Article on treatment of patients with COVID-19 and acute respiratory distress syndrome (ARDS) with the IL-1 receptor antagonist anakinra, published in *The Lancet Rheumatology*.[1]

We agree with Valette and du Cheyron that treating patients with non-invasive ventilation outside the intensive care unit (ICU) can be challenging. However, during the COVID-19 outbreak, our high-volume teaching hospital managed more than 800 patients with pneumonia, and the management of many patients with COVID-19 and ARDS with non-invasive ventilation outside the ICU was simply unavoidable. We have extensive experience with non-invasive ventilation outside the ICU setting; training for medical and nurse personnel, as well as systems for patient monitoring, were implemented at our hospital years before the COVID-19 outbreak and were associated with good clinical outcomes.[2] Nonetheless, our study was not aimed at proposing an intensive care approach to patients with COVID-19 and ARDS. Rather, we aimed to evaluate whether high-dose anakinra might reduce hyper-inflammation and result in incremental benefits over the best available treatment, which included maximal respiratory support with non-invasive ventilation outside the ICU.[3]

The derived PaO_2:FiO_2 ratio we used in our study[1] was adopted to maximise utility and avoid widespread invasive monitoring in a truly high-intensity situation. As noted by Valette and du Cheyron, it is formally correct that invasive ventilation is required to define ARDS other than mild.[1] However, the aim of this definition was to avoid including transient forms of ARDS. Our patients with COVID-19 clearly did not have transient ARDS, with a median PaO_2:FiO_2 ratio of 77 (IQR 68–86) and a positive end-expiry pressure of 10 cm H_2O at baseline, which could have further worsened even after orotracheal intubation.

We agree with Aouba and colleagues that it is possible that during the initial phases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, even a low dose of subcutaneous anakinra might prevent escalation of inflammation. However, high doses and intravenous administration are likely to be needed to control hyperinflammation and improve clinical outcomes in patients with COVID-19-associated ARDS,[3] and dose escalation is made feasible by the robust record of safety of anakinra.[4] Opportunistic infections are very rare, and the rate of bacteraemia for anakinra-treated patients in our study (4 [14%] of 29) was similar to that of patients receiving the standard of care (2 [13%] of 16), suggesting that these events were not attributable to the drug. In addition, the frequency of serum liver enzyme elevations was lower in anakinra-treated patients (3 [10%] of 29) than those receiving standard of care (5 [31%] of 16). Considering our findings in hindsight, we agree with Aouba and colleagues that anakinra should not be discontinued in the presence of moderately elevated liver enzymes, and possibly even in the presence of uncomplicated bacteraemia.

The relationship between autophagy and IL-1β secretion has long fascinated scientists, as noted by Nicolas Martin-Silva and colleagues. The prevalent view is that autophagy acts as a regulatory mechanism by removing inflammasome components and intracellular triggers.[5] The clinical significance of autophagy in the context of the host response to SARS-CoV-2 is an area of utmost interest, particularly given the extensive and often controversial use of hydroxychloroquine in this patient population.

We declare no competing interests.

*Giulio Cavalli, Giovanni Landoni,
Alberto Zangrillo MD, Lorenzo Dagna
cavalli.giulio@hsr.it

Unit of Immunology, Rheumatology, Allergy and Rare Diseases (GC, LD) and Anesthesia and Intensive Care Department (GL, AZ), IRCCS San Raffaele Scientific Institute, Milan, Italy; and Vita-Salute San Raffaele University, Milan 20132, Italy (GC, GL, AZ, LD)

1 Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020; **2:** 325–31.
2 Cabrini L, Landoni G, Bocchino S, et al. Long-term survival rate in patients with acute respiratory failure treated with noninvasive ventilation in ordinary wards. *Crit Care Med* 2016; **44:** 2139–44.
3 Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; **307:** 2526–33.
4 Cavalli G, Dinarello CA. Anakinra therapy for non-cancer inflammatory diseases. *Front Pharmacol* 2018; **9:** 1157.
5 Cavalli G, Cenci S. Autophagy and protein secretion. *J Mol Biol* 2020; **432:** 2525–45.

Detection of IgM and IgG antibodies against SARS-CoV-2 in patients with autoimmune diseases

In December, 2019, an outbreak of the novel coronavirus (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) occurred in Wuhan, China,[1] and soon spread all over the world. Rapid and accurate diagnosis of SARS-CoV-2 infection is the cornerstone of all efforts to stem its advancement. Molecular detection via RT-PCR can result in falsely negative results due to the low viral loads in a sample. Serological methods are being developed and have proven to be a useful supplementary approach in confirming SARS-CoV-2 infection.[2] The US Food and Drug Administration has issued numerous Emergency Use Authorisations, including serological tests; however, the potential for cross-reactivity with antibodies present in the sera of patients with other diseases remains largely unknown. Cross-reactivity of antibodies against SARS-CoV-2 with antibodies against other coronaviruses, such as SARS-CoV, has been shown.[3] In addition, cross-reactivity has been observed from autoantibodies in serum samples from patients with autoimmune disease when testing for SARS-CoV,[4] which shares high sequence identity

	Rheumatoid arthritis (n=98)	SLE (n=100)	Sjogren's syndrome (n=92)
Men	17 (17%)	10 (10%)	8 (9%)
Women	81 (83%)	90 (90%)	84 (91%)
Age, years	52·3 (13·4)	40·1 (15·2)	42·6 (12·4)
Anti-nuclear antibody positive	35 (36%)	100 (100%)	92 (100%)
Anti-dsDNA positive	0	63 (63%)	11 (12%)
Anti-Smith antibody positive	0	22 (22%)	2 (2%)
Anti-Sjogren's syndrome antigen positive	3 (3%)	48 (48%)	58 (63%)
Anti-SSB positive	0	8 (8%)	26 (28%)
Anti-U1RNP positive	0	34 (34%)	7 (8%)
Anti-Rib-P positive	0	14 (14%)	4 (4%)
Anti-phospholipid antibodies	0	23 (23%)	3 (3·3%)
Rheumatoid factor	47 (48%)	14 (14%)	21 (23%)
Anti-CCP	51 (52%)	3 (3%)	1 (1%)

Data are n (%) or mean (SD). SLE=systemic lupus erythematosus. dsDNA=double-stranded DNA. SSB= Sjogren's B. U1RNP=U1 ribonucleoprotein. Rib-P=ribosome P protein. CCP=cyclic citrullinated peptide.

Table: Clinical characteristics and auto-antibody profile of patients

with SARS-CoV-2. As such, we wanted to determine whether autoantibodies interfere with detection of SARS-CoV-2 antibodies.

We collected 290 serum samples from patients with autoimmune disease in our serum library, consisting of 98 patients with rheumatoid arthritis, 100 patients with systemic lupus erythematosus, and 92 patients with Sjogren's syndrome. The samples were collected from Jan 1, 2016, to June 30, 2019, which predates the COVID-19 pandemic. Written informed consent was obtained from all patients. The serological test for SARS-CoV-2 IgM and IgG monoclonal antibodies was done with colloidal gold-labelled kits supplied by Innovita Biotechnology Co, Tangshan, China. The nitrocellulose filter of these colloidal gold-labelled assays are coated with two antigens of SARS-CoV-2 (N protein and S protein). The overall testing sensitivity was 89% (352/397) and specificity was 91% (116/128).

Our results showed that both IgG and IgM antibodies against SARS-CoV-2 were not detected in the serum of patients with autoimmune disease, indicating that there was no cross-reactivity between autoantibodies and

SARS-CoV-2 antibodies (table). It should be noted, however, that these sera were only analysed using one kit and other kits with different test operating characteristics might produce different results.

In conclusion, the serological test we assessed showed no cross-reactivity with autoantibodies present in patients with autoimmune disease. Asymptomatic carriers could spread SARS-CoV-2,[5] and this type of test could make large scale screening of asymptomatic SARS-CoV-2 carriers possible. We propose that serological testing of IgM and IgG antibodies, along with RT-PCR, in clinical practice should help provide an accurate COVID-19 diagnosis, including in patients with autoimmune disease.

*Jialin Teng†, *Jin Dai†, Yutong Su†, Zhuochao Zhou, Huihui Chi, Liyan Wan, Jianfen Meng, Zhihong Wang, Fan Wang, Yuning Ma, Qiongyi Hu, Xiaobing Cheng, Honglei Liu, Junna Ye, Hui Shi, Yue Sun, Chengde Yang, Xuefeng Wang*
wzdjsx@sina.com

†Contributed equally

Department of Rheumatology and Immunology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China (JT, YSu, ZZ, HC, LW, JM, ZW, FW, YM, QH, XC, HL, JY, HS, YSun, CY); Department of Laboratory Medicine, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China (XW, JD); and China Department of Rheumatology and Immunology, The First People's Hospital of Yancheng, The Forth Affiliated Hospital of Nantong University, Yancheng, China (JM)

1 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395:** 497–506.
2 Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect* 2020; **9:** 386–89.
3 Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579:** 270–73.
4 Wang Y, Sun S, Shen H, et al. Cross-reaction of SARS-CoV antigen with autoantibodies in autoimmune diseases. *Cell Mol Immunol* 2004; **1:** 304–07.
5 Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med* 2020; **382:** 970–71.

Hydroxychloroquine: balancing the needs of LMICs during the COVID-19 pandemic

I want to thank the Editor for bringing attention to the effect of a potential shortage of hydroxychloroquine on existing patients with autoimmune diseases during the ongoing COVID-19 crisis.[1] The drug has shown both promising and not so promising results against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and more testing needs to be done to fully assess its efficacy in this context; however, hydroxychloroquine is already known to be an effective treatment for patients with autoimmune disorders such as systemic lupus erythematosus.[2]

Patients with autoimmune disorders living in low-income and middle-income countries (LMICs) could be left particularly vulnerable to hydroxychloroquine shortages as high-income countries call for additional supplies of hydroxychloroquine for potential COVID-19 prophylaxis.