Correspondence on ‘Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry’

Strangfeld and colleagues recently reported that sulfasalazine usage was a risk factor for death from COVID-19 with an HR of 3.6, roughly comparable to the HR from the use of rituximab. This conclusion was based on data provided by rheumatologists for patients with a broad spectrum of rheumatic diseases.

We have previously reported in ARD on a survey of 2992 patients with spondyloarthritis and their experience with COVID-19. The survey was reviewed and approved by the Oregon Health & Science University Institutional Review Board. The survey design included input from a patient. At the time of that initial report in spring 2020, we had only 14 subjects with a confirmed diagnosis of COVID-19. We have continued to follow up this cohort longitudinally. We now have data from 4310 respondents who were surveyed from 10 April 2020 to 4 March 2021. Subjects were asked for follow-up information on multiple occasions with 66.3% of the patient cohort providing updated information at least once. The cohort with spondyloarthritis includes 2734 women, 1559 men and 17 non-binary respondents. The respondents came from 72 countries, but 63.5% of the respondents were from the USA. The median age of the respondents was 51 years. Among the respondents with spondyloarthritis, 84.5% self-described their diagnosis as ankylosing spondylitis. At the time of the data lock on 4 March 2021, 212 patient respondents reported a confirmed diagnosis of COVID-19. An additional 55 respondents believed they had had COVID-19 but did not have a confirmed diagnosis by PCR. Including these respondents in the analysis did not change the statistical significance of the conclusions discussed as follows.

Our data regarding medication use and the development of COVID-19 are shown in table 1. Since the likelihood to develop COVID-19 increases as the pandemic continues, the data were expressed as patient-months with the onset of the pandemic dated as March 2020. The data were compared with those on no medications, which were given an arbitrary risk value of 1. It is readily seen from the table that none of the six most common classes of medication taken for spondyloarthritis had a statistically significant impact on the likelihood to develop COVID-19. Specifically, the increased risk attributable to sulfasalazine is not statistically significant. The number of subjects taking a medication is based on the most recent survey or at the time of developing COVID-19. A minority of subjects discontinued medication because of fear that it might increase the risk to develop COVID-19. Twenty-seven subjects taking sulfasalazine discontinued this medication. If these subjects are included as taking sulfasalazine, sulfasalazine still would not affect susceptibility to COVID-19 in a statistically significant way.

Patients who developed COVID-19 were asked to rate the severity of this viral illness from 1 (most mild) to 10 (most severe). In table 1, we present the subjective rating of COVID-19 severity for each of the medication classes. None of the medicines impacted the subjective scoring significantly. Patients taking sulfasalazine tended to rate the severity of the COVID-19 infection as milder than those taking no medication.

Our study differs from that reported by Strangfeld et al in that we surveyed a specific subset of rheumatic disease (spondyloarthritis) and we captured data provided by subjects, not physicians. Our database was slightly larger than the Strangfeld et al database. Spondyloarthritis is arguably the most common reason why a patient with a rheumatic disease would take sulfasalazine. The number of subjects taking sulfasalazine in our database, 363, is 64% greater than the number taking sulfasalazine, 222, reported in the Strangfeld et al database. The Strangfeld et al report also cites an inflammatory bowel disease database, but that database includes only 117 taking either sulfasalazine or mesalazine, so the number taking sulfasalazine is relatively small. The strengths of the Strangfeld et al database include data provided by a physician and the ability to capture death as an endpoint. We are concerned, however, that physicians would be far more likely to report a patient who died from COVID-19 as opposed to a patient who was asymptomatic.

Our data provide reassurance that the use of sulfasalazine does not increase the risk of developing COVID-19. Our data, of course, were based solely on spondyloarthritis and might not extrapolate to patients with rheumatoid arthritis. Our data were supported by the widely accepted concept that sulfasalazine does not impair the immune response. The intestinal microbiome can affect COVID-19 trafficking from the gut, so a theoretical possibility is that sulfasalazine increases the severity of COVID-19 by virtue of its impact on the microbiome, but this hypothesis is not supported by our data.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Spondyloarthritis, medication and COVID-19 risk and severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number taking</td>
<td>Number with COVID-19</td>
</tr>
<tr>
<td>None</td>
<td>298</td>
</tr>
<tr>
<td>Mtx</td>
<td>461</td>
</tr>
<tr>
<td>Hcq</td>
<td>135</td>
</tr>
<tr>
<td>Pred</td>
<td>277</td>
</tr>
<tr>
<td>Sulfasal</td>
<td>363</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>1922</td>
</tr>
<tr>
<td>NSAID</td>
<td>2128</td>
</tr>
</tbody>
</table>

*P value determined by Wald’s test.
†P value determined by Student’s t-test.
Hcq, hydroxychloroquine; Mtx, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; Pred, prednisone; Sulfasal, sulfasalazine; TNF, tumour necrosis factor.

Medications are based on information from the most recent survey or at the time of developing COVID-19. Patients could be taking more than one medication.
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Contributors All authors participated in the design of the survey instrument. All authors read and approved the manuscript, suggested edits, and provided critical input and suggestions. JTR wrote the initial draft of the manuscript and conceived of the study. DC did the statistical analysis. HH participated in the data retrieval. KO liaised with the institutional review board.

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Competing interests HH owns Any-3. CS, EA and RAH are employees of the Spondylitis Association of America. JTR has received consulting fees from Abbvie, Roche, Gilead, Novartis, Santen, Kyverna, Roivant, Revolo, Corvus, Horizon and UCB; royalties from UpToDate; and research grant support from Pfizer and Horizon. MHW has received support from Novartis, UCB, GSK and Pfizer. RAH has consulted for Novartis and owns stocks in Abbvie, Amgen, BMS, GSK, Johnson and Johnson, Lilly, Merck, Novartis, Pfizer, Teva, UCB and Viatris. KLW has received support from BMS, Pfizer, Abbvie, Eli Lilly, Galapagos, Gilead, BMS, Regeneron, Sanofi, Astra Zeneca and Novartis. The other authors report no conflicts of interest.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research.

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