Correspondence on 'Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study'

As pointed out by Ramiro *et al* in the September issue of the *Annals*,[1] trials and observational studies investigated numerous drugs against SARS-Cov2 and glucocorticoids proved effective in reducing the mortality among hospitalised patients with COVID-19 requiring respiratory support.[2 3] At first, based on the negative data in SARS and other viral infections,[4] the WHO advised against glucocorticoids in COVID-19.[5] However, up to 20% of patients with COVID-19 develop a hyperinflammatory status resembling a cytokine release syndrome with a severe respiratory deterioration and a higher mortality,[6] thus possibly benefiting from glucocorticoids and anti-interleukin biologics.[7] The CHIC trial showed that a course of high-dose methylprednisolone, followed by Interleukins (IL)-6 receptor antagonist, accelerated respiratory recovery, lowered hospital mortality and reduced the likelihood of invasive mechanical ventilation in COVID-19-associated cytokine storm syndrome defined by C reactive protein >100 mg/L, serum ferritin >900 µg/L on one occasion or a twofold increase within 48 hours, and D-dimer level >1500 µg/L.[1] The RECOVERY trial, whose results were released in June 2020, showed that glucocorticoids were effective in reducing the mortality among severe hospitalised patients with COVID-19 needing invasive ventilatory support.[3] Subsequently, a prospective meta-analysis including the RECOVERY and other six trials (1703 patients) concluded that dexamethasone 6 mg intravenously for up to 10 days, compared with usual care or placebo, led to a lower 28-day all-cause mortality without differences in serious adverse events.[2] More recently, another meta-analysis including 73 studies and 21 350 patients with COVID-19 confirmed a mortality benefit with glucocorticoid only in severely ill patients with COVID-19 (OR: 0.65; 95% CI: 0.51 to 0.83; p=0.0006) (8mg/kg body weight) single infusion.[8]

Based on the growing evidence, the WHO issued a strong recommendation for glucocorticoids (dexamethasone 6 mg/day or hydrocortisone 50 mg intravenously/every 8 hours for 7–10 days) in hospitalised patients with COVID-19 requiring oxygen and a conditional recommendation against the use of glucocorticoids in patients with a non-severe infection (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-5 (accessed 30 Sept 2020)). The available data, in fact, suggest that glucocorticoids in the early COVID-19 phases (<7 days from respiratory symptoms), in milder forms of disease (SOFA Score <7 or not requiring oxygen therapy or with C reactive protein <100 mg/L) or at higher doses (>150 mg hydrocortisone equivalent), may be harmful by favouring the virus evasion of immune surveillance or virus clearance while higher doses may prove immunosuppressive rather than anti-inflammatory.[5] Nevertheless, oral glucocorticoids have begun to be prescribed to patients positive for SARS-CoV2 without respiratory failure in the homecare setting in order to prevent hospitalisation.

Data discouraging glucocorticoids to prevent hospitalisation and respiratory worsening have been indirectly gathered from patients with rheumatic diseasesin which the use of prednisone ≥10 mg/day prior to SARS-CoV2 infection was associated with a higher risk of hospitalisation.[9] In this cohort most patients had rheumatoid arthritis in remission, thus suggesting that disease activity did not influence the observation.

Table 1 Clinical features of 1171 patients positive for SARS-CoV-2 admitted to the Humanitas Hospital Emergency Department between September 15 and December 15 in 2020 arrayed according the outcome of the evaluation (discharged/admitted) and the prior use of oral glucocorticoids (OGC)

	Discharged		Admitted	
	Without OGC (n=358)	With OGC (n=27)	Without OGC (n=264)	With OGC (n=522)
Age (years)	55.0 (19.0)	55.4 (19.3)	72.2 (15.1)	71.2 (13.9)
Female sex (n)	168 (47%)	13 (48%)	111 (42%)	192 (37%)
Death (n)	28 (7.8%)	1 (3.7%)	48 (18.2%)	105 (20.1%)
Respiratory rate (/min)	18.0 (2.4)	17.7 (1.2)	18.5 (4.8)	18.9 (2.4)
Heart rate (/min)	85.8 (15.9)	84.0 (11.1)	85.1 (15.1)	82.7 (14.4)
Glasgow Coma Scale	14.6 (1.6)	14.9 (0.2)	14.9 (0.6)	14.9 (0.8)
O_2 saturation (%)	99.0 (4.8)	96.3 (4.0)	95.4 (5.2)	91.3 (5.6)
Systolic pressure (mm Hg)	126.8 (21.2)	123.5 (12.5)	128.2 (20.6)	127.0 (16.0)
Diastolic pressure (mm Hg)	79.6 (7.4)	74.9 (6.8)	72.7 (14.0)	74.1 (11.3)
Body temperature (°C)	36.7 (0.7)	36.8 (0.4)	37.7 (16.9)	37.1 (3.4)

Variables are expressed as number (%) or mean (SD).

Based on our experience in a high-impact area, we analysed 1171 consecutive patients positive for SARS-CoV-2, presenting at our emergency department between September 15 and December 15 in 2020, based on the outcomes: that is, discharged versus admitted and on the prior use of oral glucocorticoids (table 1). Of the 385 (31%) discharged patients, 27 (8%) had been on oral glucocorticoids for at least 3 days prior to emergency evaluation compared with 522 (66%) of the patients who required hospital admission (p<0.001 χ^2; raw OR: 26.2, 95% CI: 17.3 to 39.8). Among hospitalised patients, the overall mortality was not different based on the use of glucocorticoids prior to admission (20% vs 18% not taking glucocorticoids), thus reducing the possibility of a selection bias for which only patients with a more severe disease prior to admission had received glucocorticoids.

Despite current medical recommendations do not encourage the use of glucocorticoids for the home management of patients positive for SARS-CoV-2, a significant number of patients are prescribed with glucocorticoids in domiciliary setting without a beneficial effect in preventing hospitalisation. Based on the rheumatologic experience and our own series, we strongly advise against the widespread use of glucocorticoids in the homecare setting to prevent hospitalisation; the potential risks may significantly outweigh the unclear benefit in the absence of randomised trials.

Maria De Santis ,[1] **Antonio Voza**,[2] **Victor Savevski**,[3] **Salvatore Badalamenti**,[4] **Maurizio Cecconi**,[5,6] **Alberto Mantovani**,[6,7,8] **Carlo Selmi** [1,6]

[1]Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano, Lombardia, Italy
[2]Emergency Department, IRCCS Humanitas Research Hospital, Rozzano, Lombardia, Italy
[3]Artificial Intelligence Research, IRCCS Humanitas Research Hospital, Rozzano, Lombardia, Italy
[4]Nephrology, IRCCS Humanitas Research Hospital, Rozzano, Lombardia, Italy
[5]Anesthesiology and Intensive Care, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
[6]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
[7]Department of Immunology and Inflammation, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

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[8]The William Harvey Research Institute, Queen Mary University of London, London, UK

Correspondence to Professor Carlo Selmi, Biomedical Sciences, Humanitas University, 20090 Pieve Emanuele, Milan, Italy; carlo.selmi@hunimed.eu

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ORCID iDs
Maria De Santis http://orcid.org/0000-0002-3196-1336
Carlo Selmi http://orcid.org/0000-0002-0323-0376

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