Incidence of severe COVID-19 in a Spanish cohort of 1037 patients with rheumatic diseases treated with biologics and JAK-inhibitors

The recent outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for COVID-19, has brought about a great concern for the management of patients with inflammatory rheumatic diseases. Rheumatologists and patients are worried about the risk of contagion and suffering a more severe disease, derived from immunosuppressive treatment. Also, for the risk of relapse in case of discontinuing medications. To date, most of these questions remain to be answered.

Accordingly, we read with interest the recent paper from D'Silva and coauthors.[1] They analysed the outcomes of 52 patients with rheumatic diseases (18 under biologics or targeted synthetic disease-modifying antirheumatic drugs (DMARDs)) hospitalised for COVID-19, identifying an independent increased risk of intubation and similar to mortality. These results are welcome and of relevance, but some issues need to be commented. Controls were matched for age, gender and disease duration, but multivariate models repeated adjustment for age. For outcome assessment in COVID-19, some laboratory markers—lymphopenia, troponins[2]— should have been considered as covariates for the model. Besides, the absence of a denominator (population with rheumatic diseases without COVID-19) impedes assessing susceptibility.

Other related works have been published. Monti *et al*[3] described, after a survey among 320 patients with rheumatic diseases under biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs), eight (2.50%) cases of COVID-19 (four PCR proven), none requiring hospitalisation.

Another survey,[4] among 520 patients with inflammatory rheumatic diseases under immunosuppressive treatment, found three (0.58%) cases with COVID-19, one of them hospitalised.

Haberman *et al*[5] reported a similar incidence of hospitalisation after SARS-CoV-2 contagion in patients with immune-mediated inflammatory diseases than in New York City general population (16% vs 26%, respectively).

Spain is one of the most affected European countries by SARS-CoV-2 infection.[6] In Alicante health area (274 122 inhabitants coverage), 306 (0.11%) people have been admitted for severe COVID-19 infection from 3 March to 2 May2020.

In Alicante rheumatology clinics, we see patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, connective tissue diseases, vasculitis, idiopathic juvenile arthritis and other inflammatory conditions such as uveitis, Behcet's disease, adult-onset Still disease, relapsing polychondritis or IgG4-related disease. Most of them are under conventional DMARDs, and 1037 patients receive bDMARDs or tsDMARDs at the time of the analysis. In accordance to European League Against Rheumatism (EULAR),[7] since the pandemic outbreak we advise patients to continue with immunosuppressive therapy (unless patients present symptoms like fever or respiratory symptoms) and, unquestionably, to take measures to prevent contact from infected subjects and virus spread.

Up to 2 May 2020, three (0.29%) patients were hospitalised due to COVID-19 infection. Rheumatic diagnoses were rheumatoid (n=2) and psoriatic (n=1) arthritis (table 1), on anti-TNFα or JAK-inhibitor, and one also received hydroxychloroquine and methotrexate.

Table 1 Clinical features and management of three patients under bDMARD or tsDMARD during COVID-19 admission

Characteristics	Patient 1	Patient 2	Patient 3
Sex (M/F)	F	F	M
Age (years)	75	54	66
Rheumatic disease	Rheumatoid arthritis RF+	Rheumatoid arthritis (RF−, ACPA−)	Psoriatic arthritis
Years since diagnosis	18	2	9
Current bDMARD/ tsDMARD	Baricitinib 4 mg/day	Etanercept 50 mg/ week	Adalimumab 40 mg/2 weeks
Current DMARD		Methotrexate 10 mg/week Hydroxychloroquine 400 mg	
Previous treatment	Etanercept Baricitinib Methotrexate Leflunomide	Etanercept Methotrexate Leflunomide Hydroxychloroquine	Adalimumab Methotrexate
Disease activity (date)	DAS28 4,26 (9 March 2020)	DAS28: 4,08. (27 January 2020)	DAS28: 1,61. DAPSA: 0,2. (12 December 2019)
Hypertension and treatment	Yes Valsartan Hydrochlorothiazide	No	Yes No treatment
Diabetes mellitus and treatment	No	No	No
Dyslipidaemia and treatment	Yes Atorvastatin	No	Yes Pravastatin Gemfibrozil
BMI (kg/m^2)	21.9	28.4	35.38
Other comorbidities	Asthma	No	No
Smoking	No	Former smoker	No
Alcohol	No	No	Yes
Recreational drugs	No	No	No
Days from symptoms onset to hospital admission	22	15	10
Clinical symptoms	Cough	Cough, fever, fatigue	Cough, dyspnoea
Radiological pattern	Normal	Peripheral bilateral interstitial infiltrate	Peripheral bilateral interstitial infiltrate
PCR for SARS-CoV-2	+	+	+
Ferritin at admission and maximum	42 61	404 690	1044 1179
IL-6 at admission	11	36	22
LDH on admission and maximum	219 253	252 327	201 264
D-Dimer at admission	0.59	3,72	0.75
Lymphocytes	570	660	850
Treatment for COVID-19	Hydroxychloroquine	Hydroxychloroquine Azithromycin	Hydroxychloroquine Azithromycin Methylprednisolone Colchicine
Worst PaO_2/FiO_2 (PaFi) or $SatO_2/O_2$ (SpaFi)	SpaFi 452	SpaFi 443	SpaFi 448
Oxygen therapy, nasal cannula, non-invasive ventilation, high-flow oxygen support	No	No	No
Intensive care unit	No	No	No
Orotracheal intubation or invasive mechanical ventilation	No	No	No
Complications (deep vein thrombosis, pulmonary embolism, cardiac arrhythmia, bacterial infection, death)	No	Acute pyelonephritis	No

bDMARD, biological DMARD; BMI, body mass index; DMARD, disease-modifying antirheumatic drug; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; tsDMARD, targeted synthetic DMARD.

All of them were treated for COVID-19 with hydroxychloroquine, two of them combined with azithromycin, and patient 3 also received corticosteroids and colchicine. Unlike D'Silva

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data,[1] none of them required oxygen supply, intensive care or mechanical ventilation. As collateral complications, patient 2 developed acute pyelonephritis. Evolution was favourable in all cases and were discharged after a few days.

Therefore, the occurrence of COVID-19 hospitalisation was 0.29% (3/1037) in patients with rheumatic diseases under bDMARD/tsDMARD, and 0.11% (306/274122) in Alicante population without biologics for rheumatic diseases. Estimated OR was 2.61 (95% CI 0.84 to 8.16) for COVID-19 hospitalisation.

Patients with rheumatic diseases usually require immunosuppressive therapy to achieve disease control, but with a parallel risk of infection. However, during this pandemic, in our health area from a country with high impact of COVID-19, we have noted no increased risk of developing severe COVID-19 compared with the general population. Even the severity of the identified cases might be questionable, as no oxygen support, use of tocilizumab or mechanical ventilation was required; on the other hand, as COVID-19 derives from a hyperinflammatory reaction to SARS-CoV-2, perhaps biologics and DMARDs would have impeded a more aggressive disease. Considering the limitations of D'Silva data,[1] this report and previous papers[3–5] support the advice to maintain bDMARD/tsDMARD in patients with immune-mediated inflammatory disease during the SARS-CoV-2 pandemic.

Vega Jovani ,[1] **Irene Calabuig** ,[1] **Maria Luisa Peral-Garrido,**[1] **Ernesto Tovar-Sugrañes,**[1] **María-del-Carmen López-González,**[1] **Pilar Bernabeu,**[1] **Agustín Martínez,**[1] **Joaquim Esteve-Vives,**[1] **Jose-Manuel León-Ramírez,**[2] **Oscar Moreno-Perez,**[3,4] **Vicente Boix,**[4,5] **Joan Gil,**[2] **Esperanza Merino,**[5] **Paloma Vela,**[1,4] **Mariano Andrés** [1,4]

[1]Reumatología, Hospital General Universitario de Alicante, Alicante, Spain
[2]Neumología, Hospital General Universitario de Alicante, Alicante, Spain
[3]Endocrinologia y Nutricion, Hospital General Universitario de Alicante, Alicante, Spain
[4]Medicina Clínica, Universidad Miguel Hernandez de Elche, Elche, Spain
[5]Unidad de Enfermedades Infecciosas, Hospital General Universitario de Alicante, Alicante, Spain

Correspondence to Dr Vega Jovani, Reumatología, Hospital General Universitario de Alicante, Alicante, Spain; vegajovani@gmail.com

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ORCID iDs
Vega Jovani http://orcid.org/0000-0001-8529-4551
Irene Calabuig http://orcid.org/0000-0002-8755-0149
Mariano Andrés http://orcid.org/0000-0002-0219-9055

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