

**Rapid Communication**

Changes in treatment adherence and behaviour during the COVID-19 pandemic in Japanese patients with rheumatoid arthritis: results from cross-sectional study in the IORRA cohort

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During the coronavirus disease 2019 (COVID-19) pandemic, the behaviour and adherence to medications in patients with rheumatic diseases have become major concerns. The American College of Rheumatology guidance (1) and European League Against Rheumatic Diseases recommendation (2) indicated that medical treatment of patients with rheumatic diseases should be continued during the COVID-19 pandemic when COVID-19 infection is not suspected. The Japan College of Rheumatology also announced that patients with rheumatic diseases should continue currently prescribed medications such as immunosuppressants, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological DMARDs (bDMARDs), and corticosteroids at the same dose, and not discontinue these medications using self-judgment, to prevent worsening of symptoms of rheumatic diseases (3). Studies from Greece (4), Germany (5), Mexico (6), Denmark (7), and Saudi Arabia (8) reported high adherence to medications in patients with rheumatoid arthritis (RA) during the COVID-19 pandemic. In Japan, > 1.7 million people were infected with the severe acute respiratory syndrome coronavirus 2, and > 18,000 people have died as of October 2021, but there are no large-scale studies on this issue, including the status of COVID-19 infection in patients with RA in Japan. Therefore, we conducted a cross-sectional study using the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) survey on the treatment adherence and behaviour of Japanese patients with RA during the COVID-19 pandemic.

The IORRA survey, a prospective, large, single-institute-based observational cohort study of patients with RA, is being conducted since 2000 at the Tokyo Women's Medical University (9). To briefly explain the IORRA cohort, all Japanese patients with RA who visit our hospital are registered in the IORRA cohort. Data are collected biannually, including patients' self-assessment, physician assessment, and laboratory data. Data have been accumulated for 21 years. The IORRA study was approved by the Ethics Committee of Tokyo Women's Medical University School of Medicine (No. 2922-R16), and informed consent was obtained from the patients at study entry and each survey.

In the IORRA survey conducted from October to December 2020, adherence to RA medications and self-reported changes in RA disease activity, behaviour including frequency of hospital visits, and COVID-19 infection status during the COVID-19 pandemic were cross-sectionally investigated. This information was obtained from the patients' self-reported response. Of the 2,996 RA patients who participated in this survey, 2,785 (93.0%) continued to use RA medications as usual. Similar to previous reports from around the world (4-8), adherence to RA medications was shown to be high in Japanese patients with RA. RA medications were reduced in 96 (3.2%) patients (interval extension, 47 patients; dose reduction, 50 patients), and were discontinued in 89 (3.0%) patients. Of the 89 patients who discontinued RA medications, the number of patients

who discontinued DMARDs was as follows: methotrexate (MTX) 47 (52.8%); immunosuppressants other than MTX, such as tacrolimus and leflunomide 11 (12.4%); immunomodulators such as salazosulfapyridine, bucillamine, and iguratimod 7 (7.9%); molecular targeted drugs such as bDMARDs and Janus kinase inhibitor 27 (30.3%), and corticosteroids 10 (11.2%). Thus, MTX and bDMARDs were more frequently discontinued, which might reflect high proportion of MTX (72.0%) and bDMARDs (32.8%) users in the whole group in this survey (note that these percentages were same as those of the patients without COVID-19). The most common reason for reducing or discontinuing RA medications (n = 185) was “My doctor and I made a decision together” (53.5%), followed by “I made a decision by myself” (43.8%) and “I followed advice from my family members and friends” (1.1%). Among 185 patients who reduced or discontinued RA medications, the proportion of patients whose self-reported RA activity A: did not worsen; B: worsened, and RA medications were returned to usual dosages; and C: worsened, but RA medications remained reduced or discontinued was A: 63.8%, B: 26.5%, and C: 3.8%. Approximately one-third of the patients experienced worsening of RA disease activity due to reduction in or discontinuation of RA medications.

Regarding the frequency of hospital visits (n= 2,996), the proportion of patients with RA who visited our clinic as usual, visited our clinic at a longer interval than usual, consulted a doctor over telephone, and were transferred to nearby hospitals or clinics was 70.4%, 23.1%, 11.8%, and 0.8%, respectively. During the COVID-19 pandemic, remote medical-care strategies, rather than face-to-face consultations, might be useful in patients with rheumatic diseases who are prescribed immunosuppressive medications, as reported in Switzerland (10) and Egypt (11).

Among 2,996 RA patients who participated in this survey, 46 and 2,915 RA patients self-reported that they had been diagnosed with and without COVID-19 until September 2020, respectively. We did not ask how RA patients were diagnosed with COVID-19 in the questionnaire. Table 1 shows the differences in characteristics between patients with RA with (n = 46) and without (n = 2,915) self-reported COVID-19. Patients with COVID-19 were young, had low disease activity, and had good physical function, suggesting that these patients seemed to have good activity of daily living; however, no specific tendency was observed with regard to the RA medication used. In addition, of the 46 RA patients with COVID-19, source of infection was confirmed in only one patient. The symptoms of COVID-19 were fever in two (4.3%) patients, and cough, dyspnoea or shortness of breath, hyposmia, and hyposmia in one (2.2%) patient each; no patient with RA presented with pneumonia or required hospitalization. Several reports have described COVID-19 in patients with rheumatic diseases (12, 13). Of the 47 patients with COVID-19 with rheumatic diseases in Saudi Arabia, 48.9% required

hospitalisation, and elderly patients with a mean age of 65 years had an increased risk of hospitalisation and development of severe COVID-19 pneumonia (12). Corticosteroid use > 10 mg/day was significantly associated with an increased risk, and tumour necrosis factor inhibitor use was associated with a decreased risk of hospitalisation in 600 patients with COVID-19 with rheumatic diseases from 40 countries (13). It is expected that the accumulation of data of Japanese patients with COVID-19 with rheumatic diseases will clarify which patients are susceptible to COVID-19, how we should modify RA medications in patients with RA with COVID-19, and the risk of severe COVID-19 in Japan.

The strength of this study was that a large population of patients with RA was analysed using real-world data. However, a limitation of this study was that the IORRA cohort study is a single-centre study and our hospital is located at the centre of Tokyo, which may limit the generalizability of the results.

In conclusion, most (93.0%) Japanese patients with RA continued to use RA medications as usual, and adherence to RA medications was high during the COVID-19 pandemic. Some patients reduced or discontinued RA medications such as MTX and bDMARDs, resulting in approximately one-third of the patients experiencing worsening of self-reported RA disease activity. Patients with RA with COVID-19 had good activities of daily living; however, no specific tendency was observed with regard to the RA medication used.

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### **Conflict of interest**

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Table 1. Differences in characteristics between RA patients with and without self-reported COVID-19.

	RA patients with COVID-19 (n=46)	RA patients without COVID-19 (n=2,915)	P-value
Female	37 (80.4)	2543 (87.2)	0.26
Age, years*	51.8 (42.1–62.3)	64.3 (53.2–72.6)	< 0.01
Disease duration, years	13 (10–20)	16 (10–24)	0.08
BMI, mg/m <sup>2</sup>	21.0 (19.8–25.5)	21.2 (19.2–23.3)	0.08
DAS28-ESR*	1.8 (1.3–2.2)	2.3 (1.7–3.0)	< 0.01
CDAI*	2.0 (0.8–5.5)	2.7 (0.8–6.1)	0.02
SDAI*	2.0 (1.0–5.7)	3.0 (1.0–6.5)	< 0.01
EQ-5D*	0.90 (0.79–1.0)	0.89 (0.76–1.0)	0.05
J-HAQ*	0 (0–0.34)	0.25 (0–1.0)	< 0.01
RF positive	20 (55.6)	1744 (79.2)	< 0.01
ACPA positive	32 (80.0)	2203 (82.5)	0.70
Medication			
NSAIDs use	22 (47.8)	1340 (46.0)	0.81
Corticosteroid use	7 (15.2)	655 (22.5)	0.19
Corticosteroid dose, mg/day	5.0 (2.5–6.5)	3.0 (2.0–5.0)	0.32
csDMARDs use	42 (91.3)	2500 (85.8)	0.20
MTX use	35 (76.1)	2098 (72.0)	0.52
MTX dose, mg/week	8.4 (6.4–10.0)	8.0 (6.0–10.0)	0.95
BUC use	3 (6.5)	177 (6.1)	0.90
SASP use	7 (15.2)	467 (16.0)	0.88
TAC use	1 (2.2)	129 (4.4)	0.31
IGU use	5 (10.9)	272 (9.3)	0.74
bDMARDs use	17 (37.0)	957 (32.8)	0.57
TNF inhibitor use	8 (17.4)	506 (17.4)	0.99
Non-TNF inhibitor use	9 (19.6)	461 (15.8)	0.53
JAK inhibitor use	1 (2.2)	47 (1.6)	0.80

Continuous variables are summarised as medians with interquartile ranges (IQRs). Categorical variables are presented as number (%). For descriptive purposes, group differences were evaluated using the Wilcoxon rank-sum test and Fisher's exact test for continuous and categorical variables, respectively.

\* Statistically significant differences between RA patients with and without COVID-19 ( $p < 0.05$ ).

ACPA: anti-cyclic citrullinated peptide antibody, bDMARDs: biological DMARDs, BMI: body mass index, BUC: bucillamine, CDAI: Clinical Disease Activity Index, csDMARDs: conventional synthetic DMARDs, DAS28-ESR: disease activity score 28-joint count using erythrocyte sedimentation rate, DMARDs: disease-modifying anti-rheumatic drugs, EQ-5D: EuroQoL 5 Dimension, IGU: iguratimod, IQR: interquartile range, JAK: Janus kinase, J-HAQ: Japanese version of health assessment questionnaire, MTX: methotrexate, NSAID: non-steroidal anti-inflammatory drug, RA: rheumatoid arthritis, RF: rheumatoid factor, SASP: salazosulfapyridine, SDAI: simplified disease activity index, TAC: tacrolimus, TNF: tumour necrosis factor.