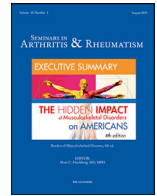




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## Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying anti-rheumatic drugs

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### ABSTRACT

**Objectives:** To investigate the incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases receiving targeted biologic and synthetic disease modifying anti-rheumatic drugs (tDMARDs) and to explore the possible effect of these treatments in the clinical expression of COVID-19.

**Methods:** A cross-sectional study comprising of a telephone survey and electronic health records review was performed including all adult and paediatric patients with rheumatic diseases treated with tDMARDs in a large rheumatology tertiary centre in Barcelona, Spain. Demographics, disease activity, COVID-19 related symptoms and contact history data were obtained from the start of the 2020 pandemic. Cumulative incidence of confirmed cases (SARS-CoV-2 positive PCR test) was compared to the population estimates for the same city districts from a governmental COVID-19 health database. Suspected cases were defined following WHO criteria and compared to those without compatible symptoms.

**Results:** 959 patients with rheumatic diseases treated with tDMARDs were included. We identified 11 confirmed SARS-CoV-2 positive cases in the adult cohort and no confirmed positive cases in the paediatric cohort. COVID-19 incidence rates of the rheumatic patient cohort were very similar to that of the general population [(0.48% (95% CI 0.09 to 0.87%)] and [0.58% (95% CI 0.56 to 0.60%)], respectively. We found significant differences in tDMARDs proportions between the suspected and non-suspected cases ( $p=0.002$ ).

**Conclusion:** Adult and paediatric patients with rheumatic diseases on tDMARDs do not seem to present a higher risk of COVID-19 or a more severe disease outcome when compared to general population.

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### Introduction

The Coronavirus 19 disease (COVID-19) caused by the SARS-CoV-2 virus has been declared a global health emergency in 2020. Health systems around the globe are struggling to find efficacious treatments against COVID-19 and the associated acute respiratory distress syndrome (ARDS). Previous experience with SARS and MERS-CoV infection demonstrated a marked pro-inflammatory response (Th1 and Th17) in patients with ARDS which is also seen in COVID-19 [1–3]. This evidence has prompted the off-label use of IL-6 inhibitors in severe COVID-19 disease as well as the initiation of randomised clinical trials to test these

drugs (clinicaltrials.gov, NCT04320615). Additionally, other inflammatory cytokine pathways such as the IL-1 pathway are currently being explored (clinicaltrials.gov, NCT04324021). Hydroxychloroquine, a commonly used antirheumatic medication, has been shown to have *in vitro* protective effects against SARS-CoV-2 infection [4], although its clinical efficacy still needs to be adequately assessed via randomised clinical trials [5]. A recently approved RA drug, JAK1/2 inhibitor baricitinib, could also be protective by reducing the ability of the virus to infect lung cells [6]. Therefore, patients with rheumatic diseases provide an opportunity to rapidly learn the impact of immunosuppressive agents as protective drugs against SARS-CoV-2 infection and against the development of more severe outcomes in COVID-19 disease.

Targeted biological and synthetic disease modifying antirheumatic drugs (tDMARDs) could also have a detrimental effect in COVID-19

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disease. There is a major need in the rheumatological community to determine which, if any, tDMARDs increase the vulnerability to infection and should therefore be stopped. The European League Against Rheumatism (EULAR), American College of Rheumatology (ACR), National Institute for Health and Care Excellence (NICE) and the Paediatric Rheumatology European Society (PRES) have published preliminary guidance in this scenario [7–10]. EULAR and PRES suggest that patients should discuss treatment discontinuation with their rheumatologists. ACR recommendations also favour to temporarily stop treatment with tDMARDs if exposure to SARS-CoV-2. NICE and ACR advocate the suspension of tDMARDs if COVID-19 is confirmed or suspected with the ACR considering IL-6 inhibitors an exception, which may be continued under specific circumstances. So far, these recommendations are based on expert opinion as there is yet very limited epidemiological evidence on the potential risk conferred by tDMARDs with regards to severe COVID-19 disease complications in patients with rheumatic diseases. Recent reports from Italy show no evidence of increased risk in a cohort of 320 adult rheumatic patients and in a cohort of 123 patients with connective tissue diseases [11, 12]. To date, only one report from a paediatric centre in Milan (Italy) shows no confirmed COVID-19 cases in children [13]. With this scant evidence, rheumatologists worldwide are in the dark as to how to manage patients on immunosuppressive therapies during the pandemic and more information is urgently needed [14]. Different initiatives are being established worldwide to attempt to resolve this issue. Among them, the best positioned to lead this objective is the COVID-19 Global Rheumatology Alliance, an international coalition that is collecting data on rheumatic patients affected with COVID-19. At present, however, they have published an initial report of only 110 rheumatic patients with COVID-19 disease outlining their characteristics and comorbidities [15]. The aim of our study was to report the incidence of COVID-19 in a large cohort of adult and a cohort of paediatric patients with rheumatic diseases receiving tDMARDs from a reference tertiary hospital in Spain, and to explore the possible effect of these treatments in the expression of COVID-19.

## Methods

### Study design

A cross-sectional study consisting of a telephone interview followed by a comprehensive review of electronic health records was conducted in a tertiary centre hospital in Barcelona, Spain, during the 2020 COVID-19 pandemic. All patients had a diagnosed inflammatory rheumatic disease treated with tDMARDs attending the Rheumatology Department in Vall d'Hebron University Hospital, Barcelona, Spain. Vall d'Hebron University Hospital is the largest hospital complex in the Catalonia region and one of the most important in Spain being a reference centre for adult and paediatric rheumatology.

### Study population

All adult and paediatric patients with the following clinical diagnosis: rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA), juvenile idiopathic arthritis (JIA) and autoinflammatory syndromes (AIS) who were receiving any of the following treatments: anti-TNF alpha drugs (etanercept, adalimumab, infliximab, golimumab and certolizumab), IL-1 inhibitors (anakinra), IL-6 inhibitors (tocilizumab and sarilumab), IL 12/23 inhibitors (ustekinumab), IL-17 inhibitors (secukinumab and ixekizumab), CTLA4-Ig (abatacept), JAK inhibitors (tofacitinib, baricitinib and ruxolitinib) and PDE4 inhibitors (apremilast) at the time of the study were invited to take part.

### Demographic, clinical and questionnaire data

The following variables were retrieved from the hospital electronic health record: age, sex, smoking status, comorbidities (obesity,

hypertension, diabetes, previous lung disease, cardiovascular diseases, neoplasia), rheumatic disease diagnosis, current targeted immunosuppressive agent, concomitant treatment with methotrexate and hydroxychloroquine and present glucocorticoids dose. The most recent disease indexes (<4 months) encompassing the Disease Activity Score-28 (DAS-28) for RA, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for axSpA and the Disease Activity in Psoriatic Arthritis score (DAPSA) for PsA were included in the analysis.

The phone survey was performed by experienced professionals from the rheumatology department after adequate training during a 2-week period (March 26<sup>th</sup>–April 10<sup>th</sup> 2020) after lockdown was implemented by the Spanish government on March 14<sup>th</sup> 2020. COVID-19-related symptomatology as well as epidemiological and contact data since the start of the pandemic in the Barcelona area was obtained from all patients. The detailed questionnaire can be found in the supplementary material 1.

For this analysis, we considered “confirmed” cases when the SARS-CoV-2 polymerase chain reaction (PCR) was performed and resulted positive. Due to regional health policies [16], SARS-CoV-2 PCR testing was restricted to patients that had to be admitted to the hospital due to lung involvement. Additionally, clinical and radiological features, blood analysis results and outcome were investigated in patients with confirmed COVID-19 disease.

Following the World Health Organisation (WHO) guidance [17], we considered “suspected” cases when patients reported fever plus one other respiratory symptom (dyspnoea, persistent cough or odynophagia) OR presented 1 of the previous symptoms (fever, dyspnoea, persistent cough or odynophagia) and had had a contact with a confirmed or probable case.

### Statistical analysis

Data are presented for both adult and paediatric subjects, defining adults as subjects above 18 years old. Descriptive statistics were used to compare patient and disease characteristics according to classification as suspected cases. The association between disease activity and suspected cases was explored considering active disease when DAS28 > 2.6 in RA, BASDAI  $\geq$  4 in axSpA and DAPSA > 14 in PsA. Pearson's chi square, Fisher's exact test, Student's t-test and Wilcoxon rank sum test were used for comparisons as appropriate. Odds ratio (OR) for being classified as suspected were calculated using anti-TNF as reference (most prevalent treatment in our cohort) for tDMARDs and stratified by rheumatic disease. A test for linear trend was used to explore the relationship between the level of contact exposure with the proportion of suspected cases.

Cumulative incidence was adjusted for sex and age by direct standardisation, using a COVID-19 epidemiological database from Barcelona generated by the local health institution [18]. This database is updated daily and contains district-level information of COVID-19 confirmed cases. For this analysis we selected the data from the most frequent postal codes within our cohort, globally representing 50% of the patients. Cumulative confirmed cases were updated until April 10<sup>th</sup> 2020. An additional analysis only considering confirmed cases who presented pneumonia in the chest x-ray hence requiring hospital admission (same testing criteria as for general population) was performed. Analyses were performed with STATA v.16.0 and RStudio v.3.5.1.

### Ethical approval

The study was approved by the Hospital Universitari Vall d'Hebron Clinical Research Ethics Committee (Approval Number 5633). This study was conducted according to the principles of the Declaration of Helsinki and patient consent was obtained.

## Results

A total of 1,045 patients with rheumatic diseases currently taking tDMARDs were contacted, and n=959 completed the survey. Following the WHO criteria, 95 patients were classified as suspected cases for COVID-19 infection, 11 of whom were subsequently confirmed to have a positive SARS-CoV-2 PCR test.

### Confirmed COVID-19 cases

Clinical characteristics of the 11 COVID-19 confirmed cases are summarised in [Table 1](#). No confirmed cases were identified in the paediatric cohort. Patients had a median age of 45 years (IQR 30–63) and there was a 54.6% male prevalence. Briefly, the most commonly reported symptom was fever (82%), followed by persistent cough (73%) and malaise (55%). Six patients had radiographic findings of pneumonia on admission. All patients successfully recovered from COVID-19 disease after a median stay of 9.5 days (IQR 5–20 days) and only 1 patient required intensive unit care being the one with more comorbidities. The tDMARD was not administered during the admission in the cases with COVID-19 pneumonia, although in 50% of cases the usual treatment dose did not coincide with that timepoint. Of the remaining 5 cases who did not require admission, the tDMARD was maintained in 4 of them with further successful recovery and no disease flare. Most patients had a contact with a confirmed or suspected case either at home (2 patients had contact with a confirmed case and 5 patients with a suspected case), at work (2 patients had contact with a confirmed case and 4 patients with a suspected case) or both (1 patient).

### Cumulative incidence rates

Crude and adjusted incidence rates stratified by sex and age group are presented in [Table 2](#). When adjusted for same age, sex and city districts, the cumulative incidence rate in our population was found to be 1.21% (95% CI 0.42–1.99%) compared to 0.58% (95% CI 0.56–0.60%) in the general population. If restricting to those confirmed cases with pneumonia, the adjusted cumulative incidence rate of rheumatic patients was found to be more similar to that of the general population [0.48% (95% CI 0.09–0.87%) vs 0.58% (95% CI 0.56–0.60%)].

### Suspected vs. non-suspected cases

Comparing the clinical characteristics of the suspected cases in the adult and paediatric cohorts with those of unaffected patients without these symptoms ([Table 3](#)), adult patients with compatible symptoms were younger (45.7 vs. 54.2 years,  $p < 0.001$ ). A total of 8 suspected cases were documented in the paediatric group. When exploring the effect of therapies between groups (suspected vs. non-suspected), we found significant differences in tDMARD proportions in adults ( $p = 0.002$ ). CTLA-4-Ig and anti-IL6 treated patients showed the lowest incidence of COVID-19-compatible symptoms (<5% at the treatment level) among adult rheumatic patients. When restricting this analysis to RA patients only (n=404, 45.1%) -where these two treatments are mainly used- the same trend was observed for both CTLA4-Ig (OR 0.77, 95% CI 0.22–2.67) and anti-IL6 (OR 0.36, 95% CI 0.08–1.57), although this difference was not statistically significant. Crude ORs for all treatments and disease are presented in supplementary material 2. In the paediatric population, all suspected cases were treated with anti-TNF therapy. However, when comparing to the adult anti-TNF treated sub-group we found no significant difference in risk ( $p = 0.33$ ).

As expected, in both adult and paediatric patients, all symptoms were significantly more frequent in the suspected case group and patients had a higher exposure to possible sources of infection with

more number of cohabitants (trend test  $p < 0.001$ ) with confirmed COVID-19, cohabitants with compatible symptoms, number of cohabitants with compatible symptoms (trend test  $p < 0.001$ ) and co-workers with confirmed disease or compatible symptoms.

### Disease activity

RA patients with active disease (DAS28 > 2.6) were more likely to be classified as suspected case [10.8% active vs 3.5% non-active, diff: -7.8% (CI 95% -12.2, -2.2%)  $p = 0.012$ ]. Active RA patients were older (59.9 vs 56.3 years,  $p = 0.010$ ) and had more prevalence of diabetes (14.2% vs 7.0%,  $p = 0.035$ ), obesity (12.1% vs 5.6,  $p = 0.041$ ) and current prednisone dose (median dose: 5 vs 4.5 mg,  $p = 0.003$ ). There were no differences in proportion of active disease patients comparing suspected and non-suspected cases in the axSpA [11.8% BASDAI active vs 10.2% BASDAI non-active, diff -1.6% (CI -10.6, 7.2),  $p = 0.71$ ] or PsA groups [8.0% DAPSA active vs 12.7% DAPSA non-active, diff: 4.7% (CI 95% -7.5, 16.9%)  $p = 0.51$ ].

## Discussion

Spain is one of the countries in the world where the SARS-CoV-2 expanded more rapidly on the first trimester of 2020. People receiving immunosuppressant therapies are considered more susceptible to viral and bacterial infections and, consequently, a major concern for rheumatologists worldwide is to know if rheumatic patients receiving these therapies have an increased risk of COVID-19. In this study, we performed an epidemiological survey of the COVID-19 incidence in rheumatic patients receiving tDMARD therapy from a large tertiary hospital from Barcelona, Spain. From a total of 959 IMID patients treated with tDMARDs, we identified 11 confirmed COVID-19 cases in adults and no cases in the paediatric population. When comparing our cohort to the epidemiological data from the same city districts and tested with the same criteria, we found that the cumulative incidence for rheumatic patients is highly similar to that of the general population. In our patient cohort, 10% of patients had COVID-19 compatible symptoms according to the WHO criteria. Analysing the tDMARD distribution in these at-risk cases, we found significant differences in tDMARDs proportions between the suspected and non-suspected cases. To our knowledge, this is the largest study outlining the extent of COVID-19 in rheumatic patients treated with tDMARDs to date.

Importantly, this study provides additional evidence that rheumatic patients on immunosuppressant therapies are not at a higher risk of COVID-19 infection than the general population. The number of confirmed cases in our cohort is comparable to that recently reported from one of the focal regions in Italy (1.2% vs. 1.2%) [11]. If considering all cases, the adjusted incidence rate appears to be higher in our patients compared to the general population (1.21% vs 0.58%). However, these results need to be contextualised. Following hospital and regional health guidance [16], SARS-CoV-2 PCR confirmation should be only performed in patients with pneumonia and hospital admission requirements. In our cohort, however, 5 additional patients with normal chest x-ray and without inpatient admission criteria were PCR-tested for SARS-CoV-2 PCR. These patients were health workers from the same hospital (n=2) or patients who were tested as considered to be vulnerable population by the treating clinician (n=3). Once these subjects are excluded from the analysis, the incidence rate is analogous to the population from the same city area. Reassuringly, tDMARD-treated inflammatory rheumatic disease patients do not seem to present a more severe clinical presentation of COVID-19, although our sample of confirmed cases is small. All of the confirmed cases had a complete recovery and only one required admittance in the intensive care unit. Of relevance, there were no confirmed cases in our paediatric cohort as shown in a previous report from Italy [13]. This result is in concordance with the low occurrence of COVID-19 reported for children from the general population [19].

**Table 1**  
Confirmed cases of COVID-19 in tDMARD treated inflammatory rheumatic disease patients.

Sex/ age	Rheumatic disease	Treatment	Comorbidities	Covid-19 contact	Symptoms	Chest X-Ray	Lymphocytes ( $\times 10^9$ )	IL-6 (pg/mL)	Ferritin (ng/ml)	DD (ng/mL)	CRP (mg/dL)	Covid-19 treatment	Days of admission	tDMARD treatment approach	Outcome
F/55	RA	IFX	ILD	Yes	Fever, persistent cough, dyspnea, malaise, anosmia, dysgeusia, diarrhea	Unilateral pneumonia	1,400	15	239	2,418	0.82	CEF, AZT HCQ, L/R	5	Continued	Recovery
M/70	RA	GOL LFN PDN 2.5mg/day	HT, DM CKD AF	Yes	Fever, dyspnea, diarrhea	Bilateral pneumonia	800	132	2057	328	24.90	CEF, AZT HCQ, TOCI	20	Stop GOL	Recovery (ICU)
F/40	PsA	UST LFN PDN 5mg/day	PE	Yes	Fever, persistent cough, malaise, anosmia, headache, odynophagia, arthromyalgia, diarrhea	Bilateral pneumonia	800	Not done	Not done	Not done	0.3	AZT CEF HCQ	10	Continued	Recovery
M/63	RA	TOFA MTX PDN 5mg/day	No	N/A	Fever, persistent cough, odynophagia, dyspnea, diarrhea	Bilateral pneumonia	900	44.65	547	775	3.18	AZT, CEF HCQ, L/R	11	Stop TOFA and MTX	Recovery
F/69	RA	ADA MTX PDN 5mg/day	AF CVD	Yes	Malaise, diarrhea, persistent cough	Bilateral pneumonia	500	24.6	227	113	2.50	AZT HCQ L/R	9	Stop ADA and MTX	Recovery
M/45	PsA	GOL	No	Yes	Fever, malaise Persistent cough, dysgeusia	Bilobar pneumonia	2,100	37.82	759	250	3.10	AZT, HCQ L/R	8	Continued	Recovery
M/24	AIS	ANK	No	Yes	Fever, persistent cough odynophagia	Not done	Not done	Not done	Not done	Not done	Not done	None	0	Continued	Recovery
M/45	RA	ABA PDN 5mg/day	PE PCV	No	Fever, headache, malaise, dyspnea, diarrhea	Normal	Not done	Not done	Not done	Not done	Not done	AZT HCQ	0	Continued	Recovery
F/21	JIA	ADA	No	Yes	Fever, headache	Normal	1,400	Not done	Not done	270	0.05	None	0	Continued	Recovery
F/46	axSpA	ADA MTX, LFN	No	Yes	Fever, asthenia arthromyalgia	Normal	Not done	Not done	Not done	Not done	Not done	HCQ	0	Stop ADA	Recovery
M/30	PsA	ETA	No	Yes	Persistent cough, fever, arthromyalgia	Normal	Not done	Not done	Not done	Not done	Not done	None	0	Continued	Recovery

DD, D-dimer; CRP, C-reactive protein; M, male; F, female; RA, rheumatoid arthritis; PsA, psoriatic arthritis; axSpA, axial spondyloarthritis; JIA, Juvenile Idiopathic Arthritis; AIS, autoinflammatory syndrome; ABA, abatacept; ETA, etanercept; MTX, methotrexate; HCQ, hydroxychloroquine; PDN, prednisone; GOL, golimumab; ANK, anakinra; IFX, infliximab; TOFA, tofacitinib; UST, ustekinumab; HT, arterial hypertension; DM, Diabetes Mellitus; CVD, cardiovascular disease; AF, atrial fibrillation; PCV, polycythemia vera; ILD, interstitial lung disease; PE, pulmonary embolism; CKD, chronic kidney disease; AZT, azithromycin; CEF, ceftriaxone; TOCI, tocilizumab; L/R, lopinavir/ritonavir; ICU, intensive care unit.

**Table 2**  
Cumulative incidence rates of COVID-19 confirmed cases in our cohort and selected sample population (crude and adjusted).

Age group (years)	Sex	District population cumulative incidence rate	Confirmed cases in our cohort		Confirmed cases in our cohort excluding patients without pneumonia	
			Crude cumulative incidence rate	Sex and age adjusted cumulative incidence rate	Crude cumulative incidence rate	Sex and age adjusted cumulative incidence rate
0-14	F	4/41052 (0.01%)	0/31	0%	0/31	0%
	M	4/43147 (0.01%)	0/14	0%	0/14	0%
15-34	F	272/77018 (0.35%)	1/85 (1.18%)	1.3%	0/85	0%
	M	157/73959 (0.21%)	2/51 (3.92%)	4.3%	0/51	0%
35-64	F	926/148893 (0.62%)	3/360 (0.83%)	1.8%	2/360 (0.56%)	1.2%
	M	837/137159 (0.61%)	3/197 (1.52%)	3.1%	2/197 (1.0%)	2.1%
65-74	F	258/40457 (0.64%)	1/98 (1.02%)	0.6%	1/98 (1.0%)	0.6%
	M	300/30590 (0.98%)	1/54 (1.85%)	0.8%	1/54 (1.8%)	0.8%
>75	F	560/50574 (1.10%)	0/48	0%	0/48	0%
	M	585/29429 (2.0%)	0/21	0%	0/21	0%
<b>All</b>	<b>All</b>	<b>0.58%</b> (95% CI 0.56-0.60%)	<b>11/959 (1.15%)</b> , 95% CI 0.06-2.04%	<b>1.21%</b> (95% CI 0.42-1.99%)	<b>6/959</b> <b>(0.63%)</b> , 95% CI 0.02-1.36%	<b>0.48%</b> (95% CI 0.09-0.87%)

The bold values significance was adjusted for same sex and age district population.

At present, as outlined in the introduction EULAR, ACR, NICE and PRES guidance regarding patient management during the COVID-19 pandemic propose individualised decisions on tDMARDs [7-10]. ACR and NICE also advocate for a tDMARD stop if COVID-19 is suspected or confirmed. In our rheumatology department, tDMARD treatment discontinuation was performed individually, based on the specific patient characteristics. Of note, in most of the confirmed cases that were not admitted (i.e. normal chest x-ray), treatment was not stopped and all patients completely recovered from the infection. This is in line with the recently published guidelines of the German Society of Rheumatology that in a situation of a positive SARS-CoV-2 PCR without signs of infection, only recommend a tDMARD pause or delay for 5-6 days [20]. Altogether, our data supports a tDMARD maintenance strategy during the pandemic, although more evidence from different registries is needed.

Similar to recent reports [21], we found that most COVID-19 infected cases do not require secondary care. This situation clearly hinders the estimation of the true population incidence. In our study, to better explore the clinical and epidemiologic characteristics of the suspected cases we decided to identify which patients had compatible symptoms based on the current WHO guidance [17]. The most frequent symptoms in both confirmed and suspected cases were fever and persistent cough as outlined in a recent meta-analysis [22]. Patients with compatible symptoms were significantly younger in the adult population. Factors that could contribute to this increase could be that younger patients tend to live with a higher number of cohabitants and are more likely to leave home for work and, therefore, have an increased risk of infection exposure. We found no differences in comorbidities between groups. This is in apparent contradiction to data suggesting that comorbidities have an important role in COVID-19 severity [23]. However, it is possible that comorbidities influence the severity of the disease rather than the probability of infection [24]. Finally, in our cohort active RA patients were more likely to be classified as suspected cases. There is evidence that RA patients are at an increased risk of infections particularly if they present high disease activity and depending on the concomitant glucocorticoids dose [25-27]. Also, when exploring the characteristics of these active patients, we found they were older, more obese and had more diabetes suggesting an effect of comorbidity in this finding [28].

Although treatment data should be interpreted with caution, we identified significant differences in tDMARDs proportions between the suspected and non-suspected cases. CTLA4-Ig and anti-IL-6 treated patients were less likely to be classified as suspected cases. When restricting the analysis to RA patients, we found suspected cases being less treated with abatacept or IL-6 inhibitors, although

this difference did not reach statistical significance. This data suggests a protective effect of these two therapies. IL-6 is one of the cytokines more highly expressed in severe forms of COVID-19, and has been associated to the reported cytokine storms [29]. For this reason, IL-6 inhibitors are currently being used in the treatment of severe COVID disease [30]. Our results are in line with a possible protective role of IL-6 inhibition in the progression of disease severity and suggest this could be applied preventively, at earlier stages of the infection [31]. There is preliminary evidence that inhibition of the CD80/86 co-stimulation by abatacept as well as IL-6 inhibition could be useful to treat interstitial lung disease [32, 33]. Moreover, abatacept has been associated with a lower risk of serious infections which adds up as a possible explanation of these findings [34]. Very recently, a case series of 86 COVID-19 affected patients with immune-mediated inflammatory diseases (IMiD) from New York showed that the percentage of patients treated with tDMARDs (72% of the cohort) was higher in the ambulatory managed patients compared to those that required admission [15]. Despite the small sample size, this study is in line with our findings, supporting the observation that some tDMARDs might have a protective effect. Together, these data should encourage the initiation of well-designed randomised controlled trials to corroborate the protective effect of these treatments in COVID-19.

Some limitations of this study need to be addressed. First, we designed an observational study based on a telephone survey with different date completion and filled by distinct operators. Patient reporting could have been influenced by the operator and symptoms could have been missed as these could have appeared after the date of completion. To address this potential bias, we reviewed the electronic health records of all patients to detect possible cases and asked all our patients to actively contact us if any of the compatible symptoms occurred. Secondly, we only included rheumatic patients treated with tDMARDs without a control group, either treated with other type of DMARDs or untreated patients. While including also rheumatic patients without these therapies would have also been useful information, the exceptional workload during the lockdown period compelled us to prioritise the group of patients who were initially considered to be the most vulnerable. Thirdly, our study is mainly focused on chronic inflammatory arthritis and we did not include, for example, patients with systemic lupus erythematosus or giant cell arteritis that could provide additional insights into the protective effect of hydroxychloroquine and anti-IL6 therapies. Further, the lockdown effect might be more pronounced in IMiD patients since they are considered an immunosuppressed cohort protecting them from possible exposure to infection and, therefore, distorting their comparison with general population. With regards to the

**Table 3**  
Suspected and non-suspected case characteristics in adult and paediatric population.

Variables	Adults			Paediatric		
	Non suspected N = 797	Suspected N= 90	<i>p</i> -value	Non suspected N= 64	Suspected N=8	<i>p</i> -value
Age, mean (SD)	54.17 (15.28)	45.73 (12.65)	<0.001	12.36(3.77)	15 (2.33)	0.058
Sex (female), n (%)	517 (64.9%)	57 (63.2%)	0.77	43 (67%)	5 (62%)	0.79
<b>Rheumatic diseases, n (%)</b>			0.24			0.93
-Rheumatoid arthritis	368 (46.2%)	36 (40%)	-	-	-	-
-Axial spondyloarthritis	200 (25.1%)	24 (26.7%)	-	-	-	-
-Psoriatic arthritis	160 (20.1%)	22 (24.4%)	1 (2%)	0 (0%)		
-Juvenile idiopathic arthritis	61 (7.7%)	5 (5.6%)	54 (84%)	7 (88%)		
-Autoinflammatory syndromes	8 (1.0%)	3 (3.3%)	9 (14%)	1 (12%)		
<b>Treatment, n (%)</b>			0.002			0.77
-Abatacept	42 (5.3%)	3 (3.3%)	1 (2%)	0 (0%)		
-Anakinra	2 (0.3%)	3 (3.3%)	8 (12%)	0 (0%)		
-Apremilast	6 (0.8%)	2 (2.2%)	-	-		
-JAKi	46 (5.8%)	8 (8.9%)	1 (2%)	0 (0%)		
-Rituximab	4 (0.5%)	1 (1.1%)	-	-		
-anti-IL17	23 (2.9%)	4 (4.4%)	-	-		
-anti-IL23	16 (2%)	4 (4.4%)	1 (2%)	0 (0%)		
-anti-IL6	63 (7.9%)	2 (2.2%)	5 (8%)	0 (0%)		
-anti-TNF	595 (74.5%)	63 (70%)	48 (75%)	8 (100%)		
Hydroxychloroquine, n (%)	24 (3.0%)	4 (4.4%)	0 (0%)	0 (0%)		-
Methotrexate, n (%)	202 (25.3%)	20 (22.2%)	0.48	21 (33%)	2 (25%)	0.64
Glucocorticoids, mg, median (IQR)	5 (2.5, 5) (n=333)	5 (4.5) (n=37)	0.089	2.5 (2.5, 2.5)	-	-
<b>Activity index</b>						
-DAS28, median (IQR) (n=374)	2.94 (2.12, 4)	3.35 (2.96, 4.8)	0.007	-	-	-
-BASDAI, median (IQR) (n=204)	3.35(1.4, 5.2)	3.7 (1.3, 4.6)	1.00	-	-	-
-DAPSA, median (IQR) (n=143)	6.06 (3.12, 11.37)	5 (2.67, 12)	0.67	-	-	-
<b>Comorbidities</b>						
-Hypertension, n (%)	228 (28.6%)	18 (20%)	0.084	1 (2%)	0 (0%)	0.72
-Diabetes, n (%)	84 (10.5%)	6 (6.7%)	0.25	0 (0%)	0 (0%)	-
-Obesity, n (%)	88 (11.0%)	7 (7.8%)	0.34	0 (0%)	0 (0%)	-
-Pulmonary disease, n (%)	107 (13.4%)	14 (15.6%)	0.58	2 (3%)	0 (0%)	0.61
-Smoking, n (%)	162 (20.3%)	23 (25.6%)	0.25	0 (0%)	0 (0%)	-
-Cardiovascular disease, n (%)	84 (10.5%)	5 (5.6%)	0.14	0 (0%)	0 (0%)	-
-Neoplasia, n (%)	19 (2.4%)	2 (2.2%)	0.92	0 (0%)	0 (0%)	-
<b>Symptoms, n (%)</b>						
-Dyspnoea	14 (1.8%)	19 (21.1%)	<0.001	0 (0%)	0 (0%)	-
-Persistent cough	31 (3.9%)	70 (77.8%)	<0.001	2 (3%)	4 (50%)	<0.001
-Fever	7 (0.9%)	49 (54.4%)	<0.001	0 (0%)	6 (75%)	<0.001
-Odynophagia	22 (2.8%)	28 (31.1%)	<0.001	0 (0%)	3 (38%)	<0.001
-Arthralgia/myalgia	28 (3.5%)	38 (42.2%)	<0.001	1 (2%)	1 (12%)	0.076
-Malaise	34 (4.3%)	36 (40.0%)	<0.001	0 (0%)	1 (12%)	0.004
-Headache	49 (6.1%)	39 (43.3%)	<0.001	1 (2%)	1 (12%)	0.076
-Anosmia	11 (1.4%)	16 (17.8%)	<0.001	0 (0%)	0 (0%)	-
-Dysgeusia	10 (1.3%)	11 (12.2%)	<0.001	0 (0%)	0 (0%)	-
-Diarrhoea	36 (4.5%)	20 (22.2%)	<0.001	1 (2%)	1 (12%)	0.076
<b>Contacts</b>						
-N° of cohabitants, median (IQR)	2 (2, 4)	3 (2, 4)	<0.001	4 (4, 5)	4 (3.5, 5)	0.30
-Confirmed COVID cohabitant, n (%)	4 (0.5%)	7 (7.8%)	<0.001	3 (5%)	1 (12%)	0.36
-Cohabitant with symptoms, n (%)	43 (5.4%)	52 (57.8%)	<0.001	9 (14%)	7 (88%)	<0.001
-N° of cohabitant with symptoms, median (IQR)	1 (1, 6)	2 (1, 3)	<0.001	6 (1, 6)	2.5 (2, 3.5)	0.34
-Confirmed COVID coworker, n (%)	54 (6.8%)	17 (18.9%)	<0.001	8 (12%)	3 (38%)	0.068
-Coworker with symptoms, n (%)	73 (9.2%)	35 (38.9%)	<0.001	8 (12%)	4 (50%)	0.008

JAKi: JAK inhibitors, DAS-28: Disease Activity Score-28, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, DAPSA: Disease Activity in Psoriatic Arthritis score (DAPSA).

analysis, the small number of cases did not allow for the adjustment for potential confounders other than age and sex. Lastly, due to limited availability of SARS-CoV-2 testing in our setting, the estimate of COVID-19 incidence is inaccurate, thereby prompting the health community to rely on suspect cases definitions that might not precisely identify all cases.

In conclusion, adult and paediatric patients with rheumatic diseases treated with tDMARDs do not seem to present a higher risk of COVID-19 or a more severe disease outcome compared to the general population. These data suggest that tDMARDs should not be stopped in these patients during the pandemic. Our study also suggests that tDMARDs show different levels of protection against COVID-19 and supports the development of randomized clinical trials to adequately assess their individual effect. International initiatives currently under way, such as the Global Rheumatology Alliance and the EULAR

COVID-19 database will provide invaluable data for rheumatic disease management, but epidemiological studies from large national reference centres can be extremely helpful as an interim guidance [14, 35]. In this unprecedented time, when therapies commonly used in rheumatic diseases could prove useful to manage a pandemic disease, rheumatologists are required to provide all their expertise to accelerate the generation of scientific data to protect the lives of people, not only those affected by rheumatic diseases, but also for the global population.

#### Declaration of Competing Interest

XM received speaker fees from Novartis and Sanofi-Genzyme. HB received speaker fees from Lilly, MSD and Pfizer. RCR received speaker fees from MSD. ETA received speaker fees from Roche and

Bristol-Myer-Squibb outside this work. SM received speaker fees, grant and honoraria from Roche and Bristol-Myer-Squibb outside this work. MLC, MLL, EM, MPP, AED, MSL, EE, SA, GAS, APS, MBB, MAB, JDD, JL and AJ have nothing to disclose

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.semarthrit.2020.05.001](https://doi.org/10.1016/j.semarthrit.2020.05.001).

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