaccination from June to July 2021.

The demographic characteristics are shown in table 1. AEs were reported by 228 patients (46.7%) (figure 1). The most common systemic AE after the first dose was malaise (16.4%), followed by headache (12.9%) and asthenia (10.5%). After the second dose, there were more systemic AEs, such as malaise (26.4%), fever (20.7%) and headache (19.7%). Regarding local AEs, 220 (45.1%) and 186 (38.1%) patients experienced pain at the site of injection after the first and second dose, respectively. Finally, no severe allergic AEs were reported. The overall rate of AEs was similar to that reported in the general population.⁶

GI symptoms suggestive of current bowel disease such as 'increase of bowel movements', 'abdominal pain', 'blood in stool' and 'vomiting' were reported by 11.1%, 6.6%, 3.5% and 1.2% of patients, respectively. Globally, GI symptoms were reported by 15.6% (76 of 488) of patients at a mean±SD of 3±3.4 days after the vaccine, with a minimum of 1 day and a maximum of 15 days. However, virtually all cases were mild and self-limiting, and only one patient needed hospitalisation and consequent surgery due to a pre-existing substenotic pouchitis.

According to univariate and multivariate analyses (online supplemental file 1) and in line with a recent survey by Botwin *et al*,⁷ AEs are more common among younger patients (OR 0.96, $p < 0.0005$) and in cases of previous COVID-19 infection (OR 2.3, $p = 0.021$). Regarding ongoing therapy, we found azathioprine (OR 0.39) to be inversely correlated to the presence of any AEs, while anti-tumour necrosis factor therapy (OR 2.01) was statistically significant only in the univariate analysis. Moreover, in the multivariate analysis, female gender was found to be a risk factor for developing any AEs (OR 1.96).

Regarding GI symptoms, we observed a higher rate of diarrhoea and abdominal pain compared with that reported by trials in the general population.^{6,8} Age (OR 0.97) and disease remission (OR 0.43) inversely correlated with onset of GI symptoms both in the univariate and multivariate analyses (online supplemental file 1). To date, there has been no evidence that COVID-19 vaccination can trigger a flare-up, in accordance with prior

experience which did not report any flares after vaccination.⁹

In conclusion, COVID-19 vaccination is highly recommended to patients with IBD and the rate of reported AEs is similar to the general population. In our cohort, a slightly higher rate of GI symptoms was observed, especially in younger patients with a concomitant active disease. However, the course of reported clinical flares is benign and self-limiting and should not discourage vaccine administration. Our findings suggest that in patients with active IBD, the decision to provide or postpone the vaccine in active disease should be tailored to each patient. Moreover, our data were based on a short-term follow-up and further studies on long-term AEs with objective markers are needed to state clearer recommendations.

Rosanna Cannatelli , **Francesca Ferretti**, **Stefania Carmagnola**, **Irene Maria Bambina Bergna**, **Maria Camilla Monico**, **Giovanni Maconi** , **Sandro Ardizzone**

Gastroenterology and Digestive Endoscopy Unit, Department of Biochemical and Clinical Sciences 'L Sacco', University of Milan, ASST Fatebenefratelli Sacco, Milano, Italy

Correspondence to Dr Rosanna Cannatelli, Gastroenterology and Digestive Endoscopy Unit, Department of Biochemical and Clinical Sciences "L. Sacco", University of Milan, ASST Fatebenefratelli Sacco, Milano, Lombardia, Italy; cannatelli.rosanna@asst-fbf-sacco.it

Contributors RC, FF, SA and GM: planning the study, drafting the article, statistical analysis and interpretation of data. All other authors: data collection and critical revision of the article for important intellectual content. All authors approved the final version of the manuscript including the authorship list.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

© Author(s) (or their employer(s)) 2021. No commercial re-use. See rights and permissions. Published by BMJ.

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/gutjnl-2021-326237>).



To cite Cannatelli R, Ferretti F, Carmagnola S, *et al*. Gut Epub ahead of print: [please include Day Month Year]. doi:10.1136/gutjnl-2021-326237

Received 1 October 2021

Accepted 16 November 2021

Gut 2021;0:1–2. doi:10.1136/gutjnl-2021-326237

ORCID iDs

Rosanna Cannatelli <http://orcid.org/0000-0001-8378-0724>

Giovanni Maconi <http://orcid.org/0000-0003-0810-4026>

REFERENCES

- Kennedy NA, Goodhand JR, Bewshea C. Contributors to the clarity IBD study. Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. *Gut* 2021;70:865–75.
- Kennedy NA, Lin S, Goodhand JR, *et al*. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. *Gut* 2021;70:1884–93.
- Siegel CA, Melmed GY, McGovern DP. International organization for the study of inflammatory bowel diseases (IOIBD). SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut* 2021;70:635–40.
- Maconi G, Bosetti C, De Monti A, *et al*. Risk of COVID 19 in patients with inflammatory bowel diseases compared to a control population. *Dig Liver Dis* 2021;53:263–70.
- Ferretti F, Cannatelli R, Benucci M, *et al*. How to manage COVID-19 vaccination in immune-mediated inflammatory diseases: an expert opinion by IMIDs Study Group. *Front Immunol* 2021;12:656362.
- Polack FP, Thomas SJ, Kitchin N, *et al*. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383:2603–15.
- Botwin GJ, Li D, Figueiredo J, *et al*. Adverse events after SARS-CoV-2 mRNA vaccination among patients with inflammatory bowel disease. *Am J Gastroenterol* 2021;116:1746–51.
- Kadali RAK, Janagama R, Peruru S, *et al*. Side effects of BNT162b2 mRNA COVID-19 vaccine: a randomized, cross-sectional study with detailed self-reported symptoms from healthcare workers. *Int J Infect Dis* 2021;106:376–81.
- Rahier J-F, Papay P, Salleron J, *et al*. H1N1 vaccines in a large observational cohort of patients with inflammatory bowel disease treated with immunomodulators and biological therapy. *Gut* 2011;60:456–62.

Supplementary Table 1. Any adverse event (AE) and GI AEs at univariate and multivariate regression.

| Variable | Any AE | | | |
|------------------------------|------------------|-------------------|------------------|-------------------|
| | Univariate | | Multivariate | |
| | OR (95% CI) | <i>p</i> | OR (95% CI) | <i>p</i> |
| Age | 0.96 (0.95-0.97) | <0.0005 | 0.96 (0.95-0.98) | <0.0005 |
| Male gender | 0.47 (0.32-0.68) | <0.0005 | 0.51 (0.35-0.75) | 0.001 |
| Disease duration | 0.97 (0.96-0.99) | 0.006 | 0.99 (0.97-1.01) | 0.504 |
| Any therapy | 1.38 (0.92-2.07) | 0.118 | | |
| Mesalamine | 1.14 (0.80-1.63) | 0.473 | | |
| Steroids | 0.98 (0.32-2.95) | 0.967 | | |
| Azathioprine | 0.42 (0.19-0.94) | 0.034 | 0.39 (0.16-0.90) | 0.028 |
| Anti-TNFa | 2.01 (1.22-3.33) | 0.006 | 1.53 (0.89-2.64) | 0.128 |
| Vedolizumab | 0.99 (0.46-2.12) | 0.974 | | |
| Ustekinumab | 1.04 (0.43-2.49) | 0.933 | | |
| Previous COVID | 1.96 (1.02-3.76) | 0.042 | 2.31 (1.14-4.69) | 0.021 |
| Vaccine type | 1.83 (0.70-4.81) | 0.219 | | |
| Remission of disease | 0.92 (0.58-1.46) | 0.730 | | |
| State of mind before vaccine | 0.99 (0.86-1.14) | 0.879 | | |
| State of mind after vaccine | 0.96 (0.87-1.06) | 0.386 | | |

| Variable | Gastrointestinal AEs | | | |
|------------------------------|----------------------|-------------------|------------------|-------------------|
| | Univariate | | Multivariate | |
| | OR (95% CI) | <i>p</i> | OR (95% CI) | <i>p</i> |
| Age | 0.96 (0.95-0.98) | <0.0005 | 0.97 (0.95-0.98) | <0.0005 |
| Male gender | 0.65 (0.39-1.06) | 0.086 | | |
| Disease duration | 0.99 (0.96-1.00) | 0.289 | | |
| Any therapy | 0.97 (0.56-1.67) | 0.901 | | |
| Mesalamine | 0.86 (0.53-1.41) | 0.556 | | |
| Steroids | 0.99 (0.21-4.54) | 0.985 | | |
| Azathioprine | 1.00 (0.37-2.70) | 0.993 | | |
| Anti-TNFa | 1.04 (0.53-2.03) | 0.912 | | |
| Vedolizumab | 1.52 (0.59-3.88) | 0.382 | | |
| Ustekinumab | 1.29 (0.42-3.95) | 0.654 | | |
| Previous COVID | 1.80 (0.84-3.83) | 0.128 | | |
| Vaccine type | 0.67 (0.15-2.97) | 0.597 | | |
| Remission of disease | 0.42 (0.24-0.73) | 0.002 | 0.43 (0.24-0.77) | 0.004 |
| State of mind before vaccine | 1.02 (0.84-1.24) | 0.822 | | |
| State of mind after vaccine | 0.96 (0.84-1.10) | 0.561 | | |