
COVID-19 in patients with chronic inflammatory rheumatic joint disease

ORIGINAL ARTICLE

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BACKGROUND

Since patients with chronic inflammatory rheumatic joint diseases may be more prone to infections, we wished to investigate the incidence of COVID-19 in this group, and explore the possible significance of factors related to the rheumatic disease, the patient or the treatment.

MATERIAL AND METHOD

Altogether 27 907 patients registered in the Norwegian Arthritis Registry (NorArthritis) were linked to the Norwegian Surveillance System for Communicable Diseases and the Norwegian Intensive Care and Pandemic Registry in order to find the incidence of COVID-19 in 2020, and the proportion of patients who were hospitalised. A standardised incidence ratio (SIR) was calculated by comparing with sex and age-specific incidence in the general population. Logistic regression analysis was used to investigate whether diagnosis, age, sex, disease activity, comorbidity or drug therapy had any bearing on the incidence.

RESULTS

A total of 185 of the patients in NorArthritis tested positive for COVID-19, of whom 10 % were hospitalised. The incidence was lower than in the general population (SIR 0.84; 95 % confidence interval (CI): 0.72–0.97, $P = 0.02$). Young age and low disease

activity were associated with higher incidence of infection. The other factors had no significant effect.

INTERPRETATION

The fact that the incidence of COVID-19 was lower than in the general population, and that within the group it was lower in those with moderate/high disease activity and greater age, is most likely attributable to patients of advanced age with chronic active disease having protected themselves against infection to a greater degree.

Main findings

Patients with chronic inflammatory rheumatic joint diseases had a lower incidence of COVID-19 than the general population.

Within the group, younger patients and patients with low disease activity had a higher incidence of infection.

'Chronic inflammatory rheumatic joint diseases' is a generic term for conditions characterised by non-infectious inflammation in the joints and/or spinal column. This group of diseases includes, for example, rheumatoid arthritis, psoriatic arthritis and spondyloarthritis. Both the disease itself and treatment of the disease, which often involves immunosuppression, can entail a heightened risk of infection [\(1–3\)](#). After the outbreak of COVID-19, rheumatology departments have received many enquiries from patients and healthcare personnel about potential risks associated with the use of immunosuppressants and whether this patient group is considered to be at special risk. Based on national and international recommendations, our advice to patients has been to continue with their usual medication as long as they have no symptoms of an infection [\(4, 5\)](#). There has been limited documentation for this recommendation.

Some studies have found that patients with rheumatic diseases had a higher incidence of COVID-19 [\(6, 7\)](#), while others have not indicated this, including when the patients were taking conventional disease-modifying drugs [\(8\)](#). In one study, the use of biological or targeted synthetic disease-modifying drugs was found to be a risk factor for infection [\(8\)](#), while two other studies found no such association [\(9, 10\)](#). In many of these studies, the diagnosis is based on symptoms and exposure to infection, with no requirement for a positive laboratory test. The studies are small, and even though the number of published works is rising, it remains uncertain whether patients with chronic inflammatory rheumatic disease are at a higher risk of infection than others.

Nor is it clear whether these patients have a more serious course of the COVID-19 disease. Some studies have found a higher incidence of intensive care [\(11\)](#) and a need for mechanical ventilation [\(11, 12\)](#) in patients with rheumatic diseases. A higher risk of hospitalisation has also been found in patients with rheumatic diseases who use prednisolone in doses ≥ 10 mg on a daily basis [\(13\)](#). Other studies have not found any more serious courses of disease than in the general population [\(14, 15\)](#).

In a recently published Norwegian study, no elevated incidence of inflammatory rheumatic joint diseases was found among patients who had tested positive for SARS-CoV-2 or patients who were hospitalised for COVID-19 compared to the general population (16).

The objective of our study was to investigate the incidence of COVID-19 among patients with chronic inflammatory rheumatic joint diseases in Norway compared to that of the general population. We wished to see whether factors associated with the rheumatic disease, the patient or the medication impacted on the incidence rate. Furthermore, we wished to identify the proportion of the infected patients who needed hospitalisation and intensive care.

Material and method

Data material

The Norwegian Arthritis Registry (NorArthritis) contains data from approximately 30 000 patients with chronic inflammatory rheumatic joint diseases, and has a 60 % coverage rate nationwide (17). Details recorded include information about the disease, comorbidity, height, weight and medication. The Norwegian Surveillance System for Communicable Diseases (MSIS) helps monitor communicable diseases in Norway. Cases of COVID-19 are reported directly from the laboratory. The Norwegian Intensive Care and Pandemic Registry contains information on all patients with COVID-19 who are admitted to hospital. This registry has a 90 % coverage rate (18).

We conducted a registry-based historic cohort study where the incidence of COVID-19 was investigated among patients in NorArthritis. Data were retrieved from NorArthritis on 10 September 2020, and all patients who were alive on 1 January 2020 were included in the cohort. Data from the registry were linked to MSIS in order to find patients who had been infected with SARS-CoV-2 before 31 December 2020. A linkage was also made to the Norwegian Intensive Care and Pandemic Registry to investigate the incidence of hospitalisation, intensive care admissions and mechanical ventilation.

In this study, we have categorised the patients into four diagnosis groups – rheumatoid arthritis, psoriatic arthritis, spondyloarthritis and other peripheral arthritis – according to the most recently registered ICD-10 diagnosis codes (International Classification of Diseases, Tenth Revision (19)). Disease activity and other background variables were retrieved from the most recent registration for patients who were not infected and from the most recent registration before a positive PCR test for SARS-CoV-2 for patients who were infected. The disease activity for peripheral arthritis is rated according to the *Disease Activity Score 28* (DAS28-CRP) scale. DAS28-CRP < 3.2 is considered remission/low disease activity and DAS28-CRP ≥ 3.2 indicates moderate/high disease activity (20).

Disease activity for spondyloarthritis is rated according to the *Ankylosing Spondylitis Disease Activity Score* (ASDAS-CRP). ASDAS-CRP < 2.1 is considered remission/low disease activity, and ASDAS-CRP ≥ 2.1 indicates moderate/high disease activity (21). We also examined the use of prednisolone and disease-modifying drugs.

To determine whether the frequency of COVID-19 was higher or lower than average, figures showing the number of infected persons in the general Norwegian population by sex and single-year age groups (age as of 1 January 2020) were retrieved from MSIS. These were linked to population figures from Statistics Norway (22). For the patients in NorArthritis, we also received information on their date of infection.

Everyone included in the study consented to participation in NorArthritis and linkage to data from other health registries. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK Western Norway, no. 139796), and the data protection officer at Bergen Health Trust assessed the potential implications for privacy before the data were linked.

Statistical analyses

The main outcome measure was cases of COVID-19 reported to MSIS. To determine whether the rate was above average, we compared the number of patients with COVID-19 in NorArthritis with the expected number based on the sex and age-specific incidence in the Norwegian population (indirect standardisation). We report the relative frequency as the standardised incidence ratio (SIR) with a 95 % confidence interval (CI).

To identify background variables that were linked to the incidence of COVID-19, we used multiple logistic regression analysis. The explanatory variables were age, sex, diagnosis group, remission status, C-reactive protein (CRP), body mass index (BMI), number of comorbidities and medication. Drug treatment was split into three groups: corticosteroids, conventional synthetic disease-modifying drugs and biological or targeted synthetic disease-modifying drugs (see Table 1 for a description of the drug classes).

Table 1

Groups of anti-rheumatic disease-modifying drugs and some examples of drug classes and drugs.

Abbreviation	Description	Drug classes	Drugs
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug		Methotrexate, sulfasalazine
bDMARD	Biologic disease-modifying anti-rheumatic drug	Tumour necrosis factor- α (TNF- α) inhibitors, B-cell inhibitors	Infliximab, etanercept, rituximab
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drug	Janus kinase (JAK) inhibitors	Baricitinib, tofacitinib

We assumed the possibility of a non-linear correlation with age, and the age effect was therefore modelled as a natural spline with knots at the 10th, 50th and 90th percentiles. The continuous variables CRP, BMI and number of comorbidities were modelled as linear effects, but limited upwards (winsorised) to 100 mg/L, 50 kg/m² and

5 respectively, both to avoid any unreasonable impact from high/extreme values and because we assumed that the effects would level off for high values. We aimed to have at least ten cases of COVID-19 per explanatory variable/coefficient.

We also estimated the proportion of infected patients in NorArthritis who were hospitalised and needed intensive care or mechanical ventilation. All statistical analyses were undertaken in R, version 4.0.4 (23). The significance level was set to 5 %.

Results

The number of patients in each analysis is presented in Figure 1. Of 27 907 patients with chronic inflammatory rheumatic joint disease, 185 (0.66 %) had been registered with confirmed SARS-CoV-2. The expected number based on the sex and age-adjusted Norwegian population was 220, which gives a standardised incidence ratio of 0.84 (95 % CI: 0.72–0.97, $P = 0.02$). By sex, the incidence ratio was 0.93 for women and 0.73 for men (Table 2), but this disparity was not statistically significant ($P = 0.09$). The number of infected patients in each age and sex category is presented in Table 2. Figure 2 shows the number of infections per month.

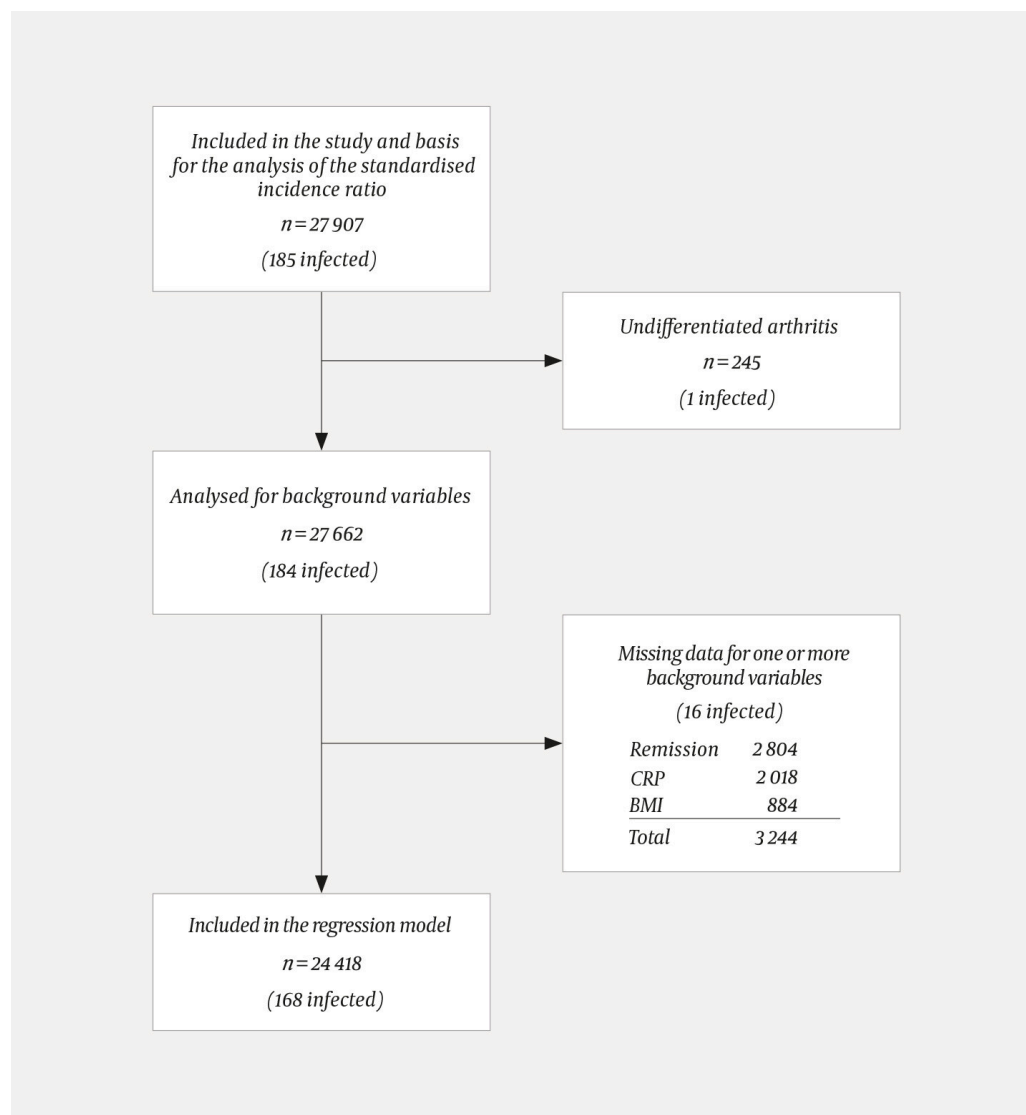


Figure 1 Flowchart for patients included in each analysis. CRP = C-reactive protein, BMI = body mass index.

Table 2

SARS-CoV-2 infections in 2020 among patients in NorArthritis (n = 27 907) and the general Norwegian population stratified by sex and age (as per 1 January 2020, MSIS data). There was a relative paucity of infections among NorArthritis patients, with a standardised incidence ratio of 0.84 (95 % CI: 0.72–0.97). By sex, it was 0.93 (95 % CI: 0.77–1.11) for women and 0.73 (95 % CI: 0.57–0.91) for men.

Age	Women				Men			
	NorArthritis		Norway		NorArthritis		Norway	
	Positive	Total	Prop. (%)	Prop. (%)	Positive	Total	Prop. (%)	Prop. (%)
16–29	8	640	1.25	1.43	4	457	0.88	1.44
30–39	11	1 425	0.77	1.06	9	1 121	0.80	1.29
40–49	30	2 495	1.20	1.04	19	1 919	0.99	1.14
50–59	17	3 699	0.46	0.88	21	2 832	0.74	1.00
60–69	17	4 194	0.41	0.52	10	2 762	0.36	0.64
70–79	21	3 127	0.67	0.41	9	1 896	0.47	0.46
80+	9	922	0.98	0.57	0	418	0.00	0.53
Total	113	16 502	0.68	0.94	72	11 405	0.63	1.05
Expected¹	121	16 502	0.73	–	99	11 405	0.87	–

¹Expected number of infected patients in the NorArthritis registry if the sex and age-specific incidence (based on single-year age groups) was the same as that in the Norwegian population in general.

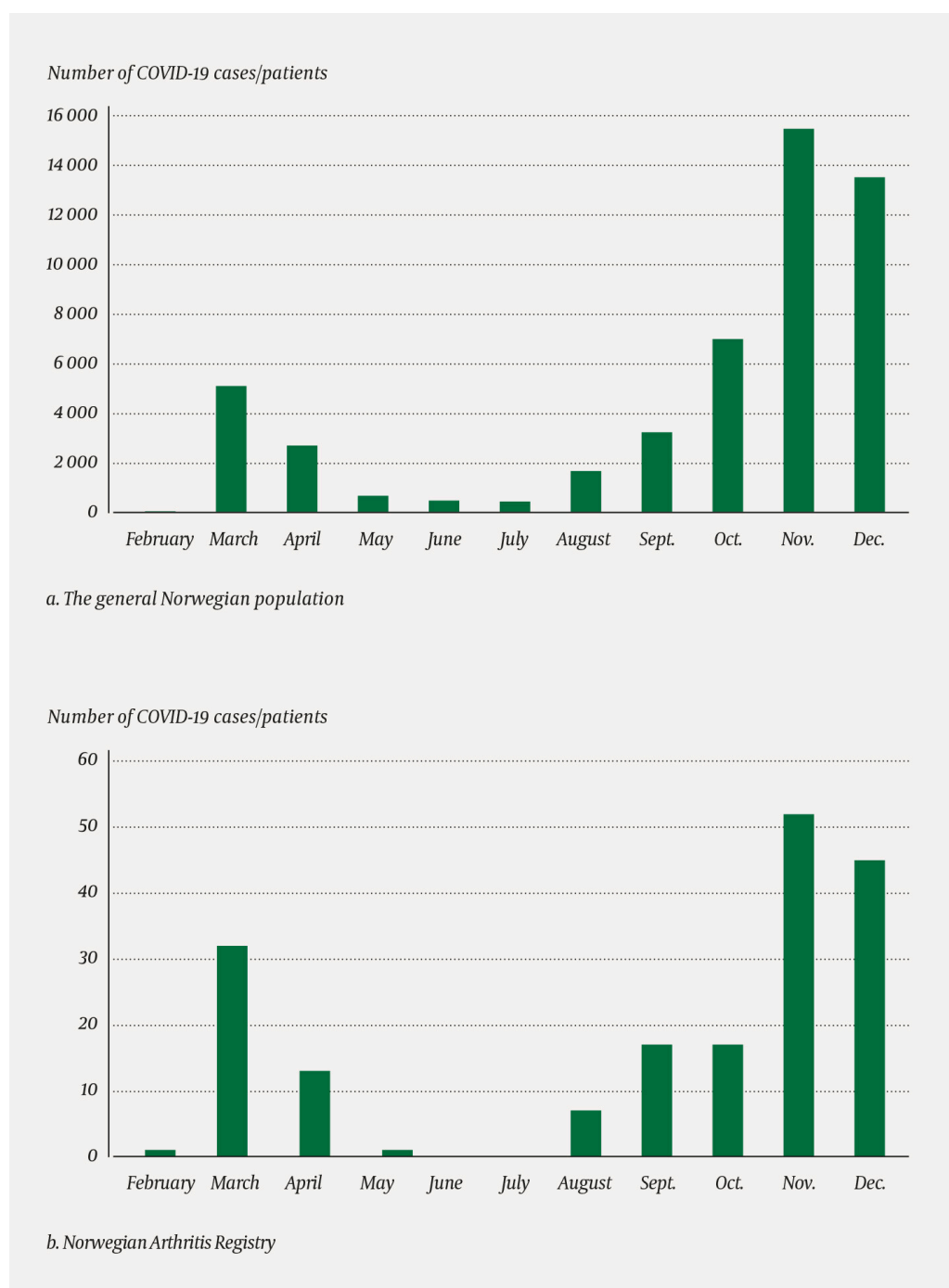


Figure 2 Number of COVID-19 cases per month in 2020 in the population in general (n = 50 148) and in patients registered in the Norwegian Arthritis Registry (n = 185). The sex and age composition is not identical in the two populations, but the pattern of number of infections is the same. Data for infections in the general Norwegian population were retrieved from the Norwegian Institute of Public Health (29).

The number of infected persons in the NorArthritis population and in each subgroup is shown in Table 3. One patient could not be classified into any of the four diagnosis groups (undifferentiated arthritis) and was excluded from the analysis. The results from the regression analysis are provided in Table 4. Lower age and remission or lower disease activity in the patient were associated with a higher incidence of COVID-19. Sex, diagnosis, drug treatment, BMI and comorbidity had no significant effect.

Table 3

Background variables and SARS-CoV-2 infections among NorArthritis patients (n = 27 662). Figures under the column 'Patients' show the percentage distribution of demographic and medical variables in the population as a whole. Figures under the column 'COVID-19' show how many had tested positive for SARS-CoV-2 among all those included in the given category (e.g. number/proportion positive among patients in the 16–39 age group). For example, we can see a higher incidence of infections in the youngest age groups. See Table 1 for an explanation of the drugs.

	Patients		COVID-19	
	Number	Proportion (%)	Number	Proportion (%)
Age, years (n = 27 662)				
16–39	3 257	12	29	0.89
40–59	10 469	38	87	0.83
60–79	12 302	44	59	0.48
80+	1 634	6	9	0.55
Sex (n = 27 662)				
Women	16 339	59	113	0.69
Men	11 323	41	71	0.63
Diagnosis group (n = 27 662)				
Rheumatoid arthritis	12 956	47	84	0.65
Psoriatic arthritis	7 040	25	51	0.72
Spondyloarthritis	5 385	19	34	0.63
Other peripheral arthritis	2 281	8	15	0.66
Drug: csDMARD (n = 27 662)				
No	10 992	40	77	0.70
Yes	16 670	60	107	0.64
Drug: biological or tsDMARD (n = 27 662)				
No	16 204	59	110	0.68
Yes	11 458	41	74	0.65
Drug: Prednisolone (n = 27 662)				
No	23 361	84	156	0.67
Yes	4 301	16	28	0.65
Low disease activity/remission (n = 24 858)				
No	6 109	25	31	0.51
Yes	18 749	75	139	0.74
Last registered BMI (n = 26 778)				

	Patients		COVID-19	
	Number	Proportion (%)	Number	Proportion (%)
< 25	10 126	38	79	0.78
≥ 25 and < 30	10 394	39	64	0.62
≥ 30 and < 35	4 578	17	21	0.46
≥ 35	1 680	6	15	0.89
All (n = 27 662)	27 662	100	184	0.67

Table 4

Risk factors for SARS-CoV-2 infection among NorArthritis patients. Multiple logistic regression model (n = 24 418). All explanatory variables were adjusted for the other explanatory variables. Young age and low disease activity were associated with a higher incidence of infection. OR: odds ratio; CI: confidence interval; CRP: C-reactive protein; BMI: body mass index.

	OR	95 % CI	P-value
Age (non-linear curve)	–	–	< 0.001
Men (ref.: women)	1.0	0.7 to 1.4	0.91
Diagnosis (ref.: rheumatoid arthritis)			0.96
Psoriatic arthritis	1.0	0.7 to 1.5	0.95
Spondyloarthritis	0.9	0.6 to 1.5	0.77
Other peripheral arthritis	0.9	0.5 to 1.5	0.62
Drug: csDMARD ¹	0.9	0.7 to 1.3	0.64
Drug: biological or tsDMARD ¹	0.9	0.7 to 1.2	0.53
Drug: Prednisolone ¹	1.2	0.7 to 1.8	0.52
Low disease activity/remission	1.6	1.1 to 2.6	0.02
Last registered CRP ² , mg/L	1.0	1.0 to 1.0	0.31
Last registered BMI ² , kg/m ²	1.0	1.0 to 1.0	0.53
Number of comorbid conditions ²	1.1	1.0 to 1.2	0.09

¹It is possible for a patient to use drugs in more than one drug group. See Table 1 for an explanation of the drug classes.

²CRP values > 100 were set to 100. BMI values > 50 were set to 50. Number of comorbid conditions > 5 was set to 5.

Of the 185 infected persons, 21 (11 %) were hospitalised, whereof 18 (10 %) had COVID-19 as their main diagnosis. Eight (4 %) were admitted to intensive care, and seven (4 %) needed mechanical ventilation.

Discussion

In our study we found that adjusted for sex and age, patients with inflammatory rheumatic joint diseases had a lower incidence of COVID-19 than the population as a whole in 2020. In a meta-analysis of patients with rheumatic diseases, the prevalence of COVID-19 was found to be significantly higher than in the control group (24). This patient group also included patients with vasculitis and systemic connective tissue diseases, who tend to have more systemic inflammation and be more seriously ill than patients with inflammatory rheumatic joint diseases. These patients also use prednisolone more frequently. The increased risk was mainly found to be attributable to the use of prednisolone. In our study, we did not find that patients who used prednisolone had an elevated incidence of infection.

The incidence of COVID-19 in our patient group was lower than in the population in general. We believe this is because patients with chronic diseases have shielded themselves from situations that could represent a risk of infection to a greater extent than healthy persons. The results from the regression analysis indicate the same, i.e. less infection among patients with moderate or high disease activity. Since neither the diagnosis nor the drug treatment had an effect, this is also most likely due to the sickest patients shielding themselves from situations that involved a potential risk of infection. Correspondingly, the higher incidence among the young patients is likely to be due to them having a higher number of close contacts and taking greater risks than the older patients.

A Dutch study found that patients with inflammatory rheumatic joint diseases were twice as likely to follow the advice on isolation and social distancing as the healthy control group (25), and those who were using biological disease-modifying drugs isolated themselves to a greater extent than the rest. If the sickest patients who are taking the strongest anti-rheumatic drugs protect themselves against infection to a greater extent, this could be a confounding factor in the assessment of the extent to which chronic inflammatory rheumatic joint diseases and their treatment affect the risk of infection.

Of the 185 infected patients, 18 (10 %) were hospitalised with COVID-19 as their main diagnosis. These are too few to permit any statistical analysis of this material. As of 3 January 2021, 4.2 % of those infected with COVID-19 in the general population had been admitted to hospital (26). The proportion in the general population that needed intensive care amounted to 0.8 %, compared to 4 % in our material (26). These figures are not directly comparable because of the different age and sex composition of the patients in the NorArthritis registry. Our material included a smaller proportion of hospitalisations than that seen in studies of patients with rheumatic diseases in other countries. A study from the United States showed that the risk of hospitalisation of patients with rheumatic diseases and COVID-19 fell during the course of the pandemic (27). The explanation was that increased testing capacity helped diagnose more patients with less serious illnesses towards the end of the period. The fact that Norway has had

a consistently high testing capacity and been able to diagnose even those with a mild form of COVID-19 may explain why the proportion of hospitalised patients in our material was significantly lower than what was seen in the United States.

Strengths and limitations

Norway's high rate of testing for COVID-19, including at the early stage of the pandemic, represents a strength in this study (28). As a result, the material also contains mild cases of the disease that did not require hospitalisation, and thereby gives a more accurate picture of the risk of infection. The direct reporting of positive tests to MSIS by the laboratories ensures a high degree of reporting and a good overview of cases of the disease. The study describes a relatively large cohort of patients with rheumatic joint diseases.

NorArthritis has a total coverage rate of 60 %, but this varies between hospitals. Hospitals with a low coverage rate have often selected their sickest patients with the strongest anti-rheumatic medication for inclusion, and any potential bias in this study sample would be towards patients with more serious joint diseases (17). Since we did not detect a preponderance of COVID-19 in the patient group, we find it unlikely that inflammatory rheumatic joint disease is a risk factor for COVID-19.

The differences identified are reliable, and do not reflect an excess frequency in the patient group as a whole. There were few infected patients, which means that an absence of identified differences does not necessarily exclude the possibility that differences may exist. This applies to, for example, possible differences between the sexes in the below-average frequency and differences between the various rheumatic conditions, or in terms of drug use. Since the use of prednisolone is often intermittent and varies in dosage, not all use of prednisolone may have been registered in NorArthritis. Nor is information on prednisolone updated until the next check-up, even though the course of treatment might have been terminated before that. If the patients were using prednisolone to a greater or lesser extent than what had been registered, it is possible that prednisolone may actually have had an impact on the incidence, even if we were unable to show this.

Conclusion

Adjusted for sex and age, patients with chronic inflammatory rheumatic joint diseases had a lower incidence of COVID-19 than the population in general. Within the patient group, young age and low disease activity were associated with a higher incidence of infection. The most likely explanation is that patients who were concerned about belonging to a risk group because of chronic illness, high age or high disease activity, protected themselves against infection to a greater extent than others.

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