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Medication Interruptions and Subsequent Disease Flares During the COVID-19 Pandemic: A Longitudinal Online Study of Patients With Rheumatic Disease

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Objective. We aimed to assess trends in anxiety and interruptions in disease-modifying antirheumatic drug (DMARD) use among patients with rheumatic diseases during the COVID-19 pandemic and to evaluate whether DMARD interruptions were associated with disease flares.

Methods. ArthritisPower, the Vasculitis Patient-Powered Research Network, and other patient organizations invited members to join a 52-week longitudinal study, with baseline surveys completed March 29 to June 30, 2020, with follow-up through May 2021. Logistic regression incorporating generalized estimating equations evaluated associations between interruptions in DMARD use and self-reported disease flares at the next survey, adjusting for demographic characteristics, medications, disease, and calendar time.

Results. Among 2,424 patients completing a median of 5 follow-up surveys, the mean age was 57 years, 87% were female, and the most common conditions were rheumatoid arthritis, vasculitis, and psoriatic arthritis. Average Patient-Reported Outcomes Measurement Information System (PROMIS) anxiety T scores decreased from April 2020 (58.7) to May 2021 (53.7) ($P < 0.001$ for trend). Interruptions in DMARD use decreased from April (11.2%) to December 2020 (7.5%) ($P < 0.001$) but increased through May 2021 (14.0%) ($P < 0.001$). Interruptions in DMARD use were associated with a significant increase in severe flares (rated ≥6 of 10) at the next survey (12.9% versus 8.0% [odds ratio (OR) 1.71 (95% confidence interval [95% CI 1.23, 2.36])] although not any flare (OR 1.18 [95% CI 0.89, 1.58])].

Conclusion. Anxiety and interruptions in DMARD use initially decreased over time, but DMARD interruptions increased during 2021, possibly related to an increase in COVID-19 cases or vaccine availability. Interruptions in DMARD use were associated with increased rates of severe disease flares, highlighting the importance of avoiding unnecessary DMARD interruptions.

INTRODUCTION

SARS–CoV-2, a novel coronavirus, is a highly pathogenic virus that causes COVID-19 and rapidly led to a global pandemic (1). The COVID-19 pandemic has been a particular concern for patients with autoimmune rheumatic diseases (ARDs), who are known to be at a higher risk for infections due to their autoimmune conditions, comorbidities, and use of immunosuppressive therapies (2–4). Despite ongoing research, the risk of severe COVID-19 due to use of different immunosuppressive therapies

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remains uncertain (5–9). The impact of immunosuppressive therapies on vaccination response has also emerged as a concern for patients with ARDs (10). There is an urgent need to determine how patient care has been affected by the pandemic to better understand barriers to effective care during this and future public health crises.

Prior studies have shown that patients with ARDs had frequent health care disruptions and interruptions in the use of their disease-modifying antirheumatic drugs (DMARDs) early in the COVID-19 pandemic (11,12). Little is known, however, about how these disruptions affected patient health or how patient concerns and behaviors changed over time. The goals of this study were to use longitudinal data contributed by an online sample of patients to examine trends in anxiety, as a proxy for mental health, and interruptions in DMARD use throughout the pandemic and to evaluate whether interruptions in DMARD use were associated with disease flares.

PATIENTS AND METHODS

Study population. Adults >18 years of age in the ArthritisPower and vasculitis patient-powered research networks (PPRNs), the CreakyJoints patient community, and partnering patient organizations were sent email invitations. The ArthritisPower PPRN (13,14) is a patient-led online registry of patients with inflammatory arthritis and other rheumatic conditions created as a joint venture of the patients and patient advocates of the Global Healthy Living Foundation, the CreakyJoints patient community, and researchers at the University of Alabama at Birmingham. The Vasculitis PPRN, a collaboration between the Vasculitis Clinical Research Consortium and the Vasculitis Foundation, is an online research registry utilizing patient-reported data. Participants of partnering patient organizations (the Vasculitis Foundation, the Relapsing Polychondritis Foundation, American Bone Health, the Lupus and Allied Diseases Association, Myositis Support and Understanding Association, and the International Foundation for Autoimmune and Autoinflammatory

Arthritis) were directed to a landing page (https://autoimmunecovid. org). Patients were invited to complete a survey at baseline (week 0), weeks 2, 4, 6, and 8, monthly until week 28, and then at weeks 38 and 52 (for a maximum of 11 follow-up surveys) (see Covid registry surveys in Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/ 10.1002/acr.24837/abstract). We analyzed patients with ARDs who completed baseline surveys between March 29 and June 30, 2020, and who completed at least 1 follow-up survey, with follow-up captured through May 2021.

Data collection. At baseline, patients were asked to report demographic data, including country, city, and zip code, as well as rheumatologic conditions, comorbidities, and medications used to treat their ARD. For participants indicating multiple rheumatologic conditions, a hierarchical approach was taken. Patients from the ArthritisPower PPRN and CreakyJoints were classified as having systemic lupus erythematosus (SLE) > psoriatic arthritis (PsA) > ankylosing spondylitis (AS) > rheumatoid arthritis (RA) > vasculitis > myositis, similarly to prior studies (15,16). Patients in the Vasculitis PPRN were thought to be more likely to have vasculitis as a primary diagnosis and so were preferentially categorized as having vasculitis. Patients were considered to have antineutrophil cytoplasmic antibody–associated vasculitis if they reported diagnoses of eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, or microscopic polyangiitis or were otherwise characterized as having "other vasculitis."

County rural versus urban status was defined using National Center for Health Statistics classification (17). Zip code–based median household income and education from the 5-year estimates of the American Community Survey 2014–2018 were also divided into tertiles (18).

At baseline and at each follow-up survey, patients reported respiratory illnesses within the prior 2 weeks, any COVID-19 testing/diagnosis since the prior survey, use and availability of telemedicine, current DMARD use, interruptions in DMARD use because of COVID-19 concerns ("Have you stopped or temporarily paused any of your medications for your rheumatic/ autoimmune disease because of concerns about coronavirus/ COVID-19?"), and anxiety in the prior week using the 4-question Patient-Reported Outcomes Measurement Information System (PROMIS) anxiety short form. PROMIS anxiety responses were converted to T scores, where a score of 50 represents the general population mean with a 10-point SD (19). In addition, at each follow-up visit, patients reported whether they were currently experiencing a flare of their autoimmune condition and, if so, how severe the flare had been the prior week on a scale ranging from 0 (no flare) to 10 (extremely bad). As agreement between physicians and patients on the presence of flare is associated with greater patient-reported flare severity (20), we a priori created a definition of "severe flare" defined as a severity ≥6 of 10 based on the distribution of flare severities observed, hypothesizing that

these severe flares would be more likely to represent true inflammatory disease flares.

Statistical analysis. Characteristics of patients who completed at least 1 follow-up survey versus those who completed only the baseline survey were compared descriptively. Among patients with ≥1 follow-up survey, changes over time in PROMIS anxiety T scores were assessed using generalized estimating equation (GEE) models to account for within-person correlations, with PROMIS anxiety scores as the

Table 1. Baseline characteristics of study participants*

Characteristic	Completed ≥1 follow-up survey (n = 2,424)	Baseline survey only (n = 619)
Age, mean ± SD years	56.8 ± 12.0	52.6 ± 12.6
Female	2,098 (86.6)	534 (86.3)
Hispanic	612 (4.0)	35 (5.6)
Race		
White	2,200 (90.8)	531 (85.8)
Black	57 (2.4)	21 (3.4)
Asian	23 (1.0)	11 (1.8)
Other/multiracial	144 (5.9)	56 (9.1)
Autoimmune disease		
Rheumatoid arthritis	1,012 (41.8)	232 (37.5)
ANCA-associated vasculitis	359 (14.8)	82 (13.3)
Psoriatic arthritis	300 (12.4)	89 (14.4)
Ankylosing spondylitis	183 (7.6)	46 (7.4)
Other vasculitis	176 (7.3)	62 (10.0)
Lupus	123 (5.1)	37 (6.0)
Myositis	61 (2.5)	14 (2.3)
Other†	210 (8.7)	57 (9.2)
Patient organization		
ArthritisPower	1,162 (47.9)	363 (58.6)
Vasculitis PPRN	521 (21.5)	142 (22.9)
CreakyJoints	567 (23.4)	90 (14.5)
Partnering patient organizations	174 (7.2)	24 (3.9)
Rural residence	276 (12.6)	78 (13.7)
Region		
South	844 (37.0)	220 (37.2)
West	545 (23.9)	138 (23.3)
Midwest	492 (21.6)	136 (22.97)
Northeast	401 (17.6)	98 (16.6)
Medications		
Biologic/JAK inhibitor	1,274 (52.6)	300 (48.5)
Methotrexate	727 (30.0)	161 (26.0)
Hydroxychloroquine	518 (21.4)	121 (19.6)
Glucocorticoids <10 mg/day	581 (24.0)	155 (25.0)
Glucocorticoids ≥10 mg/day	112 (4.6)	41 (6.6)
Illness reported at baseline		
No respiratory illness	2,160 (89.1)	520 (84.0)
Respiratory illness without COVID-19 diagnosis	239 (9.9)	92 (14.9)
COVID-19 diagnosis	25 (1.0)	7 (1.1)
PROMIS anxiety, T score‡	58.9 (8.6)	60.1 (8.5)
Health-related behaviors (baseline visit)		
Avoided an office visit	1,430 (59.0)	380 (61.4)
Avoided getting laboratory tests	1,015 (41.9)	293 (47.3)
Avoided getting an infusion	322 (13.3)	94 (15.2)
Interrupted use of a DMARD because of COVID-19 concerns, no./total no. (%)§	191/1,748 (10.9)	75/405 (18.5)
Any flare during follow-up	1,414 (58.3)	NA

* Values are the number (%) unless indicated otherwise. ANCA = antineutrophil cytoplasmic antibody; DMARDs = disease-modifying antirheumatic drugs; NA = not applicable; PPRN = patient-powered research network; PROMIS = Patient-Reported Outcomes Measurement Information System.
† "Other" includes patients with other autoimmune conditions (most commonly inflammatory bowel disease, Sjögren's syndrome, or psoriasis) or patients who reported a non-listed autoimmune condition.
‡ From the PROMIS anxiety short form, with a range of 1–100 and a mean ± SD US adult population of 50 ± 10.
§ Interruptions in the use of a DMARD among patients receiving DMARDs who did not report a respiratory illness.

dependent variable, and month (as a categorical variable) as the independent variable, adjusting for baseline PROMIS anxiety scores. Marginal predictions of scores by month were used to create graphical representations of trends. Similar GEE logit models were used to assess trends in interruptions in DMARD use over time (among patients receiving a DMARD who did not report a respiratory illness or COVID-19 diagnosis) and the cumulative use of telemedicine. For these models, DMARD interruption or use of telemedicine (at the current or any prior survey) were the dependent variables, and month (categorical) was the independent variable. Statistical evaluations of trends over time were assessed by modeling month as a continuous variable, using a linear spline with a knot at December 2020 for interruptions in DMARD use because of changes in trends visualized at this time point. Differences in use of telemedicine by region or by rural status over time were assessed in models including month and either region or rural status, with differences in rates over time assessed with models that included region, month (continuous), and month–region interaction terms. Differences in reasons for interruptions in DMARD use between 2020 and 2021 were compared with chi-square or Fisher's exact testing.

To evaluate whether interruptions in DMARD use were associated with disease flares, we examined patients who were receiving a DMARD, not currently in a flare, and not reporting a current respiratory illnesses or diagnosis of COVID-19. Among this population, we examined whether the DMARD interruptions were associated with the frequency of self-reported flares of any severity or severe flares (severity ≥6 of 10) at the next survey using GEE models with a logit link, adjusting for age, sex, race (White versus non-White), medication type, disease type, and calendar time (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24837/abstract). Marginal predictions were used to estimate flare rates in patients who interrupted versus those who had not interrupted DMARDs at the mean of all covariates in the model.

In sensitivity analyses, we evaluated associations between interruptions in DMARD use and flares only among patients with RA, PsA, AS, or SLE, adjusted for season instead of calendar time, and repeated analyses among patients with at least 6 months of follow-up. Analyses were performed using Stata, version 15.1. All patients provided informed consent and participated without compensation. The study protocol was approved by the Advarra institutional review board.
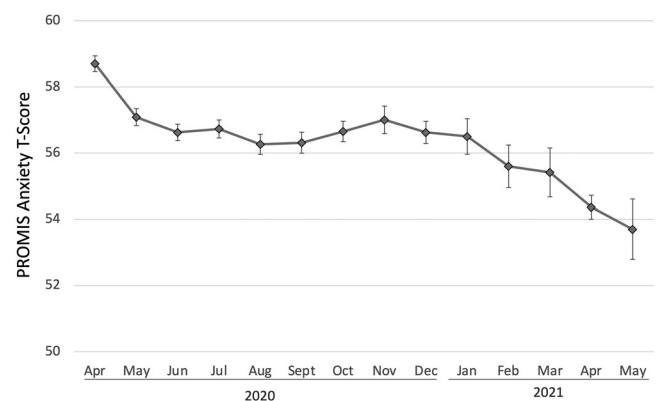
RESULTS

Between April and June 2020, 45,977 patients opened emails with information about the study, 6,065 (13.2%) opened a link to the study, and a total of 3,338 (55.0%) of these patients completed the baseline survey. Among these patients, 295 did not report having an autoimmune disease and were excluded from analysis. Of the remaining 3,043 patients, 2,424 completed at least 1 follow-up survey (a median of 5 follow-up surveys completed [interquartile range (IQR) 2–8]) and are included in this analysis. The mean age was 57 years (range 18–93), 87% were female, and the most common ARDs were RA, vasculitis, and PsA (Table 1). At baseline, 53% of patients were taking biologics or JAK inhibitors, 30% were taking methotrexate, and 29% were taking glucocorticoids.

Longitudinal trends in anxiety, telemedicine use, and interruptions in DMARD use. Average PROMIS anxiety T scores decreased significantly from 58.7 in April 2020 to 53.7 in May 2021 ($P < 0.001$ for trend) (Figure 1). Anxiety was greater in patients who reported avoiding a doctor's office visit on their baseline survey (coefficient 3.2 [95% confidence interval (95% CI) 2.6, 3.9], $P < 0.001$), with no differences among patients who reported versus who did not report use of telemedicine (coefficient –0.2 [95% CI –0.5, 0.1], $P = 0.17$).

On the baseline survey, 42% of patients reported completing a telemedicine visit. Over time, the proportion of patients reporting ever using telemedicine increased to >80% of patients from all US regions by May 2021 (Figure 2). The Midwestern and Southern US showed lower telemedicine usage overall compared to the West (both $P < 0.01$), and increases in telemedicine over time were slower in the Midwest ($P < 0.001$), South ($P < 0.01$), and Northeast ($P = 0.04$) versus the West. Rural areas were also associated with lower telemedicine use ($P < 0.001$). Rates of telemedicine visits did not vary significantly by tertiles of household income or education (data not shown).

Figure 1. Changes in anxiety over time. Results were graphed using predictions from a generalized estimating equation model adjusted for baseline anxiety. There was a significant reduction in scores over time ($P < 0.001$ for trend; mean ± SD US adult population 50 ± 10). PROMIS = Patient-Reported Outcomes Measurement Information System. Diamonds represent predictions at each month. Bars show the 95% confidence intervals.
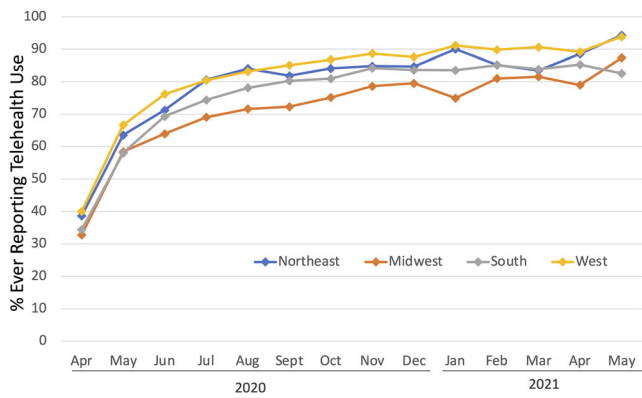
Figure 2. Telemedicine use over time. Results were graphed using predictions from generalized estimating equation logit models. The Midwest region was associated with significantly lower telemedicine use ($P < 0.04$) overall versus the Northeast. Time interactions demonstrate significantly slower increase in telemedicine use in the Midwest ($P < 0.001$) and faster increase in the West ($P = 0.04$) versus the Northeast. Diamonds represent predictions at each month.

Among patients who were not currently reporting a respiratory illness, who had not been diagnosed with COVID-19, and who were taking a DMARD, 191 of 1,748 (10.9%) reported stopping a DMARD at baseline because of concerns regarding COVID-19. Baseline rates of discontinuation of a DMARD were higher (75 of 405 [18.5%]) among patients who did not complete follow-up surveys than among those who had at least 1 additional response (Table 1). Interruptions in DMARD use decreased significantly from April (11.3%) to December 2020 (7.5%) ($P < 0.001$ for trend) but increased from December through May 2021 (14.0%) ($P < 0.001$ for trend) (Figure 3). Discontinuation of a biologic/JAK inhibitor DMARD demonstrated a similar trend, decreasing from April (10.7%) to December (4.8%) ($P < 0.001$), and then increasing through May 2021 (12.2%) ($P < 0.001$) (see Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24837/abstract). A minority of these interruptions in DMARD use was reported to have been recommended by a physician: 214 of 864 (25%) in 2020 versus 53 of 147 (36%) in 2021 ($P < 0.01$). Patients were more likely to report worry about getting sick as a reason for stopping in 2020 versus 2021 (59% versus 28%; $P < 0.001$) and were less likely to give their reason as "other" (16% versus 31%; $P < 0.001$) (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24837/abstract). Interruptions in DMARD use were more common in those with higher anxiety, occurring in 10.6% with PROMIS anxiety T score ≥60 versus 8.4% with PROMIS score <60 (odds ratio [OR] 1.29 [95% CI 1.12, 1.49], $P < 0.001$). Telemedicine use was not associated with interruptions in DMARD use (OR 1.15 [95% CI 0.97, 1.36], $P = 0.12$), although interruptions were more likely in patients who

reported avoiding an office visit at baseline (10.5% versus 7.6% [OR 1.43 (95% CI 1.13, 1.79)], $P = 0.002$).

Influence of interruptions in DMARD use on subsequent disease flares. A total of 1,464 patients with an ARD had at least 1 survey response during which they were receiving a DMARD, did not report a current flare, and had a subsequent survey available (5,800 total responses). Among this population, 925 (16.0%) reported any flare (median severity 6 [IQR 5–7]), while 516 (8.9%) reported a severe flare (≥6 of 10) at their next survey. In adjusted models, interruptions in DMARD use were associated with a significant increase in severe flares at the next survey (OR 1.71 [95% CI 1.23, 2.36]), with predicted severe flare incidence of 12.9% versus 8.0% (Figure 4). Differences in flares of any severity were not statistically significant (OR 1.18 [0.89, 1.58]) (Figure 4). Both severe flares and flares of any severity were more common in patients receiving glucocorticoids, in younger patients, and in those with PsA or AS (versus RA) but were less common in patients with vasculitis; flares were not associated with the type of DMARDs that patients were receiving (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24837/abstract). Results were similar in analyses restricted to patients with RA, PsA, AS, or SLE (see Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24837/abstract), in analyses restricted to patients with at least 6 months of follow-up (see Supplementary Table 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24837/abstract), and in analyses adjusted for season (not shown).
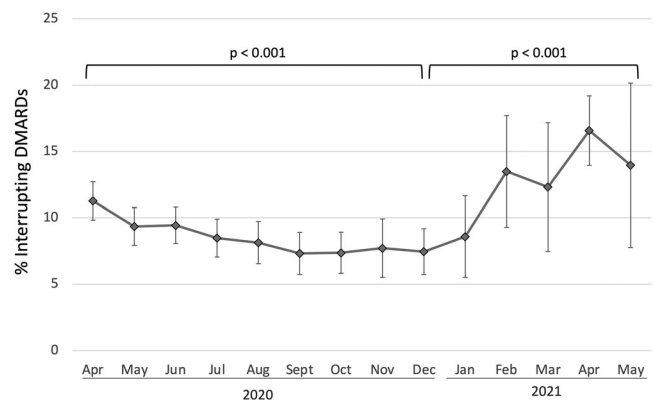
Figure 3. Frequency of interruption in disease-modifying antirheumatic drugs (DMARDs) among patients who reported that they were not sick, did not have COVID-19, and who were taking DMARDs. Results were graphed using predictions from a generalized estimating equation logit model. There was a significant trend for reduction in interruptions from April 2020 to December 2020 ($P < 0.001$) and a significant trend for increase from December 2020 to May 2021 ($P < 0.001$). Diamonds represent predictions at each month. Bars show the 95% confidence intervals.
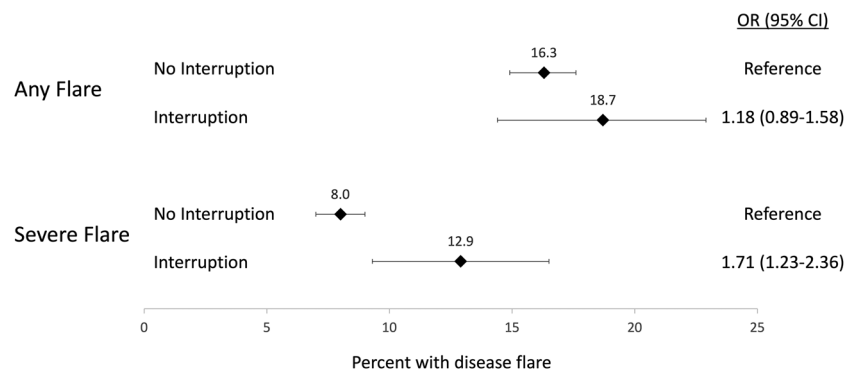
Figure 4. Association between interruptions in disease-modifying antirheumatic drug (DMARD) use and disease flares. Results are from generalized estimating equation logit models assessing the frequency of any flare or of severe flares (rated ≥6 of 10) at the subsequent visit among patients receiving immunomodulatory medications who did not report a respiratory illness or COVID-19 and who did not report currently having a flare. Models also included age, sex, race, autoimmune disease type, glucocorticoid use, DMARD type, and month (full models in Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24837/abstract). 95% CI = 95% confidence interval; OR = odds ratio.

DISCUSSION

In this study of patients with ARDs followed over the course of 14 months, we found frequent interruptions in DMARD use. Importantly, interruptions in DMARD use were associated with self-reported severe disease flares, demonstrating the impact of these DMARD interruptions on patient health. While both interruptions in DMARD use and anxiety decreased during 2020, interruptions in DMARD use increased in 2021, even though anxiety among participants continued to decline.

Several studies have shown that patient concerns early in the pandemic led to frequent health care disruptions, as well as patient interruptions in DMARD use, because of concerns about COVID-19 (11,12,16). Little was known, however, about how rates of interruptions in DMARD use changed as the pandemic progressed. We found that interruptions in DMARD use decreased by >30% by December 2020, with a >50% decrease in biologic/JAK inhibitor interruptions. This reduction may have been due in part to greater comfort with social distancing, discussions with health care providers, and guidance released from the American College of Rheumatology (ACR) in late April 2020 recommending that DMARDs be continued unless patients developed COVID-19 or had a close exposure to an infected person (21). Anxiety, which was strongly associated with interruptions in DMARD use, also decreased substantially over this time period.

Surprisingly, we found a substantial increase in interruptions in DMARD use after December 2020. This increase could be related to a surge of COVID-19 cases during this time period, but because anxiety continued to decrease, it seems possible that interruptions in DMARD use were related to patient or physician concerns about the effect of medications on vaccine efficacy, which were not fully captured in this study. Supporting this assertion, during January to May 2021, patients were less likely to cite "worry about getting sick" as a reason for stopping medications

and were more likely to note the reason as "other" (which may include vaccine-related interruptions). Additionally, the proportion of interruptions in DMARD use that were recommended by a physician increased in 2021, although still only accounting for one-third of interruptions. It is possible that some interruptions in DMARD use may have been appropriate even when patients did not discuss with their physician; patients may have independently followed guidance released by the ACR in February 2021 (10,22) to briefly interrupt use of some DMARDs around the time of vaccination, although the intention of this guidance was to encourage shared decision-making. Given the low rate of interruptions directed by a physician, however, it seems likely that some patients stopped DMARDs for longer periods of time because of general concerns about vaccine efficacy.

Few studies have evaluated how interruptions in DMARD use directly affect patient health. One study from Iran found that ~10% of patients with medication nonadherence during the pandemic experienced a worsening of disease symptoms (23). A cross-sectional study from Saudi Arabia also reported that patients with worse medication adherence and more self-titration of medication had worsening of disease activity (24). The longitudinal nature of our study allowed us to examine patients not currently reporting a flare and to evaluate predictors of subsequent flares. We found that interruptions in DMARD use were associated with a substantial increase in self-reported severe disease flares at the next survey. We did not find an association between interruptions in DMARD use and more mild flares, perhaps because of challenges for patients in distinguishing whether a mild increase in symptoms is related to a true inflammatory disease flare or to other causes. Although patient-reported flares may not always match physician assessments (25), previous studies have shown better agreement between patients and physician measures of flares when patient report of flare severity was higher (20), suggesting that flares rated

more severe by patients are more likely to represent true increases in inflammatory disease activity. Additionally, flares rated as more severe by patients presumably have a greater effect on patient health and are more clinically important. As expected, we also found that glucocorticoid use was associated with flares, presumably because patients receiving glucocorticoids are less likely to start in states of lower disease activity.

Some interruptions in DMARD use may be appropriate, and guidance from the ACR recommends brief interruptions in DMARD use in several situations (10). We excluded interruptions in DMARD use due to COVID-19 or to illness but did not capture whether DMARDs were interrupted because of vaccination. We were not able to examine the duration of interruptions in DMARD use, but previous work has shown that short interruptions in DMARDs are less likely to lead to flares than longer interruptions (26). Because our results combine interruptions of different lengths in use of a DMARD, it seems likely that the actual risk of flare with prolonged interruptions is higher than what we found. These results highlight the importance of maintaining continuity of care and avoiding unnecessary or prolonged interruptions in DMARD use during the pandemic and in future public health crises.

We previously found that patients who avoided office visits early in the pandemic were the most likely group to stop a DMARD, but that patients who replaced these missed visits with telemedicine were less likely to stop a DMARD (11,16). In the current study, avoiding office visits at baseline was associated with increased future interruptions in DMARD use, but there was no association between telemedicine and interruptions in DMARD use. This difference may be due to the rapid uptake of telemedicine in this cohort, with >80% of patients reporting telemedicine use within 4 months. In addition, while telemedicine may help maintain continuity of care, use of telemedicine may reflect higher local rates of COVID-19 or greater patient anxiety. Additionally, patients with the highest likelihood of stopping DMARDs (those who lost contact with the health care system) may have been less likely to participate in this study; notably, we found that patients who did not complete follow-up surveys were substantially more likely to have stopped a DMARD than patients who completed follow-up surveys. Methods to proactively identify patients who lose contact with the health care system may help prevent unnecessary interruptions in DMARD use.

Several limitations are important to note. The majority of the survey population were White, female, and of higher socioeconomic status, and responses may not reflect those of underrepresented populations. Given that patients who answered only the baseline survey were more likely to stop medications than those that were followed over several months, our results likely underestimate rates of interruptions in DMARD use in the general population. Not all patients answered every survey, but results were similar in analyses restricted to patients with at least 6 months of follow-up. Flares were based on patient self-report; we did not

include the Rheumatoid Arthritis Flare Questionnaire because many patients in the study did not have RA, although a key question in this questionnaire is a patient self-report of flare (27). We also did not capture details on the duration of interruptions in DMARD use and could not compare the effects of brief interruptions in DMARD use (as might occur around the time of vaccination) to longer duration interruptions. Lack of time anchors could also have led some patients to continue to report that a medication had been interrupted even once it had been resumed, but this misclassification would tend to bias time trends and associations with disease flares toward the null.

In conclusion, the COVID-19 pandemic led to substantial anxiety and high rates of interruptions in DMARD use among patients with ARDs, and these interruptions were associated with a higher frequency of self-reported severe disease flares. While anxiety and interruptions in DMARD use improved throughout 2020, interruptions in DMARD use increased in 2021, perhaps related to self-discontinuation or physician-directed discontinuation around the time of vaccination. Avoiding unnecessary and prolonged interruptions in DMARD use may help avoid disease flares. Ensuring that patients have continuity of care and continued communication with their physicians is critical to helping patients navigate a confusing and constantly changing landscape.

AUTHOR CONTRIBUTIONS

ROLE OF THE STUDY SPONSOR

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