Association between 5-aminosalicylates in patients with IBD and risk of severe COVID-19: an artefactual result of research methodology?

We have read the paper by Ungaro et al with great interest, in which the authors present an assessment of the association between IBD-related medications and the disease course of COVID-19 based on the Surveillance Epidemiology of Coronavirus Under Research Exclusion for IBD (SECURE-IBD) registry.¹ Based on data from 1439 patients from this ongoing multinational registry, the authors confirm their previous suggestion that 5-aminosalicylates and/or sulfasalazine (collectively 5-ASA) might be associated with severe outcomes of COVID-19.² The authors found that 5-ASA was significantly and independently associated with severe COVID-19 in comparison with patients not receiving 5-ASA and patients receiving monotherapy with tumour necrosis factor antagonists. However, no association was found when comparing with patients not receiving any medication and no dose–response relationship of 5-ASA was observed.

The authors are to be applauded for establishing this innovative registry enabling updated evidence-based decision-making for IBD clinicians. However, as the authors acknowledge, cases are reported to the registry from all over the world making the cohort prone to reporting and selection bias and selection of inadequate reference groups. Therefore, population-based estimates of risk are important. We have recently published the initial results of two Danish population-based cohort studies demonstrating no association between COVID-19 outcomes and 5-ASA in patients with IBD and other immune-mediated inflammatory diseases.³ ⁴ To further investigate the potential association between COVID-19 outcomes and 5-ASA, we updated our database with population-based data on 320 patients with IBD as shown in table 1. When replicating the statistical method of the paper including its adjustments, we did not observe any association between severe COVID-19 and the use of 5-ASA (OR=1.56 (95% CI 0.44 to 5.81)). Furthermore, no association was revealed when stratifying the results according to type of IBD, dosing of 5-ASA, applying different control groups or applying a less rigorous definition of severe COVID-19 in terms of the need for COVID-19-related hospitalisation (table 2).

We believe these results merit a discussion of optimal ways to appropriately weighting the results. As already highlighted, the replication of the association in the multivariate analysis in this second report of SECURE-IBD is, indeed, difficult to explain.³ While robust data on 5-ASA are still limited,⁵ this conundrum might be considered by evidence borrowed from a recent report from the Global Rheumatology Alliance physician-reported registry.⁶ The authors included a total of 3729 patients and revealed a statistically significant and independent association between 5-ASA and COVID-19-related mortality (adjusted OR (aOR)=3.6 (95% CI 1.66 to 7.78)). However, the effect measure of 5-ASA attenuated (aOR=2.77 (95% CI 0.88 to 8.69)) when conducting a complete case analysis excluding patients with missing values and 5-ASA was not associated with COVID-19-related death among patients who never smoked. Of note, this report used methotrexate as the reference group. In the present study, Ungaro et al did not stratify or adjust their findings according to smoking habits. Therefore, we wonder if the authors have had the opportunity to conduct such a subanalysis on this potential effect modifier. This would provide valuable information.

To understand the role of 5-ASA in the disease course of COVID-19, large scale multinational registries must aim to adjust for any potential effect modifiers and confounders in order to determine the granular effect of IBD-related medications. In conclusion, the results by Ungaro et al as well as our updated population-based study plead for further analysis to confirm the association between 5-ASA and COVID-19-related outcomes.

### Table 1: Demographics and clinical characteristics of included patients in the Danish COVID-IBD cohort and SECURE-IBD

<table>
<thead>
<tr>
<th></th>
<th>SECURE-IBD</th>
<th>P value*</th>
<th>Danish COVID-IBD cohort</th>
<th>Danish background</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>N patients</td>
<td>1439</td>
<td></td>
<td>320</td>
<td>33 169</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>44.1 (17.6)</td>
<td>&lt;0.01</td>
<td>48.5 (18.2)</td>
<td>44.3 (23.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>699 (48.6)</td>
<td>0.72</td>
<td>159 (49.7)</td>
<td>18 741 (56.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Any comorbidity, n (%)</td>
<td>535 (37.2)</td>
<td>&lt;0.01</td>
<td>164 (51.3)</td>
<td>23 218 (70.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-ASA, n (%)</td>
<td>440 (30.6)</td>
<td>0.01</td>
<td>121 (37.8)</td>
<td>35 (0.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anti-TNF, n (%)</td>
<td>554 (38.5)</td>
<td>&lt;0.01</td>
<td>51 (15.9)</td>
<td>70 (0.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>COVID-19 outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe COVID-19, n (%)</td>
<td>112 (7.8)</td>
<td>0.03</td>
<td>14 (4.4)</td>
<td>609 (1.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Death from COVID-19 or related complications, n (%)</td>
<td>49 (3.4)</td>
<td>0.00</td>
<td>8 (2.5)</td>
<td>192 (0.58)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Severe COVID-19 defined as a composite of intensive care unit admission, mechanical ventilation and/or death.

*P value indicates statistical significance.

†P value indicates the difference between the Danish COVID-IBD cohort and Danish background population.

²5-ASA, 5-aminosalicylates; SECURE-IBD, Surveillance Epidemiology of Coronavirus Under Research Exclusion for IBD; TNF, tumour necrosis factor.
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REFERENCES