COVID-19 in patients with rheumatological diseases treated with anti-TNF

We have read with great interest the recent article from Silva *et al* about the clinical course of COVID-19 in rheumatic disease.[1] In this matched cohort study of patients with COVID-19 infection, although the authors found a similar proportion of symptoms, risk of hospitalisation and mortality between patients with and without rheumatic disease, there was a threefold higher odds of intensive care admission/mechanical ventilation in the former. The authors considered that certain immunosuppressive medications could explain the higher risk of respiratory complications. However, the risk associated with severe infections differs among immunosuppressive medications; therefore, the analysis of clinical disclosures must be individualised according to therapeutic class.[2–4] In the study by Silva *et al*, there was no detailed comparison of the clinical behaviour of patients using different immunosuppressive medications. There is a record of corticosteroid use in 37 of 52 patients, probably combined with the use of other immunosuppressive medications.[1] The use of corticosteroids in patients with rheumatological disease has been associated with a higher risk of infections for different aetiologic agents, including respiratory infection.[2] Studies in patients infected with coronavirus and influenza virus treated with corticosteroids show a higher risk of complications and deaths.[5]

In the study, the second most common group of drugs used by the patients was biological disease-modifying antirheumatic drugs, with 60% of the patients using this therapy, and among them, a tumour necrosis factor (TNF) inhibitor was the most used. Patients with rheumatological diseases using immunosuppressive drugs, including biological therapy, have been considered to potentially be an at-risk group for COVID-19 infection and for complications.[6] Some medical specialty societies have recommended postponing the start or extending the use of biological therapy, including anti-TNF treatment, in areas of sustained community circulation of COVID-19, though the use of interleukin 6 (IL-6) inhibitors is considered safer.[7 8]

Recently, there have been case reports of patients infected with COVID-19 who were using TNF inhibitors and experienced no respiratory complications or death.[9–11] In the clinical practice of this group, we reported three patients with rheumatological diseases using anti-TNF who were infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). One of the patients had been diagnosed with Behçet's disease 8 years prior, with a history of several manifestations of vasculitis, including multiple painful and recurrent oral ulcers, recurrent abdominal pain and distension, peripheral venous thrombotic phenomena, neurological manifestations and human leukocyte antigen (HLA)-B51 positivity. Past use of azathioprine 100 mg/day, oral anticoagulant and mycophenolate sodium was recorded. Treatment with infliximab started 9 months prior due to a neurological condition. The second patient had ankylosing spondylitis (AS) and had used golimumab. The third patient had rheumatoid arthritis for 12 years and had used infliximab for 4 years.

The patients had a mild form of COVID-19, not presenting with dyspnoea and not requiring hospitalisation; outpatient follow-up was sufficient. They were treated only with symptomatic medication (paracetamol). None of the three patients used antivirals or hydroxychloroquine, and only the patient with AS was prescribed azithromycin. All had taken regular doses of anti-TNF before the COVID-19 infection, and the patient with Behçet's disease used it 1 day before the onset of symptoms.

Table 1 Demographic data, clinical characteristics and treatment of the patients with confirmed and clinical COVID-19

	Patient 1	Patient 2	Patient 3
Diagnosis	Behçet's disease	Rheumatoid arthritis	Ankylosin spondylitis
Age, years	40	60	65
Sex	F	M	F
Comorbidities	–	Hypertension	Hypertension Hashimoto's disease
Disease status at last visit	Remission	Remission	Remission
Diagnosis of the disease in years	8	12	4
Use of corticosteroids	No	No	No
Biological therapy: anti-TNF	Infliximab	Infliximab	Golimumab
Date of the last infusion of anti-TNF	03/16/2020	03/24/2020	03/31/2020
Symptom onset date—COVID-19	03/17/2020	04/31/2020	04/17/2020
Time interval between infusion and symptom onset in days	1	38	17
RT-PCR COVID-19 (data)	03/24/2020	05/11/2020	04/22/2020
Therapy instituted during treatment	Symptomatic medications	Azithromycin	Symptomatic medications
Symptoms (duration of symptoms in days)			
Fever	No	Yes (1)	No
Maximum temperature	37.2	38.5	36.5
Non-productive cough	No	Yes (4)	Yes (10)
Sputum production	No	No	No
Rhinorrhea	Yes (1)	No	No
Nasal congestion	Yes (1)	Yes (2)	Yes (8)
Sore throat	No	No	Yes (2)
Anorexia	Yes (2)	No	No
Fatigue	Yes (4)	No	Yes (12)
Myalgia	No	Yes (2)	Yes (5)
Arthralgia	No	No	No
Anosmia	Yes (9)	No	Yes (7)
Dysgeusia	Yes (4)	No	Yes (8)
Headache	Yes (2)	Yes (2)	Yes (2)
Diarrhoea	No	No	Yes (2)
Nausea	Yes (3)	No	No
Vomiting	No	No	No
Chest X-ray or CT scan	Not done	Not done	Not done

Twenty-one days after overcoming the resolution of symptoms, they were allowed to continue the anti-TNF treatment (table 1).

Since anti-TNF has been associated with an increased risk of infections, often severe, patients using anti-TNF have been considered a high-risk group for COVID-19 infection.[7 8] Despite the increased risk associated with anti-TNF, infections are selective, likely involving some types of viral intracellular pathogens (hepatitis B, varicella zoster, human polyomavirus JC virus) and bacteria (*Listeria monocytogenes* or *Salmonella* spp), especially granulomatous infections such as tuberculosis, which mechanism for combating infection is partially dependent on TNF, with no evidence at the moment of risk for infection by a coronavirus, including SARS-CoV-2.[4]

A cytokine storm has been associated with the immunopathogenesis of COVID-19 infection, including the participation of TNF, which has pro-inflammatory activities that can lead to extensive tissue damage, including pulmonary injury and shock by vascular leakage.[12 13] In vitro studies have shown that TNF

Ann Rheum Dis: first published as 10.1136/annrheumdis-2020-218171 on 16 June 2020. Downloaded from http://ard.bmj.com/ on July 28, 2020 by guest. Protected by copyright.

facilitates the SARS-CoV-2 interaction with ACE2, which is involved in viral entry.[14] Increased levels of cytokines can be a risk factor for severe forms of the disease. In a study conducted with 548 COVID-19 patients, Li *et al* demonstrated that increased levels of IL-2R, IL-6, IL-10 and TNF-α cytokines were significantly higher in critically ill patients than in non-critically ill patients (all $p<0.01$).[15]

Rheumatological diseases may be associated with an increased risk of severe infections associated with underlying diseases, chronic inflammatory processes and the use of immunosuppressive drugs. However, the case reports have shown a mild form of the disease, and the use of anti-TNF seems to have had a protective effect on the evolution to severe forms, thereby preventing the damaging effects of the high levels of cytokines associated with the immunopathogenesis of infection. In addition to having a mild form of infection, the reported cases did not experience recurrence of their rheumatological disease during the COVID-19 infection. Further clinical trials may help define the real benefit of anti-TNFs and their applicability to reduce the incidence of severe forms of COVID-19.

Carlos Antunes Brito ,[1,2] **José Gerardo Paiva**,[3] **Fernando Nunes Pimentel**,[2] **Rosinete Santos Guimarães**,[2] **Mariana Ribeiro Moreira**[2]

[1]Internal Medicine, Federal University of Pernambuco, Recife, Brazil
[2]Department of Immunology, Autoimmune Research Institute, Recife, Pernambuco, Brazil
[3]Department of Rheumatology, General Hospital César Cals, Fortaleza, Ceará, Brazil

Correspondence to Dr Carlos Antunes Brito, Internal Medicine, Federal University of Pernambuco, Recife, Pernambuco, Brazil; cbritoc@gmail.com

Acknowledgements The authors thank the patients for their consent to report their cases.

Contributors All authors have participated in the study to the conception or design of the work, or the acquisition, analysis or interpretation of cases; and subsequent revisions of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

© Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.

Check for updates

To cite Brito CA, Paiva JG, Pimentel FN, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2020-218171

Received 31 May 2020
Accepted 2 June 2020

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-218196

Ann Rheum Dis 2020;**0**:1–2. doi:10.1136/annrheumdis-2020-218171

ORCID iD
Carlos Antunes Brito http://orcid.org/0000-0002-5963-8178

REFERENCES

1 Km D'Silva, Serling-Boyd WR, *et al*. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. *Ann Rheum Dis* 2020;annrheumdis-2020-217888:1–7.
2 Youssef J, Novosad SA, Winthrop KL. Infection risk and safety of corticosteroid use. *Rheum Dis Clin North Am* 2016;42:157–76.
3 Fernández-Ruiz M, Meije Y, Manuel O, *et al*. Escmid Study Group for infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (introduction). *Clin Microbiol Infect* 2018;24 Suppl 2:S2–9.
4 Baddley JW, Cantini F, Goletti D, *et al*. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [I]: anti-tumor necrosis factor-α agents). *Clin Microbiol Infect* 2018;24 Suppl 2:S10–20.
5 Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020;395:473–5.
6 Minozzi S, Bonovas S, Lytras T, *et al*. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2016;15:11–34.
7 ISBD. BD and COVID-19 - management advice for clinicians. Available: http://www.behcetdiseasesociety.org/menu/56/bd-and-covid-19-management-advice-for-clinicians
8 Mikuls TR, Johnson SR, Fraenkel L, *et al*. American College of rheumatology guidance for the management of adult patients with rheumatic disease during the COVID-19 pandemic. *Arthritis Rheumatol* 2020:1–2.
9 Duret P-M, Sebbag E, Mallick A, *et al*. Recovery from COVID-19 in a patient with spondyloarthritis treated with TNF-alpha inhibitor etanercept. *Ann Rheum Dis* 2020;annrheumdis-2020-217362:1–2.
10 Monti S, Balduzzi S, Delvino P, *et al*. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis* 2020;79:667–8.
11 Tomelleri A, Sartorelli S, Campochiaro C, *et al*. Impact of COVID-19 pandemic on patients with large-vessel vasculitis in Italy: a monocentric survey. *Ann Rheum Dis* 2020;annrheumdis-2020-217600:1–2.
12 Li G, Fan Y, Lai Y, *et al*. Coronavirus infections and immune responses. *J Med Virol* 2020;92:424–32.
13 Tay MZ, Poh CM, Rénia L, *et al*. The Trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020:1–12.
14 Haga S, Yamamoto N, Nakai-Murakami C, *et al*. Modulation of TNF-alpha-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-alpha production and facilitates viral entry. *Proc Natl Acad Sci U S A* 2008;105:7809–14.
15 Li X, Xu S, Yu M, *et al*. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol* 2020. doi:10.1016/j.jaci.2020.04.006. [Epub ahead of print: 12 Apr 2020].

Ann Rheum Dis: first published as 10.1136/annrheumdis-2020-218171 on 16 June 2020. Downloaded from http://ard.bmj.com/ on July 28, 2020 by guest. Protected by copyright.