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The Interplay Between COVID-19 and Spondyloarthritis or Its Treatment

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ABSTRACT. ***Objective.*** The coronavirus disease 2019 (COVID-19) pandemic has created multiple uncertainties regarding rheumatic diseases or their treatment, with regard to the susceptibility to or severity of the viral disease. We aimed to address these questions as they relate to spondyloarthritis (SpA).

Methods. We created a longitudinal survey from April 10, 2020, to April 26, 2021. There were 4723 subjects with SpA and 450 household contacts who participated worldwide. Of these, 3064 respondents were from the US and 70.4% of them provided longitudinal data. To control for the duration of potential risk of COVID-19, the rate of contracting the disease was normalized for person-months of exposure.

Results. In an analysis of US subjects who provided longitudinal data, the incident rate ratio for the 159 (out of 2157) subjects who tested positive for COVID-19 was 1.16 compared to the US population as adjusted for age and sex (range 0.997–1.361, $P = 0.06$). A paired evaluation using patients and household members did not show a statistically significant effect to indicate a predisposition for developing COVID-19 as a result of SpA or its treatment. Our data failed to show that any class of medication commonly used to treat SpA significantly affected the risk of developing COVID-19 or increasing the severity of COVID-19.

Conclusion. These data do not exclude a small increased risk of developing COVID-19 as a result of SpA, but the risk, if it exists, is low and not consistently demonstrated. The data should provide reassurance to patients and to rheumatologists about the risk that COVID-19 poses to patients with SpA.

Key Indexing Terms: ankylosing spondylitis, axial spondyloarthritis, COVID, methotrexate, sulfasalazine, TNF inhibitor

The coronavirus disease 2019 (COVID-19) pandemic has been especially challenging for patients with inflammatory diseases, including spondyloarthritis (SpA). Although numerous studies have addressed how a COVID-19 infection affects patients with rheumatic diseases,[1–16] the conclusions from these reports have not been consistent. Many, including our own,[17] were performed early in the pandemic and as a consequence, they are often underpowered. In order to address the interplay between COVID-19 and SpA or its treatment, the Spondylitis Association of America (SAA), in collaboration with similar organizations around the world, conducted an online survey of patients with a diagnosis of SpA established by a physician. The survey began on April 10, 2020, and the data were locked as of April 26, 2021. We previously locked data on May 7, 2020, and reported our observations, but only 14 confirmed cases of COVID-19 were included at the time of report.[17]

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METHODS

The survey instrument. The survey was reviewed and approved by the Oregon Health & Science University Institutional Review Board (approval number 21375). Subjects were informed that by participating in this Web-based survey, informed consent was tacitly implied. Conclusions based on a data lock on May 7, 2020, have been previously reported.[17] The survey was distributed to approximately 40,000 individuals (mostly in North America) who had registered with the SAA. In addition, the survey was distributed based on lists provided by the Axial Spondyloarthritis International Federation (ASIF). The survey was translated into 15 additional languages to accommodate ASIF members. This study complied with principles in the Declaration of Helsinki.

Modification of the Bath Ankylosing Spondylitis Disease Activity Index. The traditional Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) includes 6 questions. The last 2 questions are both on morning stiffness. The responses to these last 2 questions are averaged and combined with the other 4 responses to create a single average. We reasoned that questions 5 and 6 are redundant and that the completion rate for the survey could be improved by combining these as a single question. In addition, as is true of many online surveys, we obtained responses as an integer from 1 to 10, whereas the traditional BASDAI uses a continuous scale. Scores are based on the time of the initial response to the survey.

Statistical methods. Categorical variables were compared using chi-square testing with a Yates correction. Continuous variables were compared by *t* test. Incident rate ratios (IRR) were compared using the Wald Test. To account for potential confounders in multiple regression analyses, Poisson regression model was also employed to estimate IRRs.

RESULTS

The present, updated survey results captured responses from 4723 subjects with SpA and 450 household contacts of these subjects. Moreover, 3289 subjects with SpA provided longitudinal data and 245 household contacts of 235 subjects with SpA also responded to the survey more than once. Of these, 64.9% of respondents were from the US and the rest were from 72 other countries, including 8% from Canada and 1.7% from the UK. The response rate from subjects with SpA living in North America was 9.3%. Of the respondents, 63% were female. Males had a median age of 54 years and females responding to the survey had a median age of 49 years. We did not find that either age or sex had a statistically significant effect on the incidence of COVID-19, recognizing that the median age for our respondents was greater than the median age globally or for the US population. Of the respondents, 83.5% identified their disease as ankylosing spondylitis (AS). Arthritis with inflammatory bowel disease (5.5%), psoriatic arthritis (PsA; 8.5%), reactive arthritis (3.2%), undifferentiated SpA (7.0%), and nonradiographic SpA (7.0%) were also chosen as appropriate diagnoses by respondents who were allowed to select > 1 diagnostic category. Respondents who believed they had been exposed to COVID-19 constituted 19.6%, and 384 (8.2%) believed that they had been infected. Of those who believed they were infected, 295 had a confirmatory positive test. The conclusions that follow are based on those with confirmed disease.

To determine if SpA affects the likelihood of developing COVID-19, we focused on the analysis of respondents from the US who provided longitudinal data. We reasoned that a global analysis would suffer because of wide variation in incident rates in different countries. By analyzing only respondents who provided longitudinal data, we were able to calculate rates and avoid an enrollment bias common to most surveys (i.e., greater likelihood to participate if one is COVID-19–infected). Two thousand one hundred fifty-seven subjects were from the US and provided serial data. One hundred fifty-nine (7.4%) of these subjects reported a positive test for COVID-19. Controlling for patient-months of exposure and comparing to the entire US population with adjustments for age and sex, we calculated an IRR of 1.16 (range 1.00–1.36, $P = 0.06$).

We analyzed our data on household contacts in 2 separate ways. Four hundred fifty household members from 434 households responded to our survey. Among the 16 households with > 1 household member participating in the survey, we found 2 instances in which both household members were infected. For statistical purposes, we based the analysis on households and counted households with > 1 reporting family member as a single household since reports were always concordant. Based on an analysis of 434 households, 11 controls developed COVID-19 and 14 subjects with SpA developed COVID-19. Thus, subjects with SpA were 27% more likely than controls to develop COVID-19, but the increase did not reach statistical significance by chi-square analysis with Yates correction ($P = 0.61$). Among the household controls, we had serial data on 245 subjects from 235 households. The incident rate of COVID-19 was calculated based on the number of subjects multiplied by the number of months of follow-up for household members or for subjects with SpA. The IRR was not statistically significant (IRR 1.15, $P = 0.74$). When we also analyzed only the US participants by using a Poisson regression model while accounting for age and sex, the estimated IRR was 1.14 ($P = 0.81$).

The small increase in COVID-19 incidence rate, if reproducible, could be due to multiple factors such as greater likelihood to be tested for COVID-19 because of SpA or increased susceptibility due to medications. The medications being taken at the time of the most recent survey are shown in Table 1 along with the BASDAI scores. The BASDAI scores were higher for all medicine groups compared to the no medication group. However,

Table 1. Relationship between the modified BASDAI and medication usage.

	N	BASDAI, Mean	SD	*P**
No SpA medication	328	4.08	2.44	NA
Sulfasalazine	454	4.61	2.22	0.002
Antimalarials	152	5.33	2.17	< 0.001
MTX	568	5.26	2.19	< 0.001
Anti-TNF	2276	4.35	2.18	0.06
Anti–IL-17	449	5.26	2.07	< 0.001
Corticosteroid	362	5.92	2.14	< 0.001
JAK inhibitor	71	5.70	2.04	< 0.001
NSAID	2525	4.84	2.11	< 0.001

* Based on *t* test against no SpA medication. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; IL: interleukin; JAK: Janus kinase; MTX: methotrexate; NA: not applicable; NSAID: nonsteroidal antiinflammatory drug; SpA: spondyloarthritis; TNF: tumor necrosis factor.

it should be noted that BASDAI scores are often evaluated for change, and these scores are from a single point in time. Higher scores for those on specific medications presumably represent a confounding by indication (i.e., more aggressive treatment for more severe disease). The lowest scores were for those on no medication and the highest scores are for those taking a corticosteroid (CS) and/or a Janus kinase (JAK) inhibitor.

We next asked whether any class of medication influenced either the susceptibility to COVID-19 or the severity of the disease as judged subjectively by the respondent using a categorical scale from 1 to 10 (Table 2). The likelihood of developing COVID-19 is partially a function of time. A longer period of risk increases the likelihood that one will eventually develop the disease. Consequently, we dated the onset of the pandemic as March 2020, and normalized the data based on the number of months of potential exposure to the virus. Table 2 indicates that none of the treatments appeared to affect the likelihood of developing COVID-19 or the subjective rating of the severity of COVID-19. Some classes of medications such as antimalarials and JAK inhibitors were not commonly used by the respondents, so the statistical meaning of the results could be confounded by the limited size of the database.

One strength of our survey lies in its international distribution, but a weakness of the study is ironically the global nature, which introduces a great deal of heterogeneity for incidence rates. Accordingly, we repeated the analysis based on only the 3065 participants who were from the US. This analysis provided similar results (data not shown). Another strength of the study is its longitudinal nature, since this approach minimizes participation bias by enrolling patients prior to developing COVID-19. Of the subjects, 69.6% provided at least 1 follow-up response. Limiting the analysis only to those who provided follow-up again resulted in the same conclusions (data not shown). Finally, we restricted the analysis to the 2157 participants (70.4% of the US total) who were both from the US and provided follow-up data. Similar to the results shown in Table 1, US patients who provided follow-up consistently had a higher BASDAI if they were on medication ($P < 0.001$ for each individual medication). As shown in Table 3, no medication had a statistically significant effect on the likelihood of contracting COVID-19 or the subjective severity of the infection.

Two recent studies[18,19] have shown that COVID-19 replication in vitro is dependent on folate. Both studies suggested that methotrexate (MTX) might be useful as a treatment for COVID-19 infection. While combining MTX with other treatments such as remdesivir[19] might prove valuable, our data did not find that MTX protected against developing COVID-19, nor was it associated with milder disease. CSs at higher dosages probably increase the risk of developing COVID-19.[11] While we did not confirm this, our data are limited because we did not capture the dosage of CSs in the survey and CS usage is limited among patients with SpA.

DISCUSSION

We are aware of only one other study that has used household members as a control for the amount of exposure to COVID-19.[4] That study was based on 42 families and included 43 subjects with a rheumatic disease and 83 family members. Twenty-seven of the 43 subjects with rheumatic disease in Hubei, China, developed COVID-19 compared to only 28 of 83 family members. In the study from China,[4] the subjects with rheumatic disease were 2.68 times as likely to contract COVID-19 based on an adjusted OR compared to household controls ($P < 0.023$). The study from Hubei explicitly excluded patients with AS based on the rationale that approximately only 10% of these subjects are treated with an anti–tumor necrosis factor.

The largest US study on COVID-19 and rheumatic diseases published at the time of our manuscript preparation was based on a review of electronic health records.[9] It included 2379 subjects with rheumatic diseases and COVID-19, but only 76 of these subjects had AS. It concluded that rheumatic diseases are associated with greater severity of COVID-19. A recent study from Denmark on COVID-19 and rheumatic disease was much larger than our own, but it was only able to identify 7 patients with SpA who had been hospitalized due to COVID-19.[16] The Global Rheumatology Alliance concluded that the use of sulfasalazine (SSZ) is associated with an increased risk of dying from COVID-19, comparable to the risk associated with rituximab

Table 2. Analysis of medication usage and the susceptibility and severity of COVID-19.

	COVID-19 Cases	Person-months	RR[a]	95% CI	*P**	Severity[b], Mean	SD	*P***
No SpA medication	14	1937.7	1.00	NA	NA	4.14	2.25	NA
MTX	31	3671.4	1.17	0.62–2.20	0.64	5.19	2.27	0.16
HCQ	5	941.0	0.74	0.26–2.04	0.58	5.40	2.30	0.33
Prednisone	12	2271.9	0.73	0.34–1.58	0.43	5.18	2.18	0.26
Sulfasalazine	31	2795.3	1.53	0.82–2.88	0.18	4.45	2.20	0.67
Anti-TNF	135	14856.9	1.26	0.73–2.18	0.42	4.75	2.40	0.35
NSAID	155	15708.7	1.37	0.79–2.36	0.26	4.72	2.32	0.37
Anti–IL-17	27	2985	1.25	0.66–2.39	0.50	4.44	2.24	0.70
JAK inhibitor	6	439.7	1.89	0.73–4.91	0.21	6.20	2.28	0.13

[a] RR is calculated relative to patients taking no medication. [b] Mean severity is the subjective severity of COVID-19 infection using a scale of 1 (mildest) to 10 (most severe). * Wald test. ** *t* test against no SpA medication. COVID-19: coronavirus disease 2019; HCQ: hydroxychloroquine; IL: interleukin; JAK: Janus kinase; MTX: methotrexate; NA: not applicable; NSAID: nonsteroidal antiinflammatory drug; RR: rate ratio; TNF: tumor necrosis factor.

Table 3. Analysis of medication usage and susceptibility and severity of COVID-19 based on US participants who provided follow-up data.

Medication (n)	COVID-19 Cases	Person-months	RR	95% CI	*P**	Severity, Mean	SD	*P***
No SpA medication (223)	8	1349.7	1.00	NA	NA	4.13	2.36	NA
MTX (271)	21	2479.2	1.43	0.63–3.23	0.40	5.10	2.21	0.33
HCQ (81)	4	759.4	0.89	0.27–2.95	0.87	4.75	2.06	0.65
Prednisone (195)	10	1722.6	0.98	0.39–2.48	0.96	5.00	2.21	0.43
Sulfasalazine (204)	14	1873.8	1.26	0.53–3.00	0.62	4.00	2.35	0.91
Anti-TNF (1089)	79	10214.7	1.30	0.63–2.70	0.49	4.96	2.45	0.37
NSAID (1171)	91	10698.7	1.44	0.70–2.96	0.33	4.55	2.31	0.64
Anti–IL-17 (239)	17	2115.6	1.36	0.59–3.14	0.49	5.07	2.15	0.36
JAK inhibitor (41)	5	361.7	2.33	0.76–7.13	0.16	6.00	2.58	0.27

* Wald test. ** *t* test against no SpA medication. COVID-19: coronavirus disease 2019; HCQ: hydroxychloroquine; IL: interleukin; JAK: Janus kinase; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug; RR: rate ratio; SpA: spondyloarthritis; TNF: tumor necrosis factor.

(RTX).[11] As we recently reported, our data do not show increased likelihood to develop COVID-19 or to suffer from more severe COVID-19 in association with the use of SSZ.[20]

We believe that our study adds to the growing literature on rheumatic disease and COVID-19 in several important ways. To our knowledge, it is by far the largest study to date on SpA and COVID-19. Studies on specific rheumatic diseases and COVID-19 are valuable. Just as a medication that benefits one rheumatic disease such as RTX for granulomatosis with polyangiitis might not benefit another rheumatic disease such as SpA, each underlying rheumatic disease could independently affect the response to a virus. Extrapolating from rheumatoid arthritis (RA) or systemic lupus erythematosus to SpA is inherently flawed. Recognizing that rates of COVID-19 infection vary widely based on date and geographic location, we analyzed specifically the subset of respondents who were both from the US and provided follow-up information. We found a 16% increase in the IRR with borderline statistical significance ($P = 0.06$). Our paired data using household controls account optimally for the likelihood of exposure to COVID-19. These data are arguably the best way to determine if SpA affects susceptibility to or severity of COVID-19. The longitudinal design is also innovative and reduces the inherent enrollment bias in survey studies. Statistics are ideal at showing differences, but they are less powerful at proving similarity. Our data do not show definitively that SpA does not affect susceptibility to COVID-19, since there is a small positive trend toward increased viral disease. However, this increase does not reach statistical significance. Additional studies or additional follow-up of our present study are required to answer the question with more confidence. The high *P* value ($P = 0.74$) from our analysis based on household controls is reassuring in that if there is an effect, it is small. Further, if an effect exists, our data cannot exclude the possibility that medications rather than the disease itself account for the increase. Our conclusion regarding SpA and the severity of COVID-19 contrasts with the conclusions from at least 3 studies[4,9,11] that included a range of rheumatic diseases rather than focusing on SpA.

All survey studies suffer from a selection bias as to who responds. However, our methodology allowed for the enrollment of subjects almost always prior to the development of infection with COVID-19, and we followed 70.4% of respondents longitudinally, with an extremely good response rate to repeated surveys after the first response. The longitudinal design reduces the bias from selective response to the survey. In addition, the inclusion of household controls allowed us to minimize confounding effects resulting from the vast range of environmental exposures. The survey nature of our study with protection of subject identity did not allow us to confirm diagnoses on the basis of a review of medical records, although we asked that participants have a diagnosis of SpA confirmed by a physician. We cannot exclude confounding because patients taking certain medications, such as a biologic, might exercise greater care to socially distance and minimize exposure. This same behavioral change could apply to those with SpA. We caution as well that our results should not be extrapolated to other rheumatic diseases, as some have comorbidities such as obesity with PsA and interstitial lung disease with RA that presumably affect susceptibility to and severity of coronaviral infection. Another limitation of our study is the inability to capture a fatal outcome from a COVID-19 infection. Similarly, subjects in an intensive care unit would be unlikely to respond to a survey. Finally, we recognize that emerging variants of COVID-19 might behave differently from the variants that predominated at the time of our survey.

Our data should reassure both patients and physicians that patients with SpA are not at a large increased risk for COVID-19 infection, nor does its treatment substantially add to this risk. Continued acquisition of longitudinal data is certainly warranted.

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DATA AVAILABILITY

Data for this study may be obtained by contacting Hedley Hamilton at Any-3.

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