







Concise Report

COVID-19 and rheumatic musculoskeletal disease patients: infection rates, attitudes and medication adherence in an Irish population

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Abstract

Objectives. To establish, amongst Irish rheumatic musculoskeletal disease (RMD) patients, rates of COVID-19 symptoms and positive tests, DMARD adherence and attitudes to virtual clinics.

Methods. An online survey assessing COVID-19 status, RMD diagnoses, adherence and information sources was disseminated via the Arthritis Ireland website and social media channels.

Results. There were 1381 respondents with 74.8% on immunosuppressive medication. Symptoms of COVID-19 were reported by 3.7% of respondents of which 0.46% tested positive, consistent with the general Irish population. The frequency of COVID-19 symptoms was higher for respondents with spondyloarthritis [odds ratio (OR) 2.06, 95% CI: 1.14, 3.70] and lower in those on immunosuppressive medication (OR 0.48, 95% CI: 0.27, 0.88), and those compliant with health authority (HSE) guidance (OR 0.47, 95% CI: 0.25, 0.89). Adherence to RMD medications was reported in 84.1%, with 57.1% using health authority guidelines for information on medication use. Importantly, adherence rates were higher amongst those who cited guidelines (89.3% vs 79.9%, $P < 0.001$), and conversely lower in those with COVID-19 symptoms (64.0% vs 85.1%, $P = 0.009$). Finally, the use of virtual clinics was supported by 70.4% of respondents.

Conclusion. The rate of COVID-19 positivity in RMD patients was similar to the general population. COVID-19 symptoms were lower amongst respondents on immunosuppressive medication and those adherent to medication guidelines. Respondents were supportive of HSE advice and virtual clinics.

Key words: COVID-19, rheumatoid arthritis, infection, immunosuppression, medication adherence

Rheumatology key messages

- The rate of COVID-19 positivity in RMD patients was similar to the general Irish population.
- Patients on immunosuppressive medications had lower rates of COVID-19 symptoms.
- DMARD adherence was high, with concern of infection the most common reason for non-adherence.

Introduction

COVID-19 has caused >900 000 deaths [1]. Male gender, older age, smoking and comorbidities are risk

factors for severe disease and death [2, 3]. It is unclear whether rheumatic musculoskeletal disease (RMD) patients on immunosuppressive medications are at increased risk of acquiring COVID-19 or having worse outcomes [4–6].

Inflammatory RMDs can increase the risk of a variety of infections including pneumonia [7]. Certain csDMARDs, biologics, Janus kinase inhibitors (JAKi) and glucocorticoids can further increase infection risk while hydroxychloroquine (HCQ) is not considered immunosuppressive [8, 9]. DMARDs are being investigated as COVID-19 therapies. HCQ has been widely used [10, 11]. Trials utilizing tocilizumab and anakinra to treat the

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cytokine storm associated with COVID-19 are underway [12]. EULAR recommends RMD patients continue immunosuppressive medications unless a physician advises otherwise [13]. Yet, some patients have discontinued DMARDs due to fear of COVID-19. To date, there is only one published study examining DMARD adherence during the pandemic [6].

Patient education is crucial to medication adherence. However, the quality and readability of health information varies [14]. Guidelines suggest this should be at a 13 to 14-year-old reading level, but this is not always the case [15]. COVID-19 has dramatically changed medical care with a paradigm shift towards virtual clinics. Benefits include limiting spread of COVID-19 and improved clinician access. Historically, patient and provider opinion on virtual clinics is mixed [16].

The relationship between RMDs, immunosuppressive medications and COVID-19 is unclear. The hypothesis is that RMD patients on immunosuppressive medication might have a higher level of symptoms and higher positive test results for the Coronavirus COVID-19. This study explores COVID-19 prevalence, DMARD adherence, information sources and attitudes to virtual clinics amongst RMD patients during the current pandemic.

Methods

Study design

This is a cross-sectional observational study. A survey (Supplementary Fig. S1, available at *Rheumatology* online) was available via the Arthritis Ireland website and associated social media channels between 28 April and 5 May 2020.

The respondents' primary information source was assessed for quality and readability using validated scoring systems, as previously described by our group [14, 17].

Ethical approval was granted by St Vincent's Healthcare Group Medical Research and Ethics Committee.

Patient and public involvement

The survey was piloted by 10 RMD patients and modified based on their feedback.

Analysis

Analysis was performed using IBM SPSS 26. Nominal data is presented as frequencies and percentages. Between-group differences were assessed using Pearson χ^2 , Fischer's exact or Mann-Whitney U tests as appropriate. Odds ratios were calculated with binary logistic regression.

Results

Respondent characteristics and symptoms

Table 1 shows respondent characteristics including diagnosis, age, gender, RMD medication and information sources. The survey questions showing the data

gathered are included in Supplementary Fig. S1, available at *Rheumatology* online. Symptoms of COVID-19 were reported by 47 (3.7%) respondents. In total, 6/1298 (0.46%) tested positive, consistent with the background rate in the Irish population (0.44%) [18]. Odds ratios (OR) for COVID-19 symptoms were higher amongst those with a spondyloarthropathy (2.06, 95% CI: 1.14, 3.70) and other RMDs (2.16, 95% CI: 1.10, 4.26) and lower in those on immunosuppression (0.48, 95% CI: 0.27, 0.88), csDMARDs (0.35, 95% CI: 0.17, 0.72), multiple immunosuppressives (0.39, 95% CI: 0.16, 0.93) and those who followed guidelines produced by the Irish government Health Service Executive (HSE) (OR 0.47, 95% CI: 0.25, 0.89).

Adherence and information sources

Overall, adherence was high with 787 (84.1%) respondents adherent with RMD medications and 57.1% using HSE guidelines for information on medication use. Other sources of information, including professional societies, patient organizations, media and social media were cited by 626 (52.8%) while 299 (25.2%) responded that they did not use any source. Only four respondents (0.3%) were identified as taking more than one class of biologic therapy. Adherence rates were higher amongst those who cited guidelines (89.3% vs 79.9%, $P < 0.001$),

TABLE 1 Baseline characteristics of respondents

Gender	
Female	1207 (87.8%)
Male	168 (12.2%)
Age	
<40	331 (24.1%)
41–60	814 (59.2%)
>60	230 (16.7%)
RMD^a	
RA	726 (52.9%)
Spondyloarthropathy	451 (32.9%)
CTD/Vasculitis	77 (5.6%)
Other RMD	193 (14.1%)
None	118 (8.6%)
COVID-19 status	
Asymptomatic, without infected contact risk	1176 (91.8%)
Asymptomatic, with infected contact risk	58 (4.5%)
Symptomatic, without infected contact risk	39 (3.0%)
Symptomatic, with infected contact risk	8 (0.6%)
COVID-19 test status	
Not tested	1203 (92.7%)
Negative	89 (6.9%)
Positive	6 (0.5%)
RMD medications	
Biologic/JAKi	664 (51.8%)
csDMARD (excluding HCQ/chloroquine)	526 (40.8%)
Glucocorticoid	116 (12.9%)
HCQ/chloroquine	118 (9.2%)
None of the above	290 (22.5%)

^aSome respondents had more than one RMD.

and conversely lower in those with COVID-19 symptoms (64.0% vs 85.1%, $P = 0.009$). The most common reason for non-adherence was concern of an increased risk of infection (58.8%). Those with symptoms of COVID-19 were more likely to have withheld medications due to clinician advice (55.6% vs 19.4%, $P = 0.025$). Online HSE guidelines on immunosuppressive medication were assessed for quality and readability [14, 17]. DISCERN quality score was 'good' (55/80) and the information met 2/4 of the JAMA criteria although the website was not HONcode certified. Readability was compliant with guidelines (13 to 14-year-old level) by all three scoring systems [15].

There have been highly publicized reports of some DMARDs being useful as treatments for COVID-19. We therefore asked about knowledge relating to use of DMARDs as COVID-19 therapies, 68.9% were unsure, although HCQ was the most commonly selected agent (10.6%). NSAIDs were selected more often (20.9% vs 8.4%, $P = 0.010$) amongst those with COVID-19 symptoms.

Virtual clinics

Respondents overwhelmingly supported virtual clinics, in the absence of normal clinics. 47.4% agreed and 23.0% strongly agreed that 'The use of virtual clinics is a good idea'. In total, 38.4% agreed and 10.0% strongly agreed with the statement 'Irish hospitals were well prepared for the current COVID-19 pandemic'.

Discussion

This is a prospective survey about COVID-19 in Irish RMD patients; it provides important information with respect to symptoms of COVID-19, immunosuppressive medications, adherence, information sources and virtual clinics. The most important finding in this population, the majority of whom had RA and continued on immunosuppressive therapies, was that the rate of COVID-19 test positivity (0.46%) was similar to the general population (0.44%) [18]. In fact, the results suggest that RMD patients taking immunosuppressive medication reported lower rates of COVID-19 symptoms. Medication adherence remained high despite the pandemic and this may reflect the high reported use of HSE guidelines as the most common information source.

Our understanding of the relationship between COVID-19, RMDs and immunosuppressive therapies remains confusing. Inflammatory RMD patients are at increased risk of certain infections, associated with the disease itself or medication-induced immune dysregulation [7]. An Italian cohort of 320 RMD patients on immunosuppressive medications reported eight suspected cases of COVID-19, with four confirmed on testing [5]. The authors do not comment on the incidence of COVID-19 cases in RMD patients on DMARDs; however, they conclude that arthritis patients treated with DMARDs do not seem at increased risk of life-threatening complications from SARS-CoV-2 compared

with the general population. Our findings further support this concept that RMD patients on immunosuppressive medications are not at an increased risk of contracting COVID-19 [4–6], as we find a similar incidence of COVID-19 positivity (0.46%) to the background Irish population (0.44%) [18]. In addition, we report that RMD patients on one or more immunosuppressive medications show a lower rate of COVID-19 infection. This suggests either the treatment is in part protective against COVID-19 infection or our cohort of patients have taken extra care with measures of social distancing and hygiene. Respondents with spondyloarthropathies or other RMDs had higher rates of COVID-19 infection. Compared with RA patients, these groups may believe they are less immunosuppressed and thus less vigilant in following guidance. It may not be possible to tease out the exact reasons for these differences, although the association of higher adherence to immunosuppressive medication and adoption of national guidelines points to better-educated RMD patients being more stringent in practising social distancing and cocooning. One respondent commented 'I am worried because of the methotrexate and my lower immune system but I'm cocooning and following advice from Health Service Executive'.

Early reports provided some anecdotal suggestions that certain DMARDs may protect against COVID-19, in particular anti-IL6 therapy and HCQ, although there is no randomized controlled trial (RCT) evidence to recommend this treatment either as prophylaxis or as treatment of COVID-19 [10]. There is always a balance between the benefits and risks of treatment, and recent reports of adverse effects of HCQ remind us to be cautious. Furthermore, increased RMD disease activity may escalate infection risk [8]; therefore, withholding DMARDs may increase disease activity and indirectly increase infection risk. Medication adherence is defined as the extent to which a person's behaviour agrees with the medication regimen as prescribed [19]. Assessing adherence is challenging and there remains no gold standard [20]. Direct methods of adherence such as measurement of concentrations of a drug or its metabolite in blood or urine or directly observed therapy are costly and labour intensive. Indirect measures of adherence such as questionnaires are cheaper but are far less accurate [21]. Self-reported measures can be subject to measurement bias such as social desirability, response bias and recall bias with respondents overestimating their level of adherence [22, 23]. Yet, despite these limitations, self-reported adherence has been linked with better clinical outcomes, including improved mortality [24].

In RMDs, non-adherence with DMARDs may also increase the risk of disease flare with attendant pain and functional impairment. There is only one published assessment of DMARD adherence during the current pandemic. This Milanese study reported 6.8% of patients decreased or suspended DMARD therapy [6]. A 2007 study reported 52% adherence with immunosuppressive

medications in RMD patients, with forgetting and fear of side effects the main causes of non-adherence [25]. Despite the current pandemic, medication adherence levels in our study were very high; however, personal concern of infection was the most common reason for non-adherence. This group of RMD patients may benefit specifically from further education on the risk/benefit of immunosuppressive medication and disease activity in relation to infection.

HSE guidelines were the most commonly cited resource for information, which was much higher than the figure given (11.1%) for the Irish population [26]. Moreover, we found this information was good quality and highly readable. Patients with RMD may be more conscious of the reliability of information sources. Interestingly, a higher proportion of respondents adherent with medications cited health authority guidelines suggesting better awareness of social distancing and cocooning guidance and that provision of high quality, readable information may significantly influence behaviour, increase adherence and decrease the spread of COVID-19.

There has been considerable media interest globally on the potential role of several DMARD therapies in the treatment of COVID-19. We therefore wanted to gauge the understanding of Irish RMD subjects in relation to this issue. Most respondents were unsure of the possible role of DMARDs in the treatment of COVID-19. Interestingly, NSAIDs were selected more often amongst those with COVID-19 symptoms. Given the concerns about the potential harmful effects of NSAID use for COVID-19, this may suggest a lack of understanding amongst these individuals.

The pandemic has placed an enormous strain on health services. Due to limited hospital capacity and in efforts to reduce footfall in the hospitals, many institutions transitioned to virtual clinics. We wanted to gather from RMD patients their views on virtual clinics and, while not all respondents agreed, the majority considered virtual clinics a good idea, at least during the pandemic.

Strengths of this study, which we believe to be important, include the anonymous nature and large sample size. A limitation of this study relates to the methodology of an online survey, in particular the risk of possible non-response bias, such that a meaningful difference may exist between respondents and non-respondents. In this study, 87.8% of respondents were female. Even allowing for the female preponderance of autoimmune disease, this seems disproportionate, although it does reflect the predominant diagnosis of RA. Gender bias has been recognized in previous surveys, with a higher proportion of female respondents [27, 28]. We did attempt to minimize the issue of bias by disseminating the survey widely through our national patient support organization website and their social media outlets. In addition, COVID-19 can present with a broad range of non-specific systemic symptoms including primarily respiratory and gastrointestinal effects [29]. It is less than a year since the first case of this virus was described

and our understanding of the different clinical phenotypes continues to evolve rapidly [30].

In conclusion, rates of COVID-19 positivity amongst RMD patients in Ireland were comparable to the Irish population. Rates of COVID-19 symptoms were lower in those on immunosuppressive medications, particularly csDMARDs. A higher rate of COVID-19 symptoms was reported by those respondents with spondyloarthropathies. Use of health authority guidelines was associated with a lower rate of COVID-19 symptoms and a higher rate of medication adherence. Finally, RMD patients appear to be highly enthusiastic about virtual clinics. This study adds greatly to our understanding of RMD, immunosuppressive therapy and the COVID-19 virus.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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