Changes in immunosuppressive medication because of COVID-19 by patients with chronic inflammatory rheumatic diseases: anxiety was not a major driver

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Abstract

Objective

To study treatment decisions of patients with chronic inflammatory rheumatic diseases (CIRD) at the beginning of the SARS- CoV-2 pandemic in relation to disease characteristics with focus on anxiety.

Methods

A total of 970 CIRD patients diagnosed with rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), psoriasis arthritis (PsA) and connective tissue diseases (CTD), selected from our records who had presented to our hospital at least twice during last year, were contacted by telephone to be asked about medication changes, health status and therapy satisfaction. Standardised tools were used to assess disease activity, anxiety and depression, the latter by Hospital Anxiety and Depression Score (HADS) with a score ≥8 denoting definite anxiety and/or depression. The cut-off for RADAI was set at ≥3.2 and for BASDAI ≥4. Compliance with prevention rules and vaccination status were assessed.

Results

Complete interviews of 557 patients (57.4%) made between April and July 2020 were available for analysis. The median age was 55 (47–63), disease duration 9.0 (4.5–17.0) years, 61.9% females. A recent change in medication was reported by 197 patients (35.4%), 51.2% of which admitted that this decision was mainly made due to the pandemic with more changes occurring with bDMARDs (21.8%) than cDMARDs (6.6%) and corticosteroids (5.4%). There was no major difference between patients who changed because of the pandemic or self-reported inactive disease versus patients who did not change therapy regarding disease activity, depression and anxiety (41%, 17.2%, 31.3% vs. 47.5%, 22.5%, 35.0% vs. 48.9%, 27.7%, 34.1%). More than 90% of patients reported that they rigorously followed Corona prevention rules. The majority of patients were vaccinated against influenza (55.3%) and pneumococci (61.3%), respectively.

Conclusion

Anxiety, depression and disease activity did not play an important role in decisions favouring change of therapy, even though many patients changed medication due to the pandemic. Patients probably protected themselves by strictly adhering to hygiene recommendations. Vaccination rates against influenza and pneumococci were better than previously reported, but still too low.

Key words

rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, connective tissue diseases, SARS-CoV-2, pandemic, anxiety

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Introduction

Whether patients with chronic inflammatory rheumatic diseases (CIRD) are more at risk for a severe course of COVID-19 infections than the general population is still unclear, but the known risk factors male gender, age, pulmonary and cardiovascular disease are also relevant for patients with common CIRD, such as rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), including ankylosing spondylitis (AS), psoriasis arthritis (PsA) and connective tissue diseases (CTD) (1). The benefits of treatment with conventional (c), biologic (b) or targeted synthetic (ts) disease-modifying anti-rheumatic drugs (DMARDs) to neutralise pro-inflammatory cytokines are well established in patients with CIRD (2). However, there are also risks such as a minor increase in infections, but no excess of mortality associated with corticosteroids, b-and tsDMARDs (3, 4). These aspects are potentially relevant for the current pandemic.

In the early days of the pandemic not much was known about the outcome of SARS- CoV-2 infections in patients with CIRD, especially under immunosuppressive therapy. This was the reason why this study had initially been started. An early report has already been published (5). In the meantime, several reports on the outcome of SARS-CoV-2 infections in patients with CIRD became available from other countries (6-9). The region our hospital is mainly serving is North Rhine-Westphalia (NRW) with 17.93 million inhabitants. By the end of February 2021 there were 544.937 subjects infected (3% of the population), 13.380 of which died (case fatality rate 2.5%) (10). These rates are not much different from national ones with 2.508.655 cases and 71.984 death (mortality rate 2.9%) (10). The care of patients with CIRD is largely based on the "treat to target" (T2T) approach, which is well implemented in Germany (2, 11). On this basis, immunosuppressive medication is supposed to be intensified if remission was not achieved. On the other hand, tapering medication is possible if sustained remission is achieved (2, 11). To give some guidance to rheumatologists, the German Society of Rheumatology (DGRh) released recommendations on how to handle the situation rather early on 29 April 2020 (12).

While public health measures restricted the primary health challenges posed by COVID-19, the unpredictability and uncertainty of the pandemic has contributed to secondary mental health issues within the general population such as increased rates of depression and anxiety (13, 14). Therefore, we were interested to understand whether these factors were also of influence in CIRD patients' treatment decisions during the pandemic.

Material and methods

This prospective study was approved by the Ethics Committee of the Ruhr-Universität Bochum (registration no. 20-6901). The function and structure of our specialised tertiary care centre has recently been described in detail (15).

Starting on April 15th 2020, 10 experienced rheumatologists interviewed patients with one of these four diagnoses as identified from the records: RA, axSpA, PsA, and CTD. All patients had been seen at least twice in our outpatient department during the last 2 years. No other selection process was in place.

At least two telephone calls were made at different times of the day to reach a high number of patients. Patients with insufficient language skills and those who did not agree to participate were not included. The interviews were based on a pre-designed questionnaire and planned to last 10 to 15 minutes. Subsequently, questionnaires assessing disease activity, anxiety and depression were mailed to patients who had been interviewed. The data obtained until July 3rd 2020 are reported here.

In addition, information about tests performed to search for a SARS-CoV-2 infection was collected. Anti-SARS- CoV-2 IgG antibodies were examined in 309 of 557 patients using the Euroimmun kit (16). Data obtained from May 6th to September 1st, 2020 are reported here.

Data management and statistics

Study data were collected and managed using REDCap (Research Electronic Data Capture) (17). Exported data were

processed in Microsoft Excel (Microsoft Inc., Redmond, WA) and prepared for statistical analyses using SigmaPlot 14 (Systat Software Inc., San Jose, CA). The data were described as numbers (percentage proportions), means ± standard deviations or medians (interquartile ranges). Groups were compared using appropriate statistical tests (Chi-square test with Yates correction for proportions, and Mann-Whitney U or ANOVA for ranks for continuous data that regularly failed the Shapiro-Wilk normality test). All *p*-values are two-tailed and a value <0.05 was considered statistically significant.

Patients

A large number of patients with RA, axSpA, PsA and CTD were contacted to obtain information about demographics, self-reported disease activity, current medication, satisfaction with the ongoing therapy and changes in treatment, as well as comorbidities, smoking, employment and self-reported health status. To assess risk factors for a COVID-19 infection we especially asked about cardiovascular events, arterial hypertension, malignancy in the last 5 years, osteoporosis, diabetes mellitus and chronic lung disease. The information obtained from the patients was confirmed by checking patients' records. Additional information about social behaviour regarding the pandemic, as well as the vaccination status against pneumococci and influenza was collected. In addition, we compared CIRD patients who changed (group 1) *versus* those who did not change (group 2) during the pandemic. The patients in group 1 were further subdivided into those who reported to have changed therapy because of the pandemic (group 1a), because of high disease activity (group 1b) or because of inactive disease (group 1c).

Any changes in DMARD and CS therapy that had taken place in the last 6–8 weeks were explicitly asked about. The timepoint of any change including changes of dose, application interval, discontinuation, and whether the change of therapy was independently decided or after consultation with the rheumatologist, and the reason for change were recorded.

Self-reported health status was assessed using patient global assessment (PGA) (18) with a numerical rating scale (NRS) ranging from 0 to 10 (0 meaning very good health and 10 very bad health). A good health status was assumed if the scores were <4 and a bad or not so good one for scores ≥4. The subjective evaluation of the effectiveness of therapy ('are you satisfied with your therapy?') was determined by dichotomous answers (yes/no).

The Bath AS disease activity index (BASDAI) was used for axSpA (19) and the RA disease activity index (RADAI) for RA and PsA to assess disease activity (20). High disease activity was assumed if RADAI ≥3.2 and BASDAI ≥4. Due to the heterogeneity of patients with CTD a simple score to assess disease activity was developed, and currently active disease was assumed if 2 out of the following 4 items were positive: whole-body pain, not being satisfied with therapy, any increase in medication, or changed medication.

The Hospital Anxiety and Depression Score (HADS) (21) was collected to assess anxiety and depression levels of our patients. This self-assessment questionnaire depicting generalised anxiety and panic attacks consists of 14 questions with four-level response options (scores from 0–3), 7 relating to anxiety and 7 to depression, respectively. This allows for differentiation between anxiety and depression scales. A cut-off value of ≥8 points in the HADS-A (anxiety) and HADS-D (depression) subscales showed a good sensitivity and specificity (22).

Questions related to social distancing as recommended by the main German authority in charge, the Robert-Koch Institute (RKI), wearing a face mask, avoiding of groups, frequent washing of hands and staying at home were asked to evaluate the compliance with COVID-19 containment measures. To approximately judge the number of contacts with other people during the pandemic, we asked about the average time spent outside of one's own property during the last week. The assessment of difficulty in complying with these rules was tested on a Likert scale (5 possible answers): very easy, easy, neither easy nor hard, rather and very hard.

Results

Out of a total of 1,519 patients of our clinic, 315 were not reached by telephone despite several attempts (20.7%), and 190 patients refused to participate during the interview (12.5%). Language barriers led to exclusion of 32 patients, and 12 patients had died before the pandemic started. Finally, a total of 970 patients agreed to be interviewed (63.9%), 557 of which (57.4%) completed both, the telephone interview and the questionnaires. Thus, 549 patients did not participate at all (36.1%) for various reasons, and complete data were available of 36.7% of all patients originally identified from the records.

Among the 557 patients, 212 were male (38.1%) and 345 female (61.9%), with a median age of 55 (47–63) years. The median disease duration was 9 (4.5–17.0) years, and the median body mass index (BMI) 26.8 (23.4–30.6) kg/m^2; 64.5% were ever smokers. There were no significant differences between groups with respect to age, disease duration and BMI. A detailed presentation of demographic and clinical data is shown in Table I.

Overall, 229 patients had RA (41.1%), 72.4% of which were anti-CCP positive, and 286 had SpA, 31.2% with axSpA (64.3% HLA B27+) and 20.1% with PsA, while 42 patients had CTD (7.5%). No significant differences between groups with regard to comorbidities were found (Table II).

A change in medication due to the pandemic (group 1a) was reported by 46 of all RA patients (20.1%) 37 axSpA (21.3%) and 17 PsA patients (15.2%), respectively (Table I).

For comparison, in group 2, no change in therapy was reported by 131 RA (57.2%), 120 axSpA (69.0%) and 73 PsA patients (65.2%), respectively. Only 1 patient with CTD changed therapy because of the pandemic (2.3%).

There were no significant differences between CIRD patients including PsA, RA, axSpA and CTD in terms of disease activity, as assessed by BASDAI, RADAI and CTD (group 1b excluded). Subgroup analyses showed that patients in group 1a with RA and PsA had lower RADAI scores than in group 2 but there was no significant difference to group

Table I. Patient demographics

Item	All	No recent change of medication (group 2)	Reason for change** Pandemic (group 1a)	Active disease (group 1b)	Inactive Disease (group 1c)	*p**
N*** (%)	557	360 (64.6)	101 (53.4)	40 (21.2)	40 (21.2)	
Age, y	55 (47–63)	55 (46.25–63)	55 (46–63)	51.5 (43.5–62.75)	55 (51–64)	0.581
Male patients	212 (38.1)	135 (63.7)	48 (47.5)	10 (25.0)	12 (30.0)	**0.048**[a]
Body mass index, kg/m^2	26.8 (23.4–30.6) [2]	26.9 (23.2–30.6) [1]	26.8 (24.0–31.2)	25.7 (23.0–29.2)	25.9 (23.5–28.9)	0.641
Currently smoking	153 (27.6)	99 (27.6)	24 (23.8)	15 (37.5)	13 (32.5)	0.373
Ever smoking	359 (64.5)	231 (64.2)	60 (59.4)	29 (72.5)	26 (65.0)	0.532
Never smoked	198 (35.5)	129 (35.8)	41 (40.6)	11 (27.5)	14 (35.0)	
Main diagnosis						
RA	229 (41.1)	131 (57.2)	46 (20.1)	17 (7.4.5)	24 (10.4)	**<0.001**[b]
axSpA	174 (31.2)	120 (69.0)	37 (21.2)	4 (2.3)	9 (5.1)	
PsA	112 (20.1)	73 (65.2)	17 (15.2)	14 (12.5)	7 (6.2)	
CTD	42 (7.5)	36 (85.7)	1 (2.3)	5 (11.9)	0	
Disease duration, y	9.0 (4.5–17.0) [34]	9 (5–17) [28]	10 (4–16) [2]	8 (4.4–17.5) [2]	8.5 (4–20.5) [2]	0.859
Active disease****	279 (50.1)	176 (48.9)	42 (41.6)	32 (80.0)	19 (47.5)	**<0.001**[c]

Numbers are N (%) or median (interquartile range). Numbers in square brackets indicate the number of missing values. *p (change *vs*. no change) and p (different reasons *vs*. no change), respectively (p-values: Chi-square test, ANOVA, or Kruskal-Wallis ANOVA on ranks).
[a]Corona *vs*. Disease activity, p=0.024; [b]Corona *vs*. No change, p=0.015 and Corona *vs*. Disease activity, p=<0.001; [c]Corona *vs*. Disease activity, p<0.001.
**Excluding 16 cases with other or unknown reasons (other reasons include undesired side effects [4], viral infection [3], accident [1]).
***Percentage across row, for reasons relative to patients who did recently change medication.
****According to BASDAI (score ≥4) or RADAI-5 (score ≥3.2) or, in case BASDAI/RADAI-5 were not available, when at least 2 of the following were true: pain, not satisfied with therapy, increase in medication or treatment start, self-claimed disease activity.

Table II. Patient demographics - comorbidities

Item	All	No recent change in medication (group 2)	Reason for change** Pandemic (group 1a)	Disease activity (group 1b)	Disease inactivity (group 1c)	*p**
N***	557	360 (64.6)	101 (53.4)	40 (21.2)	40 (21.2)	
Cardiovascular events	57 (10.4) [10]	36 (10.1) [5]	10 (10.0) [1]	5 (12.8) [1]	3 (7.7) [1]	0.904
Arterial hypertension	254 (45.8) [2]	157 (43.6)	48 (48.0) [1]	20 (51.3) [1]	18 (45.0)	0.738
Use of ACE inhibitors	180 (73.5) [9]	115 (75.2) [4]	33 (73.3) [3]	14 (70.0)	11 (64.7) [1]	0.796
Cancer	47 (8.9) [29]	29 (8.5) [19]	11 (11.5) [5]	2 (5.3) [2]	3 (7.5)	0.667
Osteoporosis	99 (18.2) [14]	65 (18.4) [7]	14 (14.3) [3]	9 (24.3) [3]	6 (15.4) [1]	0.543
Diabetes mellitus	51 (9.4) [12]	34 (9.6) [6]	7 (7.2) [3]	7 (17.9) [1]	2 (5.0)	0.187
Chronic lung disease	107 (20.4) [32]	65 (19.2) [21]	18 (18.9) [6]	10 (25.6) [1]	7 (17.9) [1]	0.792
Number of comorbidities	2 (1–3); Range 0–13	2 (1–3)	2 (1–3)	2 (0–4)	2 (0.25–2.75)	0.785

Numbers are N (%) or median (interquartile range). Numbers in square brackets indicate the number of missing values. *p (change *vs*. no change) and p (different reasons *vs*. no change), respectively (p-values: Chi-square test or Kruskal-Wallis ANOVA on ranks).
**Excluding 16 cases with other or unknown reasons (other reasons include undesired side effects [4], viral infection [3], accident [1]).
***Percentage across row, for reasons relative to patients who did recently change medication.

1c (Fig. 1). In the group with self-reported disease activity (group 1b), there were significantly more patients with active disease (80.0%) than in group 2 (48.9%), group 1c (47.5%) and group 1a (41.6%).

No significant differences were found between groups and diagnoses in terms of depression and anxiety as assessed by HADS (Fig. 1).

All 3 patient groups reported to be satisfied with the current therapy (> 87%), with no significant difference between them (Fig. 1). However, more patients in group 2 and 1a (56.4% and 57.4%) were less satisfied with their health status (PGA) as compared to patients in group 1c (35.0%), see Figure 1.

A total of 30.3% of patients were treated with corticosteroids (CS), while the majority (69.7%) were on b- (62.0%) or ts-DMARDs (7.7%), respectively. Most patients (36.4%) received tumour necrosis factor inhibitors (TNFi) and 42 patients (7.8%) rituximab (RTX). About a third of all patients (35.4%) reported a recent change in therapy (group 1), more than half due to corona (53.4%, group 1a), while 21.2% stated that they had changed therapy due to active (group 1b) or inactive disease (group 1c) respectively, see Table III.

In group 1a, more men (64.9%) than women (46.1%) changed therapy due to the pandemic (p=0.048).

There were no differences in CS intake between group 2 (26.3%) and group 1a (26.0%). This was different for b/ts DMARDs, since significantly more patients in gr.1a (81%) and gr.1c (70%) as compared to group 2 (65.9%) had a higher intake of bDMARDs, especially of TNFi: 53.0% in group 1a *versus* 35.9% in group 2 (Table III).

Significantly more patients in group 1a changed bDMARDs (n=73, 21.6%) compared to cDMARDs (n=17, 6.6%) and CS (n=9, 5.4%), (Table IV). Only

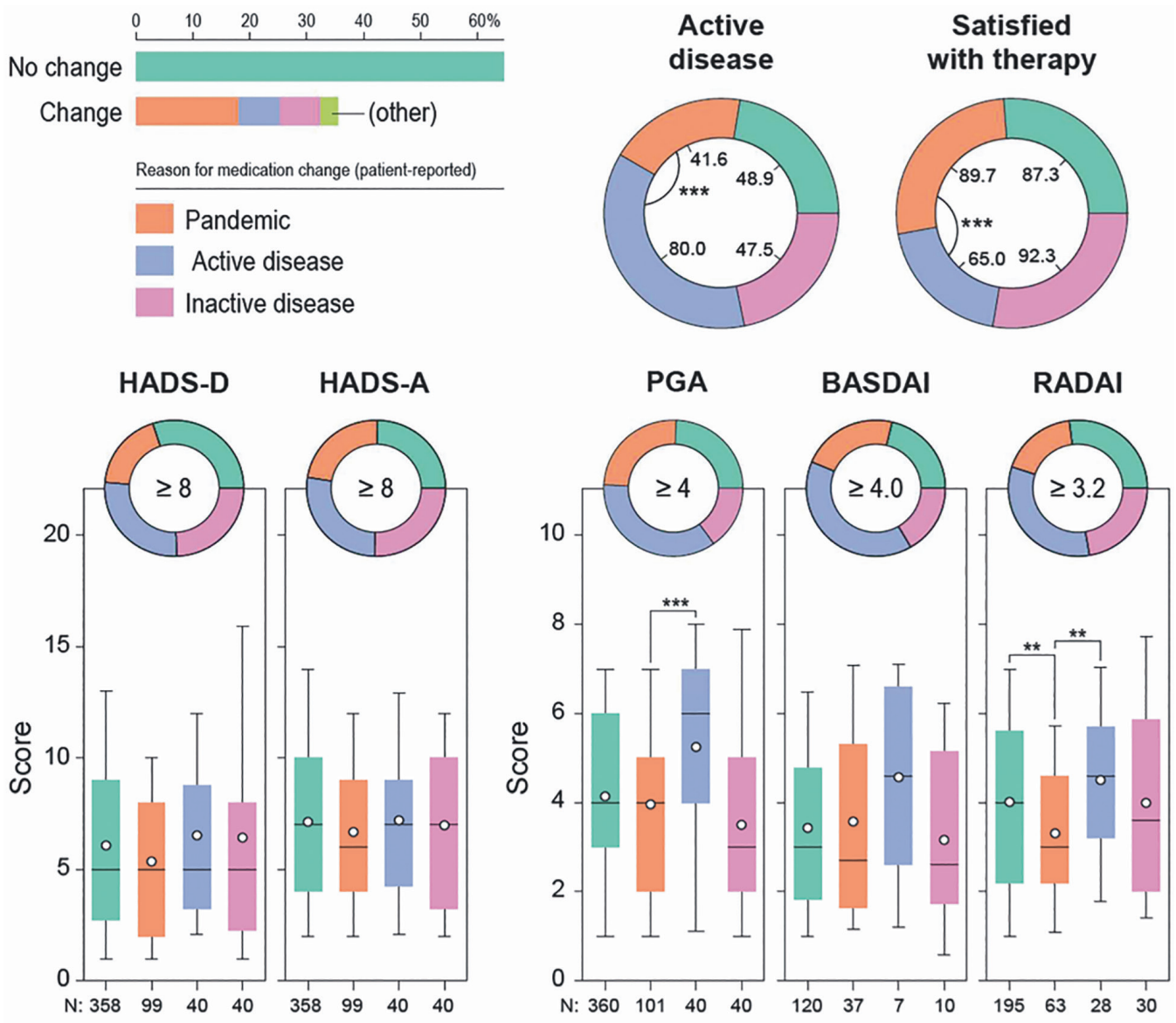

Fig. 1. Disease activity, therapy changes, HADS and therapy satisfaction of the cohort

Subgroup analysis: RA, SpA, and PsA patients who did not change their medication (n=360, 64.6%) and who changed their medication for various reasons (Pandemic, n=101, 18.1%; Disease activity, n=40, 7.2%; Disease inactivity, n=40, 7.2%; other reasons, n=16, 2.9%).

Top left panel: Legend and subgroup percentages. Top right panel: Donut plots showing the percentages of patients within subgroups who had active disease and who were satisfied with their therapy. Numbers are percentages.

Bottom panel (box and donut plots): Hospital anxiety and depression score (HADS-D, HADS-A), Bath ankylosing spondylitis disease activity index (BASDAI), 5-item rheumatoid arthritis disease activity score (RADAI), and patient global assessment (PGA, 0–10 numerical rating scale). Box plots show medians (black horizontal lines), means (white circles), 25/75th percentiles (coloured boxes), 10/90th percentiles (whiskers); numbers of data points are indicated at the bottom (N). Donut plots show the percentages of patients within subgroups with a score exceeding the indicated threshold. Statistical significance (Kruskal-Wallis ANOVA on ranks or χ^2 test) is indicated: *p<0.05, **p<0.01, ***p<0.001.

4.9% of patients in gr.1a discontinued or reduced CS, compared to 37.5% of patients in group 1c (p<0.004). The decision to change therapy in all groups was based on a shared decision between physicians and patients in >80% of cases (Table IV) - as reported by the patients.

Compliance with the required corona prevention rules was reported by >90% of patients, with only 14.2% admitting that compliance was rather/very hard. As many as 61.7% of patients said that they regularly spent <2 hours per day away from home.

A history of vaccination against pneumococci was reported by 276 (61.3%) and against influenza by 267 patients (55.3%), respectively.

Only 1 out of 37 patients under suspicion tested by PCR was positive for SARS-CoV-2 (0.2%). Patients tested had cough, sniffles and/or headache (39.1% each), sore throat (34.8%), shortness of breath (30.4%) and fever (21.7%). The only PCR-positive patient (female, age 37) suffering from cough and fever hospitalised for 7 days survived.

SARS-CoV-2 antibody tests performed in 309 patients (55.5%), only 1.0% had detectable IgG Ab against SARS-CoV-2.

Table III. Medication.

Item	All	No recent change in medication (group 2)	*Reason for change*** Pandemic (group 1a)	Disease activity (group 1b)	Disease inactivity (group 1c)	*p**
N***	557	360 (64.6)	101 (53.4)	40 (21.2)	40 (21.2)	
GC	166 (30.3) [9]	93 (26.3) [7]	26 (26.0) [1]	27 (67.5)	12 (30.0)	**<0.001**
MTX	177 (32.4) [11]	114 (32.6) [10]	28 (27.7)	13 (32.5)	15 (38.5) [1]	0.648
Leflunomide	11 (2.0) [17]	10 (2.9) [15]	0 [1]	1 (2.5)	0 [1]	0.253
HCQ	36 (6.7) [16]	29 (8.3) [12]	3 (3.1) [3]	4 (10.0)	0 [1]	0.076
SSZ	14 (2.6) [18]	10 (2.9) [16]	2 (2.0) [1]	1 (2.5)	1 (2.6) [1]	0.969
AZA	18 (3.5) [41]	17 (5.2) [32]	1 (1.0) [5]	0	0 [1]	0.067
bDMARDs	[18]	[17]	[1]			
TNFi	196 (36.4)	123 (35.9)	53 (53.0)	6 (15.0)	10 (25.0)	**<0.001**
IL-6RA	22 (4.1)	9 (2.6)	6 (6.0)	1 (2.5)	4 (10.0)	0.073
IL-17i	38 (7.1)	21 (6.1)	9 (9.0)	6 (15.0)	2 (5.0)	0.174
IL-23i	14 (2.6)	11 (3.2)	0	2 (5.0)	1 (2.5)	0.266
RTX	42 (7.8)	29 (8.5)	5 (5.0)	3 (7.5)	3 (7.5)	0.726
Abatacept	23 (4.3)	11 (3.2)	2 (2.0)	4 (10.0)	3 (7.5)	0.076
tsDMARDs	[52]	[44]		[2]	[1]	
JAKi	35 (6.9)	23 (7.3)	5 (5.2)	2 (5.3)	5 (12.8)	0.443
PDE-4	4 (0.8)	2 (0.6)	1 (1.0)	1 (2.6)	0	0.561

Numbers are N (%) or median (interquartile range). Numbers in square brackets indicate the number of missing values.
*p (change *vs*. no change) and p (different reasons *vs*. no change), respectively (p-values: Chi-square test or Kruskal-Wallis ANOVA on ranks).
**Excluding 16 cases with other or unknown reasons (other reasons include undesired side effects [4], viral infection [3], accident [1]).
***Percentage across row, for reasons relative to patients who did recently change medication.
NSAIDs, non-steroidal anti-inflammatory drugs; GC glucocorticoids; MTX, methotrexate; HCQ, hydroxychloroquine; SSZ, sulfasalazine; AZA, azathioprine; bDMARD: biological disease modifying anti-rheumatic drugs; TNFi: tumour necrosis factor inhibitor; IL-6i: interleukin 6 inhibitor; IL-17i: interleukin 17 inhibitor; IL-23i: interleukin 23 inhibitor; RTX: rituximab; tsDMARD: targeted synthetic disease modifying anti rheumatic drugs; JAKi: Janus kinase inhibitor; PDE-4: phosphodiesterase 4 inhibitor.

Table IV. Change of medication

Item	Recent change in medication (group 1)	*Reason for change** Pandemic (group 1a)	Disease activity (group 1b)	Disease inactivity (group 1c)	*p***
N***	197 (35.4)	101 (53.4)	40 (21.2)	40 (21.2)	
Base therapy	165 (83.8)	99 (98.0)	29 (72.5)	25 (62.5)	**<0.001**
cDMARDs	41 (25.8)	17 (17.9)	13 (44.8)	8 (33.3)	**0.009**
bDMARDs	110 (69.2)	73 (76.8)	15 (51.7)	14 (58.3)	**0.018**
tsDMARDs	13 (8.2)	8 (8.4)	2 (6.9)	3 (12.5)	0.756
Stopped or Net dose reduction	124 (75.1)	91 (90.0)	5 (12.5)	17 (42.5)	**<0.001**
GC therapy	51 (25.9)	9 (8.9)	22 (55.0)	16 (40.0)	**<0.001**
Stopped or Dose reduction	31 (60.8)	5 (4.9)	8 (20.0)	15 (37.5)	**0.004**
Responsible for change	**[5]**	**[1]**	**[1]**		
Patient alone	18 (9.4)	10 (10.0)	2 (5.1)	5 (12.5)	0.357
Physician alone	19 (9.9)	8 (8.0)	7 (17.9)	3 (7.5)	
Joint decision patient/physician	155 (80.7)	82 (82.0)	30 (76.9)	32 (80.0)	

Numbers are N (%) or median (interquartile range). Numbers in square brackets indicate the number of missing values. *Excluding 16 cases with other or unknown reasons (other reasons include undesired side effects [4], viral infection [3], accident [1]).
*p among reasons (Chi-square test or Kruskal-Wallis ANOVA on ranks).
**Percentage across row, for reasons relative to patients who did recently change medication.
***Multiple choice (sum may exceed 100%).

Discussion

This study was successful in reaching a large number of patients on immunosuppressive therapy during the ongoing SARS-CoV-2 pandemic. The rate of active participants (n=557) was also relatively high for such a survey. Indeed, valid information on disease activity, actual medication, anxiety and depression was obtained in a large number of patients. In addition, the population of this cohort is very much what tertiary centres as ours are usually taking care of, and this includes comorbidity and medication.

Almost 20% of patients interviewed in our survey reported to have changed therapy because of COVID-19 in the beginning of the pandemic (18.1%). This is different from other reports in which much smaller (7) but also higher percentages have been reported (23). Such differences can be possibly explained by the level of information patients had on the pandemic at a certain point in time.

Of interest, there were no major differences in disease activity between patients who changed and those who did not. However, there was one sta-

tistically significant difference for RADAI scores suggesting that RA and PsA patients were more likely to be in remission when they decided to change therapy because of the pandemic. This makes sense from a patients' perspective not knowing how the pandemic will affect them. On the other hand, about half of the patients who reported not to have changed therapy actually had an active disease as assessed by BASDAI and RADAI suggesting that patients had more respect for increased disease activity than fear of the virus. There was a high proportion of patients reporting active disease but most of them were satisfied with their current treatment, and this is consistent with other studies (24).

This study disproves the assumption that the pandemic may have induced more anxiety and depression in our patients hereby making it improbable that these factors played an important role in therapeutic decisions. In fact, there were no significant differences among the groups in this regard. However, a meta-analysis of pandemic survivors in the general population revealed a pooled prevalence of anxiety symptoms of 46% (25). Furthermore, the anxiety level of Japanese RA patients was higher than pre-pandemic levels which includes that patients using bDMARDs or those with more physical disability in the previous year had higher HADS anxiety scores during the pandemic, while – similar to our study – depression levels did not change (26).

Among patients who stated to have changed therapy because of the pandemic there were more patients on bDMARDs, especially TNFi, compared to those who did not change.

Indeed, we found that significantly more changes of therapy occurring due to fear of COVID-19 were related to bDMARDs and only rarely to CS, with the former having been either discontinued or reduced. This suggests that many patients and doctors still think that bDMARDs are associated with a higher risk of infections than CS, which is reportedly not the case (27). However, at this point in time, there was limited evidence on potential risk factors, even though an early report from Italy had shown that CS were potentially harmful (28). In contrast, dexamethasone, similar to tocilizumab (29), is now approved and used for severe COVID-19 infections to reduce the cytokine storm in some countries (30).

Nevertheless, the majority of our patients were not very active and for these a cautious tapering of therapy may have been considered. Only a few patients who made changes due to inactive disease discontinued or reduced bDMARDs whereas more patients reduced CS. The percentage of changes was similar in PsA, axSpA and RA patients suggesting that age and the type of disease was not of importance for therapeutic decisions. In any case, patients who changed therapy because of pandemic were more often in remission than patients who did not change therapy at all. Almost no therapy changes were made by CTD patients – probably because they were afraid of having to experience higher disease activity.

Finally, what do we know now after living for more than a year with the pandemic in a situation where almost 5 million people worldwide have died? Similar factors as in the general population such as age and male gender, in CIRD patients moderate/high disease activity, not receiving DMARDs and a prednisolone dosage >10 mg/day were associated with death (31). Indeed, several large cohort studies showed a higher risk for a severe course of COVID-19 in patients with higher disease activity or high dose CS (28, 32) but no risk was demonstrated for biologics, especially not for TNFi (1, 28). For JAKi the situation is now clearer (33) – even though baricitinib seems to work against COVID-19 (34) – while therapy with RTX represents a problem in this regard (1).

A bit more than half of the patients in our study were vaccinated against influenza and pneumococci. This is fortunately better than in our previous study (35). In other studies ,lower/similar (36) rates were found in CIRD patients. Since there is some evidence that vaccination against influenza may protect against severe outcomes of COVID-19 (37) this is especially unfortunate.

Expectedly, the prevalence of a SARS Cov-2 infection in our cohort was low (0.2%) and not much different from the general population (0.24%) (10). One possible explanation could be that patients with CIRD protect themselves more carefully by more strictly adhering to hygiene recommendations, which was actually the case.

One weakness of our study is the use of a disease activity tool in CTD that has not been evaluated. Since there was no tool such as RADAI or BASDAI available for CTD, we just used a simple general score. In addition, we did not use clinical or laboratory parameters but only patient reported outcome (PRO) data. Finally, due to the nature of the data collection by telephone, we were unable to personally verify much of the information.

Taken together, our study shows that 18.1% of CIRD patients changed therapy because of the pandemic, mostly biologics, and anxiety does not appear to play a major role in this context. We are currently evaluating the outcome of those patients, both in terms of disease activity and safety related to the risk of acquiring COVID-19.

References

1. STRANGFELD A, SCHAFER M, GIANFRANCESCO MA *et al*.: Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2021; 80: 930-42. https://doi.org/10.1136/annrheumdis-2020-219498
2. KILTZ U, BRAUN J, DGRH *et al*.: [Long version on the S3 guidelines for axial spondyloarthritis including Bechterew's disease and early forms, Update 2019 : Evidence-based guidelines of the German Society for Rheumatology (DGRh) and participating medical scientific specialist societies and other organizations]. *Z Rheumatol* 2019; 78: 3-64. https://doi.org/10.1007/s00393-019-0670-3
3. STRANGFELD A, EVESLAGE M, SCHNEIDER M *et al*.: Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis* 2011; 70: 1914-20. https://doi.org/10.1136/ard.2011.151043
4. RICHTER A, LISTING J, SCHNEIDER M *et al*.: Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis. *Ann Rheum Dis* 2016; 75: 1667-73. https://doi.org/10.1136/annrheumdis-2015-207838
5. ANDREICA I, KIEFER D, REZNICZEK GA *et al*.: Comment on 'Characteristics associated with hospitalisation for COVID-19 in people

with rheumatic disease: data from the COVID-19 global rheumatology alliance physician-reported registry' by Gianfrancesco M *et al*.: *Ann Rheum Dis* 2022; 10: e191. https://doi.org/10.1136/annrheumdis-2020-218609
6. YE C, CAI S, SHEN G *et al*.: Clinical features of rheumatic patients infected with COVID-19 in Wuhan, China. *Ann Rheum Dis* 2020; 79: 1007-13. https://doi.org/10.1136/annrheumdis-2020-217627
7. FAVALLI EG, MONTI S, INGEGNOLI F, BALDUZZI S, CAPORALI R, MONTECUCCO C: Incidence of COVID-19 in patients with rheumatic diseases treated with targeted immunosuppressive drugs: what can we learn from observational data? *Arthritis Rheumatol* 2020; 72: 1600-6. https://doi.org/10.1002/art.41388
8. SANCHEZ-PIEDRA C, DIAZ-TORNE C, MANERO J *et al*.: Clinical features and outcomes of COVID-19 in patients with rheumatic diseases treated with biological and synthetic targeted therapies. *Ann Rheum Dis* 2020; 79: 988-90. https://doi.org/10.1136/annrheumdis-2020-217948
9. GIANFRANCESCO M, HYRICH KL, AL-ADELY S *et al*.: Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020; 79: 859-66. https://doi.org/10.1136/annrheumdis-2020-217871
10. https://experience.arcgis.com/experience/478220a4c454480e823b17327b2bf1d4/.
11. SCHNEIDER M, BASELER G, FUNKEN O *et al*.: [Management of early rheumatoid arthritis: Interdisciplinary guideline]. *Z Rheumatol* 2020; 79: 1-38. https://doi.org/10.1007/s00393-020-00775-6
12. SCHULZE-KOOPS H, SPECKER C, IKING-KONERT C, HOLLE J, MOOSIG F, KRUEGER K: Preliminary recommendations of the German Society of Rheumatology (DGRh eV) for the management of patients with inflammatory rheumatic diseases during the SARS-CoV-2/COVID-19 pandemic. *Ann Rheum Dis* 2020; 79: 840-2. https://doi.org/10.1136/annrheumdis-2020-217628
13. JOHNSTONE G, TREHARNE GJ, FLETCHER BD *et al*.: Mental health and quality of life for people with rheumatoid arthritis or ankylosing spondylitis in Aotearoa New Zealand following the COVID-19 national lockdown. *Rheumatol Int* 2021; 41: 1763-72. https://doi.org/10.1007/s00296-021-04952-x
14. RAJKUMAR RP: COVID-19 and mental health: A review of the existing literature. *Asian J Psychiatr* 2020; 52: 102066. https://doi.org/10.1016/j.ajp.2020.102066
15. BRAUN J, KILTZ U, ANDREICA I *et al*.: [Rheumatological care in the Rheumazentrum Ruhrgebiet Rheumatism Center-a model for conurbations]. *Z Rheumatol* 2019; 78: 753-64. https://doi.org/10.1007/s00393-019-0663-2
16. THEEL ES, HARRING J, HILGART H, GRANGER D: Performance characteristics of four high-throughput immunoassays for detection of IgG antibodies against SARS-CoV-2. *J Clin Microbiol* 2020; 58: e01243-20. https://doi.org/10.1128/jcm.01243-20
17. HARRIS PA, TAYLOR R, THIELKE R, PAYNE J, GONZALEZ N, CONDE JG: Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377-81. https://doi.org/10.1016/j.jbi.2008.08.010
18. SCHWARTZ CE, ANDRESEN EM, NOSEK MA, KRAHN GL: Measurement REPoHS. Response shift theory: important implications for measuring quality of life in people with disability. *Arch Phys Med Rehabil* 2007; 88: 529-36. https://doi.org/10.1016/j.apmr.2006.12.032
19. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
20. STUCKI G, LIANG MH, STUCKI S, BRUHLMANN P, MICHEL BA: A self-administered rheumatoid arthritis disease activity index (RADAI) for epidemiologic research. Psychometric properties and correlation with parameters of disease activity. *Arthritis Rheum* 1995; 38: 795-8. https://doi.org/10.1002/art.1780380612
21. ZIGMOND AS, SNAITH RP: The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x
22. BJELLAND I, DAHL AA, HAUG TT, NECKELMANN D: The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; 52: 69-77. https://doi.org/10.1016/s0022-3999(01)00296-3
23. COSTANTINO F, BAHIER L, TARANCON LC *et al*.: COVID-19 in French patients with chronic inflammatory rheumatic diseases: Clinical features, risk factors and treatment adherence. *Joint Bone Spine* 2021; 88: 105095. https://doi.org/10.1016/j.jbspin.2020.105095
24. WOLFE F, MICHAUD K: Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. *Arthritis Rheum* 2007; 56: 2135-42. https://doi.org/10.1002/art.22719
25. DA SILVA ML, ROCHA RSB, BUHEJI M, JAHRAMI H, CUNHA KDC: A systematic review of the prevalence of anxiety symptoms during coronavirus epidemics. *J Health Psychol* 2021; 26: 115-25. https://doi.org/10.1177/1359105320951620
26. ITAYA T, TORII M, HASHIMOTO M *et al*.: Prevalence of anxiety and depression in patients with rheumatoid arthritis before and during the COVID-19 pandemic. *Rheumatology* (Oxford) 2021; 60: 2023-4. https://doi.org/10.1093/rheumatology/keab065
27. AKIYAMA S, HAMDEH S, MICIC D, SAKURABA A: Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. *Ann Rheum Dis* 2021; 80(3): 384-91. https://doi.org/10.1136/annrheumdis-2020-218946
28. FAVALLI EG, BUGATTI S, KLERSY C *et al*.: Impact of corticosteroids and immunosuppressive therapies on symptomatic SARS-CoV-2 infection in a large cohort of patients with chronic inflammatory arthritis. *Arthritis Res Ther* 2020; 22: 290. https://doi.org/10.1186/s13075-020-02395-6
29. GHOSN L, CHAIMANI A, EVRENOGLOU T *et al*.: Interleukin-6 blocking agents for treating COVID-19: a living systematic review. *Cochrane Database Syst Rev* 2021; 3: CD013881. https://doi.org/10.1002/146518 58.cd013881
30. GROUP RC, HORBY P, LIM WS *et al*.: Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; 384: 693-704. https://doi.org/10.1056/nejmoa2021436
31. HASSELI R, MUELLER-LADNER U, SCHMEISER T *et al*.: National registry for patients with inflammatory rheumatic diseases (IRD) infected with SARS-CoV-2 in Germany (ReCoVery): a valuable mean to gain rapid and reliable knowledge of the clinical course of SARS-CoV-2 infections in patients with IRD. *RMD Open* 2020; 6: e001332. https://doi.org/10.1136/rmdopen-2020-001332
32. TAN EH, SENA AG, PRATS-URIBE A *et al*.: Characteristics, outcomes, and mortality amongst 133,589 patients with prevalent autoimmune diseases diagnosed with, and 48,418 hospitalised for COVID-19: a multinational distributed network cohort analysis. *medRxiv* 2020 Preprint. https://doi.org/10.1101/2020.11.24.20236802
33. SPARKS JA, WALLACE ZS, SEET AM *et al*.: Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: Results from the COVID-19 Global Rheumatology Alliance physician registry. *Ann Rheum Dis* 2021; 80: 1137-46. https://doi.org/10.1136/annrheumdis-2021-220418
34. KALIL AC, PATTERSON TF, MEHTA AK *et al*.: Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med* 2021; 384: 795-807. https://doi.org/10.1056/nejmoa2031994
35. KILTZ U, CELIK A, TSIAMI S *et al*.: Are patients with rheumatic diseases on immunosuppressive therapies protected against preventable infections? A cross-sectional cohort study. *RMD Open* 2021; 7: e001499. https://doi.org/10.1136/rmdopen-2020-001499
36. HARRISON N, POEPPL W, MIKSCH M *et al*.: Predictors for influenza vaccine acceptance among patients with inflammatory rheumatic diseases. *Vaccine* 2018; 36: 4875-9. https://doi.org/10.1016/j.vaccine.2018.06.065
37. MARIN-HERNANDEZ D, SCHWARTZ RE, NIXON DF: Epidemiological evidence for association between higher influenza vaccine uptake in the elderly and lower COVID-19 deaths in Italy. *J Med Virol* 2021; 93: 64-5. https://doi.org/10.1002/jmv.26120