Prevalence, admission rates and hypoxia due to COVID-19 in patients with rheumatic disorders treated with targeted synthetic or biologic disease modifying antirheumatic drugs or methotrexate: a nationwide study from Iceland

Susceptibility and tolerance to COVID-19 of patients with rheumatic disorders remains poorly understood. A recent meta-analysis did not demonstrate any considerably worse outcomes.[1] Sufferers from inflammatory rheumatic disorders are, however, known to be more prone to infections than the general population and this risk is increased by targeted biologic therapy.[2 3] Therefore, we were interested in examining the risk of admission and respiratory failure in patients with rheumatic disorders with COVID-19 being treated with targeted synthetic or biologic disease-modifying anti-rheumatic drugs (ts/bDMARDs), comparing them to matched comparators and methotrexate (MTX) users within Iceland. Unique conditions exist in Iceland for this study, as the island nation is naturally isolated and performed extensive screening, tracing and systematic registration of all PCR-confirmed cases.[4 5] All diagnosed individuals received regular follow-up by a COVID-19 outpatient clinic.[6]

ICEBIO is a nationwide registry of patients with inflammatory arthritis treated with ts/bDMARDs. We included all patients in ICEBIO undergoing treatment at the start of the domestic outbreak. From the Icelandic Medicine Database we extracted all MTX prescriptions filled in the 9 months before Iceland's first recorded case of COVID-19. Each individual from the ICEBIO and MTX groups was randomly matched with up to ten controls based on age, sex and geographic location. Individuals in ICEBIO or with MTX prescriptions from haematologists and oncologists were excluded from the MTX group, although their comparator group remained unaltered. The Icelandic Directorate of Health provided data on all PCR tests and hospital admissions in our study population. Data were extracted on 3 June 2020, when the first domestic outbreak ended: 1796 individuals had been diagnosed with COVID-19, with two active cases remaining. At that time, 61 639 tests had been administered in a nation of roughly 360 000 people, and the Directorate of Health reports a successful infection tracing rate of over 95%.[4]

We identified 1438 individuals from ICEBIO, 13 815 ICEBIO comparators, 1746 individuals with an MTX prescription and 22 962 MTX comparators, see table 1. The relative risk (RR) for the ICEBIO group to undergo testing was 1.35 (1.23–1.48; p<0.001), compared with their comparators and the RR for the MTX group at 1.05 (0.96–1.15; p=0.28) compared with theirs.

Nine from ICEBIO, eighty-four ICEBIO comparators, five MTX treated and one hundred and thirty-four MTX comparators were SARS-CoV-2 positive. All infected patients from ICEBIO had received tumour necrosis factor inhibitors (online supplemental tables S1 and S2). Two of three hospitalised patients from ICEBIO, three of three ICEBIO comparators, one of one from the MTX group and ten of thirteen hospitalised MTX comparators received oxygen supplementation. One of three admitted patients from the ICEBIO comparators and two of thirteen MTX comparators received mechanical ventilation (table 1). The RR for infected patients from ICEBIO to be admitted was 9.33 (2.20–39.6; p<0.001) and 6.22 (1.19–32.46; p=0.02) to be admitted with hypoxia. The RR for hypoxia following admission was 0.67 (0.30–1.48) for patients from ICEBIO and 0.77 (0.57–1.4) for patients taking MTX. The mean length of admission for the patient from ICEBIO was 4.7±3.6 days, while it was 20.2±12.7 days for their comparators (p=0.16). As no patients with rheumatic disorders in any group required mechanical ventilation, neither OR nor RR can be calculated for that outcome.

We found that patients with COVID-19 with rheumatologic disorders on bDMARDs are at a higher risk of hospitalisation than matched comparators. This might be explained by a lower threshold for admitting patients on biologics, as hospitalised rheumatology patients on bDMARDs fared numerically better, although the small numbers prevent meaningful statistical analysis. Further studies in larger populations are needed to better quantify the risk and severity of COVID-19 in patients with rheumatic disorders treated with bDMARDs.

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Table 1 Demographics, proportion and the number of individuals who underwent nasal swab PCR test for SARS-CoV-2; numbers of hospital admission and prevalence of COVID-19 in studied groups

	ICEBIO group	ICEBIO comparators	MTX group	MTX comparators
No.	1438	13 815	1746	22 962
Mean age ±SD	54.9±14.9	54.7±15.1	60.4±14.6	59.6±14.5
% females	59.0%	58.7%	61.9%	62.0%
No. of nasopharyngeal swaps	427 (297 per 1000 population)	3016 (218 per 1000 population)	426 (244 per 1000 population)	4565 (199 per 1000 population)
No. of tested individuals (%)	383 (26.6%)	2728 (19.7%)	385 (22.1%)	4838 (21.1%)
No. of SARS-CoV-2-positive individuals (%)	9 (0.6%) *	84 (0.6%)	5 (0.3%)	134 (0.6%)
Prevalence of COVID-19 in tested subjects	2.3%	3.1%	1.3%	2.8%
No. of hospital admissions (% of infected)	3 (33%)	3 (3.6%)	1 (20%)	13 (9.7%)
No. of admitted patients with hypoxia	2	3	1	10
No. of admitted patients intubated and on mechanical ventilators	0	1	0	2
Mean length of admission ±SD	4.7±3.6	20.2±12.7	14	10.8±7.8
Mean age of admitted patients ±SD	64.7±6.1	70±14	68	62.3±9

*All were treated with tumour necrosis factor (TNF) inhibitors (85.2% of patients in ICEBIO are on TNF inhibitors).

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Patient	Age	Sex	Diagnosis	Last documented disease activity	ts/bDMARD	Conventional DMARDs or steroids	Time on current biologic	Smoking	Other comorbidities	Clinical severity category on first evaluation	Days with symptoms at first evaluation	Days with symptoms at time of PCR diagnosis
ICEBIO-1	68	Female	Ankylosing spondylitis	1.99 (ASDAS-CRP)	TNFi	None	3 years	No	Hypertensions	Green	10	9
ICEBIO-2*	66	Female	Rheumatoid arthritis, seronegative	2.7 (DAS28-CRP)	TNFi	MTX	6 years	No	None	Green	6	3
ICEBIO-3	51	Female	Psoriatic axial spondyloarthritis	1.67 (ASDAS-CRP)	TNFi	None	12 months	No	None	Green	7	4
ICEBIO-4	50	Female	Ankylosing spondylitis	1.34 (ASDAS-CRP)	TNFi	None	11 months	No	None	Yellow	10	7
ICEBIO-5*	70	Male	Rheumatoid arthritis, seropositive	HAQ score 1, DAS28crp not available	TNFi	HCQ	5 months	No	Atrial *fibrillation*	Yellow	5	2
ICEBIO-6	68	Female	Ankylosing spondylitis	1.4 (ASDAS-CRP)	TNFi	MTX	2 years	No	Hypertension	Green	7	4
ICEBIO-7	47	Female	Psoriatic arthritis	3.62 (DAS28-CRP)	TNFi	MTX	5 years	Yes	Hypertension	Green	8	5
ICEBIO-8	38	Male	Ankylosing spondylitis	2.82 (ASDAS-CRP)	TNFi	None	4 years	No	None	Green	11	3
ICEBIO-9*	58	Female	Psoriatic arthritis	3.85 (DAS28-CRP)	TNFi	MTX	3 months	No	Asthma	Yellow	3	1
MTX-1	66	Female	Suspected SLE	N/A	No	MTX	N/A	No	Hypertensions	Green	Not registered	14
MTX-2	55	Male	Psoriatic arthritis	N/A	No	MTX	N/A	No	None	Green	9	7
MTX-3*	68	Male	Rheumatoid arthritis	N/A	No	MTX and HCQ	N/A	No	Hypertension, type 2 diabetes	Red	13	9
MTX-4	75	Male	Polymyalgia rheumatica	N/A	No	MTX and 10mg prednisolone	N/A	No	None	Green	3	0
MTX-5	70	Male	Psoriatic arthritis	N/A	No	MTX	N/A	No	Type 2 diabetes	Green	20	17

Patients were risk stratified based on underlying health conditions and on clinical severity categories where patients weighted symptoms were classified into green (mild or improving symptoms), yellow (mild dyspnoea, cough or fever for less than 5 days) or red (worsening dyspnoea or cough, high and persistent fever for 5 days or longer, or severe fatigue).[11]

Note. – MTX = Methotrexate; HCQ = Hydrochloroquine; TNFi = Tumour necrosis factor alfa inhibitors; DAS28-CRP= Disease activity score 28 for Rheumatoid arthritis with CRP; ASDAS = Ankylosing spondylitis disease activity score with CRP; HAQ = Health assessment questioner; N/A = not applicable.

** admitted*

Table S1

Characteristics of all rheumatic patients on ts/bDMARDs or MTX with a PCR confirmed SARS-COV-2

Total number of patients (n)	1438
Age (years ± SD)	54.9 ± 14.9
Females, n (%)	849 (59 %)
Diagnosis, n (%)	
Rheumatoid arthritis	500 (34.8 %)
Psoriatic arthritis	378 (26.3 %)
Ankylosing spondylitis	309 (21.5 %)
Unspecified polyarthritis	77 (5.4 %)
Not registered	48 (3.3 %)
Reactive arthritis	37 (2.6 %)
Systemic lupus erythematosus	19 (1.3 %)
Juvenile idiopathic arthritis	13 (0.9%)
Giant cell arteritis	10 (0.7%)
Other disorders/diagnosis	47 (3.3 %)
Targeted DMARDS, n (%)	
TNF inhibitors	1225 (85.2 %)
Infliximab	*436 (30.3 %)*
Etanercept	*343 (23.9 %)*
Adalimumab	*309 (21.5 %)*
Golimumab	*137 (9.5 %)*
Certolizumab	*3 (0.2%)*
Tocilizumab	82 (5.7 %)
Secukinumab	51 (3.5 %)
Rituximab	26 (1.8 %)
Belimumab	17 (1.2 %)
Tofacitinib	10 (0.7 %)
Abatacept	9 (0.6 %)
Ustekinumab	8 (0.6 %)
Anakinra	5 (0.4%)
Apremilast	2 (0.1 %)

Table S2

Baseline demographics of 1438 rheumatic patients in ICEBIO in respect to disease and treatment