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Letter: risk of severe COVID-19 outcomes associated with inflammatory bowel disease medications—reassuring insights from the United Kingdom PREPARE-IBD multicentre cohort study

EDITORS,

We read with interest the study by *Taxonera et al*, describing clinical characteristics and mortality associated with COVID-19 in a Spanish inflammatory bowel disease (IBD) cohort.[1] During the early COVID-19 pandemic, the British Society of Gastroenterology (BSG) developed a risk stratification grid to inform the United Kingdom (UK) government regarding strict social isolation, termed 'shielding'.[2] IBD patients thought to be most clinically vulnerable to SARS-CoV-2 included recent commencement of combination biologic and immunomodulator therapy, prednisolone ≥20 mg/day, comorbidities, age ≥70 years or clinically active disease in those receiving immunosuppression. Mesalazine was not considered to increase risk. An acknowledged limitation was an absence of COVID-19 risk data, with extrapolation from historical cohort studies reporting opportunistic infections.[3-5]

We sought to identify patient or IBD medication-related factors associated with severe outcomes from COVID-19 in the UK. PREPARE-IBD was a national multicentre observational cohort study including adult IBD patients (≥18 years) diagnosed with COVID-19 by PCR between 1 March 2020 and 31 August 2020. There were no exclusion criteria. Sites were asked for complete identification of patients meeting the inclusion criteria to reduce bias. Clinical data were entered pseudonymised into a secure REDCap server. The study was approved by Leeds and Bradford ethics committee (Reference: 20/HRA/2578). The primary outcome was severe COVID-19 defined as requirement for intensive care admission, invasive ventilation or death. We tested associations of severe outcomes with medications and other covariates, identified from published studies of severe COVID-19 risk,[1,6-9] using multiple logistic regression. Analysis was carried out using R 4.0.2 (R Foundation for Statistical Computing).

Two hundred and eleven patients were included from 60 UK centres. Baseline characteristics, laboratory, clinical data and outcomes are shown in Table 1. Fifty-six of 211 patients (26.5%) met the primary outcome. A higher proportion of severe COVID-19 was seen in ulcerative colitis relative to Crohn's disease patients (33.9% [37/109] vs 18.6% [16/86], $P = 0.018$). Multivariable analysis identified comorbidities and age as associated with severe COVID-19 outcomes; odds ratio (OR [95% CI]) 1.68 (1.23-2.35) for each comorbidity, and an OR 1.03 (1.00-1.05) with each successive year of age. Neither clinically active IBD (OR 0.58 [0.26-1.26]), non-white ethnicity (OR 1.98 [0.92-4.28]), nor prednisolone use (OR 2.42 [0.47-11.26]) were associated with increased risk. Consistent with data from the Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) registry,[6,7] on multivariable analysis, mesalazine was associated with severe COVID-19 outcomes (OR 2.03 [1.01-4.12]). Mesalazine use was associated with older age (median 64 [IQR 49-75] vs 56 [IQR 39-73] years, $P = 0.027$) and lower use of biologics (9% [8/91] vs 34% [41/120], $P < 0.001$). Also consistent with SECURE-IBD, univariable analysis identified biologics as protective ($P = 0.031$). In contrast to SECURE-IBD data, univariable analysis showed a protective association with thiopurines ($P = 0.041$). However, on multivariable analysis, no association of severe COVID-19 outcomes with thiopurine or biologic exposure was seen.

Our data provide reassurance for continued evidence-based use of corticosteroids, immunomodulators and biologics in IBD during the ongoing COVID-19 pandemic, and is consistent with an as yet unexplained association between mesalazine use and severe COVID-19 outcomes.

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The complete list of affiliations for the authors are listed in Appendix 1.

PREPARE-IBD Study Group names and affiliations listed in Appendix S2 and Table S1.

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TABLE 1 Risk of severe COVID-19 outcomes with inflammatory bowel disease medications

Baseline demographics, comorbidities, medications and COVID-19 symptoms				
Variable	**Non-severe outcome (n = 155)**	**Severe outcome (n = 56)**	**OR (95% CI)**	***P* value***
Sex				
Female	47.7% (74/155)	35.7% (20/56)	Reference	
Male	51.6% (80/155)	64.3% (36/56)	1.7 (0.89-3.2)	0.11
Other	0.6% (1/155)	0.0% (0/56)		0.99
Age/years	55.0 (37.0-71.0)	73.0 (59.8-81.0)	1.05 (1.03-1.07)	<0.001
IBD type				
Crohn's disease	45.2% (70/155)	28.6% (16/56)	Reference	
Ulcerative colitis	46.5% (72/155)	66.1% (37/56)	2.2 (1.2-4.5)	0.018
IBD unclassified (IBD-U)	8.4% (13/155)	5.4% (3/56)	1 (0.21-3.6)	0.99
BMI	26.3 (22.6-30.1)	26.3 (21.3-29.7)	1 (0.94-1.1)	0.92
Non-white ethnicity	27.1% (42/155)	33.9% (19/56)	1.4 (0.71-2.6)	0.33
Smoking				
Non-smoker and never smoked	47.7% (72/151)	20.0% (11/55)	Reference	
Ex-smoker	17.9% (27/151)	30.9% (17/55)	4.1 (1.7-10)	0.0016
Current smoker	4.0% (6/151)	3.6% (2/55)	2.2 (0.29-11)	0.37
Unknown	30.5% (46/151)	45.5% (25/55)	3.6 (1.6-8.2)	0.0019
Count of comorbidities				
0	50.0% (69/138)	23.5% (8/34)	Reference	
1	37.0% (51/138)	41.2% (14/34)	2.4 (0.94-6.3)	0.073
≥2	13.0% (18/138)	35.3% (12/34)	5.7 (2.1-17)	<0.001
Comorbidities				
Asthma	11.6% (18/155)	21.4% (12/56)	2.1 (0.91-4.6)	0.076
Chronic obstructive pulmonary disease	5.2% (8/155)	12.5% (7/56)	2.6 (0.88-7.7)	0.076
Other chronic lung disease	0.6% (1/155)	5.4% (3/56)	8.7 (1.1-1.8e+02)	0.063
Hypertension	14.8% (23/155)	51.8% (29/56)	6.2 (3.1-12)	<0.001
Cardiovascular disease	15.5% (24/155)	33.9% (19/56)	2.8 (1.4-5.7)	0.0041
History of stroke	3.9% (6/155)	8.9% (5/56)	2.4 (0.68-8.4)	0.16
Chronic kidney disease	1.9% (3/155)	12.5% (7/56)	7.2 (1.9-35)	0.0053
Chronic liver disease	1.9% (3/155)	3.6% (2/56)	1.9 (0.24-12)	0.5
Current malignancy	7.1% (11/155)	1.8% (1/56)	0.24 (0.013-1.3)	0.17
Dementia	4.5% (7/155)	8.9% (5/56)	2.1 (0.59-6.8)	0.23
Diabetes	11.0% (17/155)	25.0% (14/56)	2.7 (1.2-6)	0.013
Inflammatory arthritis	7.7% (12/155)	16.1% (9/56)	2.3 (0.88-5.7)	0.08
Obesity	5.2% (8/155)	5.4% (3/56)	1.0 (0.22-3.7)	0.95
IBD disease activity based on PGA at onset of their illness				
Inactive disease	53.3% (81/152)	76.8% (43/56)	Reference	
Mild activity	18.4% (28/152)	5.4% (3/56)	0.2 (0.046-0.61)	0.012
Moderate activity	18.4% (28/152)	8.9% (5/56)	0.34 (0.11-0.87)	0.036
Severe activity	9.9% (15/152)	8.9% (5/56)	0.63 (0.19-1.7)	0.4
IBD treatment at presentation				
Mesalazine	37.4% (58/155)	58.9% (33/56)	2.4 (1.3-4.5)	0.006
Prednisolone	3.9% (6/155)	7.1% (4/56)	1.9 (0.47-7)	0.33

(Continues)

TABLE 1 (Continued)

Baseline demographics, comorbidities, medications and COVID-19 symptoms				
Variable	**Non-severe outcome (n = 155)**	**Severe outcome (n = 56)**	**OR (95% CI)**	***P* value***
Thiopurine	19.4% (30/155)	7.1% (4/56)	0.32 (0.092-0.86)	0.041
Vedolizumab	7.7% (12/155)	3.6% (2/56)	0.44 (0.067-1.7)	0.29
Anti-TNF	18.1% (28/155)	7.1% (4/56)	0.35 (0.1-0.94)	0.06
Biologics	27.1% (42/155)	12.5% (7/56)	0.38 (0.15-0.87)	0.031
Symptoms of COVID-19				
Fever	53.5% (83/155)	64.3% (36/56)	1.6 (0.84-3)	0.17
Cough	47.7% (74/155)	60.7% (34/56)	1.7 (0.91-3.2)	0.098
Shortness of breath	35.5% (55/155)	66.1% (37/56)	3.5 (1.9-6.8)	<0.001
Abdominal pain	6.5% (10/155)	10.7% (6/56)	1.7 (0.57-4.9)	0.31
Nausea and vomiting	2.6% (4/155)	10.7% (6/56)	4.5 (1.2-18)	0.023
Increased diarrhoea	14.2% (22/155)	8.9% (5/56)	0.59 (0.19-1.5)	0.32
Fatigue	18.7% (29/155)	28.6% (16/56)	1.7 (0.85-3.5)	0.13
Headache	5.8% (9/155)	5.4% (3/56)	0.92 (0.2-3.2)	0.9
Loss of smell	5.8% (9/155)	0.0% (0/56)		0.98
Loss of taste	6.5% (10/155)	0.0% (0/56)		0.98
Other symptoms	14.8% (23/155)	12.5% (7/56)	0.82 (0.31-1.9)	0.67
Multivariable logistic regression of non-medication factors and severe COVID-19 outcomes				
Variable	**OR (95% CI)**			***P* value****
Age (for each year)	1.03 (1.00-1.05)			0.035
Comorbidities (per comorbidity)	1.68 (1.23-2.35)			0.0014
Non-white ethnicity	1.98 (0.92-4.28)			0.078
Active IBD	0.58 (0.26-1.26)			0.17
Multivariable logistic regression of medications and severe COVID-19 outcomes (Each medication was added individually to the model including the non-medication covariates above)				
Variable	**OR (95% CI)**			***P* value****
Mesalazine	2.03 (1.01-4.12)			0.048
Prednisolone	2.42 (0.47-11.28)			0.27
Thiopurine (azathioprine/mercaptopurine)	0.47 (0.12-1.48)			0.23
Vedolizumab	0.23 (0.03-1.13)			0.10
Anti-TNF (infliximab and adalimumab)	1.06 (0.28-3.41)			0.92
All biologics	0.62 (0.22-1.63)			0.35

Note: n = 208 complete data for multivariable analysis.

Three patients were excluded from multivariable analysis as lacked complete data across all variables.

Abbreviations: BMI, body mass index, BSG, British Society of Gastroenterology, CD, Crohn's disease, COVID-19, Coronavirus disease 2019, HBI, Harvey-Bradshaw Index, IQR, interquartile range, UC, ulcerative colitis, IBD-U, inflammatory bowel disease unclassified, PGA, physicians' global assessment.

**P* value from univariable logistic regression.; ***P* value from multivariable logistic regression.

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REFERENCES

1. Taxonera C, Sagastagoitia I, Alba C, Manas N, Olivares D, Rey E. 2019 novel coronavirus disease (COVID-19) in patients with inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2020;52:276-283.
2. Kennedy NA, Jones G-R, Lamb CA, et al. British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic. *Gut*. 2020;69:984-990.
3. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. *Am J Gastroenterol*. 2012;107:1409-1422.
4. Wisniewski A, Kirchgesner J, Seksik P, et al. Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. *United European Gastroenterol J*. 2020;8:303-313.
5. Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology*. 2018;155:337-346.e10.
6. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology*. 2020;159:481-491.e3.
7. Ungaro RC, Brenner EJ, Gearry RB, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. *Gut*. 2021;70:725-732.
8. Bezzio C, Saibeni S, Variola A, et al. Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. *Gut*. 2020;69:1213-1217.
9. Lukin DJ, Kumar A, Hajifathalian K, et al. Baseline disease activity and steroid therapy stratify risk of COVID-19 in patients with inflammatory bowel disease. *Gastroenterology*. 2020;159:1541-1544.e42.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

APPENDIX 1

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