The Interplay between Covid-19 and Spondyloarthritis or Its Treatment

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HH owns Any3, the website which hosted the survey and donated its services.

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Ethics:

This study complied with principles in the Declaration of Helsinki. The study was reviewed and approved by the Oregon Health & Science University Institutional Review Board (approval number 21375). Subjects who participated in this research provided electronic consent as a first step in completing the survey. As a survey, it was not practical to obtain written, informed consent.

Data Availability:

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

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Abstract:

Objectives: The Covid-19 pandemic has created multiple uncertainties regarding rheumatic diseases or their treatment and susceptibility or severity of the viral disease.

Methods: To address these questions as they relate to spondyloarthritis, we created a longitudinal survey from April 10, 2020 to April 26, 2021. 4723 world-wide subjects with spondyloarthritis and 450 household contacts participated. 3064 of the 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 Covid-19 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 to 1.361, p=0.059). A paired evaluation using patients and household members did not show a statistically significant effect to indicate a predisposition to develop Covid-19 as a result of spondyloarthritis or its treatment. Our data failed to show that any class of medication commonly used to treat spondyloarthritis significantly affected the risk to develop Covid-19 or the severity of Covid-19.

Conclusion: These data do not exclude a small increased risk to develop Covid-19 as a result of spondyloarthritis, 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 spondyloarthritis.

Introduction:

The Covid-19 pandemic has been especially challenging for patients with inflammatory diseases including spondyloarthritis. Although numerous studies have addressed how 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 under-powered. In order to address the interplay between Covid-19 and spondyloarthritis or its treatment, the Spondylitis Association of America in collaboration with similar organizations throughout the world conducted an online survey of patients with a diagnosis of spondyloarthritis 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 the prior report included only 14 confirmed cases of Covid-19 at the time of the report (17).

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 Spondylitis Association of America. Additional surveys were distributed based on lists provided by the Axial Spondyloarthritis International Federation (ASIF). The survey was translated into 15 additional languages to accommodate ASIF members.

Modification of the BASDAI: The traditional BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) includes six questions. The last two questions are both on morning stiffness. The responses to these last two questions are averaged and combined with the other four responses to create a single average. We reasoned that questions five and six 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 one to ten, while the traditional BASDAI uses a continuous scale. BASDAI 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 student's T-test. Incident rate ratios (IRR) were compared using the Wald Test. For multiple regression analysis to account for potential confounders, Poisson regression model was also employed to estimate IRRs.

Results and Discussion: The present, updated survey results captured responses from 4723 subjects with spondyloarthritis and 450 household contacts of these subjects. Moreover, 3289 subjects with spondyloarthritis provided longitudinal data and 245 household contacts of 235

subjects with spondyloarthritis also responded to the survey more than once. Sixty-four and nine tenths percent of respondents were from the US and the rest were from 72 other countries including 8% from Canada and 1.7% from the United Kingdom. The response rate from subjects with spondyloarthritis living in North America was 9.3%. 63% of the respondents were female. Males had a median age of 54 and females responding to the survey had a median age of 49. 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 is greater than the median age globally or for the US population. Eighty-three and five tenths per cent of respondents identified their disease as ankylosing spondylitis. Arthritis with inflammatory bowel disease (5.5%), psoriatic arthritis (8.5%), reactive arthritis (3.2%), undifferentiated spondyloarthritis (7.0%) and non-radiographic spondyloarthritis (7.0%) were also chosen as appropriate diagnoses by respondents who were allowed to select more than one diagnostic category. Nineteen and six tenths percent of respondents believed they had been exposed to Covid-19 and 384 or 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 spondyloarthritis affects the likelihood to develop 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 various countries. By analyzing only respondents who provided longitudinal data, we were able to calculate rates and we avoided an enrollment bias common to most surveys, i.e. greater likelihood to participate if you are Covid infected. Two thousand one hundred fifty-seven subjects were from the US and

provided serial data. One hundred fifty-nine of these subjects (7.4%) reported a positive test for Covid. Controlling for patient months of exposure and comparing to the entire US population with adjustments for age and sex, we calculated an incident rate ratio of 1.16 (range 0.997 to 1.361, p=0.059).

We analyzed our data on household contacts in two separate ways. Four hundred fifty household members from 434 households responded to our survey. Among the sixteen households with more than one household member participating in the survey, we found two instances in which both household members were infected. For statistical purposes, we based the analysis on households and counted households with more than one reporting family member as a single household since reports were always concordant. Based on an analysis of 434 households, 11 controls developed Covid and 14 subjects with spondyloarthritis developed Covid. Thus, subjects with spondyloarthritis were 27% more likely than controls to develop Covid, 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 from 235 households. The incident rate of Covid-19 was calculated based on the number of subjects times months of follow-up for household members or for subjects with spondyloarthritis. The IRR was not statistically significant (IRR=1.15, p=0.74). When we also analyzed only the USA participants by using a Poisson regression model while accounting for age and sex, the estimated IRR was 1.14 with p-value=0.811.

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 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, it should be noted that BASDAI scores are often evaluated for change and we are providing the scores at 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 corticosteroid and/or a JAK inhibitor.

We next asked whether any class of medication influenced either the susceptibility to Covid-19 or the severity as judged subjectively by the respondent using a categorical scale from one to ten. Results are shown in Table 2. The likelihood to develop Covid 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 to develop Covid-19 or the subjective rating of the severity of Covid-19. Some classes of medications such as anti-malarials 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 United States. This analysis provided similar results (data not shown). Another strength of the study is the longitudinal nature of the study since this approach minimizes participation bias by enrolling patients prior to the development of Covid. Sixty-nine and six tenths percent of subjects provided at least one 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 who provided follow-up data. Similar to results shown in Table 1, US patients who provided follow-up consistently had a higher BASDAI if they were on medication ($p \leq 0.001$ for each individual medication). As shown in Table 3, no medication had a statistically significant effect on the likelihood to contract Covid-19 or the subjective severity of Covid-19 infection.

Two recent studies (18, 19) have shown that Covid-19 replication *in vitro* is dependent on folate. Both studies suggested that methotrexate might be useful as a treatment for Covid infection. While combining methotrexate with other treatments such as remdesivir (19) might prove valuable, our data did not find that methotrexate protected from developing Covid, nor was it associated with more mild disease. Corticosteroids at higher dosages probably increase the risk to develop Covid-19 (11). While we did not confirm this, our data are limited because we did not capture the dosage of corticosteroid in the survey and corticosteroid usage is limited among patients with spondyloarthritis.

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

The largest US study on Covid-19 and rheumatic diseases published at the time of our manuscript preparation was based on review of electronic health records (9). It included 2379 subjects with rheumatic diseases and Covid-19, but only 76 of these subjects had ankylosing spondylitis. It concluded that rheumatic diseases are associated with greater severity of Covid-19. A recent study from Denmark on Covid and rheumatic disease was much larger than our own, but it was only able to identify 7 patients with spondyloarthritis who had been hospitalized due to Covid (16). The Global Rheumatology Alliance concluded that the use of sulfasalazine is associated with an increased risk of dying from Covid-19, comparable to the risk associated with rituximab (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 sulfasalazine (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 spondyloarthritis and Covid. Studies on specific rheumatic diseases and Covid are valuable. Just as a medication that benefits one rheumatic disease such as rituximab for granulomatosis with polyangiitis might not benefit another rheumatic disease such as spondyloarthris, each underlying rheumatic disease could independently affect the response to a virus. Extrapolating from rheumatoid arthritis or lupus to spondyloarthritis 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 who provided follow-up information. We found a 16% increase in the incident rate ratio with borderline statistical significance (p=0.059). Our paired data using household controls account optimally for the likelihood of exposure to Covid. These data are arguably the best way to determine if spondyloarthritis affects susceptibility or severity of Covid-19. The longitudinal design is also innovative and reduces the inherent biased enrollment in survey studies. Statistics are ideal at showing differences, but they are less powerful at proving similarity. Our data do not show definitively that spondyloarthritis 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 own study are required to answer the question with more confidence. The high p value (p=0.74) from our analysis

based household controls is reassuring that if there is an effect, it is small. And if an effect exists, our data cannot exclude the possibility that medications rather than the disease itself account for the increase. Our conclusion regarding spondyloarthritis and the severity of Covid-19 contrasts with the conclusion from at least 3 studies (4, 9, 11) which included a range of rheumatic diseases rather than focusing on spondyloarthritis.

All survey studies suffer from a selection bias as to who responds. However, our methodology enrolled subjects almost always prior to the development of infection with Covid and followed approximately 70% 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 spondyloarthritis 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 spondyloarthritis. We caution as well that our results should not be extrapolated to other rheumatic diseases, some of which have comorbidities such as obesity with psoriatic arthritis and interstitial lung disease with rheumatoid arthritis that presumably affect susceptibility and severity of coronaviral infection. Another limitation of our study is the inability to capture a fatal outcome from Covid 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 spondyloarthritis are not at a large increased risk from Covid-19 infection. Nor does the treatment substantially add to this risk. Continued acquisition of longitudinal data is certainly warranted.

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	N	Mean BASDAI	SD	p-value*
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	0.060
Anti-IL17	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
No Med	328	4.08	2.44	

*Based on t-test against No Med

Table 1 Relationship between the modified BASDAI and medication usage.

Abbreviations: N=number of respondents; SD=standard deviation; MTX=methotrexate; TNF=tumor necrosis factor; JAK=janus kinase; NSAID=nonsteroidal anti-inflammatory drug; Med=medication for spondyloarthritis.

	C19 cases	Person-months	Rate ratio	lower	upper	p-value*	Mean severity	SD	p-value**
No Med	14	1937.7	1.00	NA	NA	NA	4.14	2.25	NA
MTX	31	3671.4	1.17	0.62	2.20	0.641	5.19	2.27	0.160
HCQ	5	941	0.74	0.26	2.04	0.579	5.40	2.30	0.327
Prednisone	12	2271.9	0.73	0.34	1.58	0.432	5.18	2.18	0.256
Sulfasalazine	31	2795.3	1.53	0.82	2.88	0.182	4.45	2.20	0.671
Anti-TNF	135	14856.9	1.26	0.73	2.18	0.423	4.75	2.40	0.353
NSAID	155	15708.7	1.37	0.79	2.36	0.261	4.72	2.32	0.370
Anti-IL17	27	2985	1.25	0.66	2.39	0.504	4.44	2.24	0.695
JAK inhibitor	6	439.7	1.89	0.73	4.91	0.210	6.20	2.28	0.126

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

* Wald test; ** t-test against No Med.

Rate ratio is calculated relative to patients taking no medication. Mean severity is the subjective severity of Covid-19 infection using a one (most mild) to ten (most severe) scale. Abbreviations: C19=Covid-19; SD=standard deviation; MTX=methotrexate; HCQ=hydroxychloroquine; TNF=tumor necrosis factor; NSAID=nonsteroidal anti-inflammatory drug; JAK=janus kinase; No Med=no medication for spondyloarthritis.

	C19 cases	Person-months	Rate ratio	lower	upper	p-value*	Mean severity	SD	p-value**
No Med (223)	8	1349.7	1.00	NA	NA	NA	4.13	2.36	NA
MTX (271)	21	2479.2	1.43	0.63	3.23	0.400	5.10	2.21	0.334
HCQ (81)	4	759.4	0.89	0.27	2.95	0.874	4.75	2.06	0.652
Prednisone (195)	10	1722.6	0.98	0.39	2.48	0.959	5.00	2.21	0.434
Sulfasalazine (204)	14	1873.8	1.26	0.53	3.00	0.616	4.00	2.35	0.906
Anti-TNF (1089)	79	10214.7	1.30	0.63	2.70	0.491	4.96	2.45	0.368
NSAID (1171)	91	10698.7	1.44	0.70	2.96	0.331	4.55	2.31	0.637
Anti-IL17 (239)	17	2115.6	1.36	0.59	3.14	0.491	5.07	2.15	0.364
JAK inhibitor (41)	5	361.7	2.33	0.76	7.13	0.158	6.00	2.58	0.271

Table 3. Analysis of medication usage and susceptibility and severity of Covid-19 based on US participants who provided follow-up data. The number of subjects taking each medication is shown in parentheses in the first column. Med= medication for spondyloarthritis. MTX=

methotrexate. HCQ=hydroxychloroquine. TNF=tumor necrosis factor. NSAID=nonsteroidal anti-inflammatory drug. JAK=janus kinase.