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CLINICAL SCIENCE

Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome

Mirko Scarsi,[1,2] Silvia Piantoni ,[3,4] Enrico Colombo,[1,2] Paolo Airó ,[4] Donata Richini,[1,2] Marco Miclini,[1,2] Valeria Bertasi,[2,5] Marta Bianchi,[2,5] Damiano Bottone,[2,6] Patrizia Civelli,[2,5] Maria-Sofia Cotelli,[2,5] Ezio Damiolini,[2,6] Gloria Galbassini,[1,2] Diego Gatta,[2,6] Maria-Laura Ghirardelli,[1,2] Roberto Magri,[2,6] Paola Malamani,[1,2] Monia Mendeni,[1,2] Stefano Molinari,[1,2] Andrea Morotti,[2,5] Luisa Salada,[2,6] Marinella Turla,[2,5] Angiola Vender,[7] Angela Tincani,[3,4] Antonio Brucato ,[8] Franco Franceschini ,[3,4] Roberto Furloni,[1,2] Laura Andreoli [3,4]

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For numbered affiliations see end of article.

Correspondence to
Dr Mirko Scarsi, Internal Medicine Department - Hospital of Esine, ASST della Valcamonica, 25050 Esine, Lombardia, Italy; m.scarsi@asst-valcamonica.it

RF and LA contributed equally.

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ABSTRACT

Objectives The outbreak of COVID-19 posed the issue of urgently identifying treatment strategies. Colchicine was considered for this purpose based on well-recognised anti-inflammatory effects and potential antiviral properties. In the present study, colchicine was proposed to patients with COVID-19, and its effects compared with 'standard-of-care' (SoC).

Methods In the public hospital of Esine, northern Italy, 140 consecutive inpatients, with virologically and radiographically confirmed COVID-19 admitted in the period 5–19 March 2020, were treated with 'SoC' (hydroxychloroquine and/or intravenous dexamethasone; and/or lopinavir/ritonavir). They were compared with 122 consecutive inpatients, admitted between 19 March and 5 April 2020, treated with colchicine (1 mg/day) and SoC (antiviral drugs were stopped before colchicine, due to potential interaction).

Results Patients treated with colchicine had a better survival rate as compared with SoC at 21 days of follow-up (84.2% (SE=3.3%) *vs* 63.6% (SE=4.1%), p=0.001). Cox proportional hazards regression survival analysis showed that a lower risk of death was independently associated with colchicine treatment (HR=0.151 (95% CI 0.062 to 0.368), p<0.0001), whereas older age, worse PaO2/FiO2, and higher serum levels of ferritin at entry were associated with a higher risk.

Conclusion This proof-of-concept study may support the rationale of use of colchicine for the treatment of COVID-19. Efficacy and safety must be determined in controlled clinical trials.

Key messages

What is already known about this subject?

- Considering the hypothesis that COVID-19 in its worst manifestations resembles a secondary, viral-driven haemophagocitic lymphohistiocytosis syndrome, a rationale for the use of antirheumatic drugs that are used for autoinflammatory disease have been placed in the algorithm of treatment.

What does this study add?

- Based on anti-inflammatory and potential antiviral properties, colchicine was administered to hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome (ARDS).
- The survival rate of patients treated with colchicine was significantly higher as compared with that of patients treated with standard of care only (84.2% vs 63.6%).

How might this impact on clinical practice or future developments?

- This proof-of-concept study supports the rationale of testing colchicine in clinical trials for the treatment of COVID-19 pneumonia with ARDS.

INTRODUCTION

Since February 2020, the epidemic of COVID-19 has severely affected Lombardy, a region in Northern Italy, where hospitals were faced with the need for quick reorganisation and increased demand for critical care.[1] This emergency posed urgent questions for treatment strategies. The main challenge was to understand the natural course of the disease, which is triggered by viral infection but may evolve into uncontrolled inflammation causing lung damage and progression into acute respiratory distress syndrome (ARDS). A subgroup of patients with severe COVID-19 might have a hyperinflammatory syndrome (HIS).[2] Based on the assumption that a 'cytokine storm' drives the progression of the disease, the anti-interleukin-6 receptor monoclonal antibody tocilizumab has been used in 20 patients in China.[3] It has been suggested that there may be

a 'window of opportunity' for downmodulating the immune response against the virus, without preventing its clearance.[4] In this context, colchicine, an old anti-inflammatory drug, may play a role in reverting the disease course of COVID-19.

Colchicine is an alkaloid derived from *Colchicum autumnale*,[5] currently considered as the first-line treatment for autoinflammatory syndromes, such as gout, recurrent pericarditis, familiar Mediterranean fever, Behçet's syndrome and others.[6] Colchicine inhibits the formation of microtubules, thus affecting a variety of cellular processes.[7] Microtubule functionality was demonstrated to be crucial for coronavirus infection and intracellular vacuole formation *in vitro*.[8] Colchicine interferes with several inflammatory pathways including adhesion and recruitment of neutrophils, superoxide production and inflammasome activation by acting on the cytokine network through the inhibition of IL-1beta.[5]

The benefits of colchicine were described in different viral-mediated inflammatory conditions such as EBV/CMV-induced myocarditis,[9] pericarditis triggered by influenza B,[10] interstitial pneumonia of unknown origin[11] and interstitial pneumonia caused by autoimmune process.[12]

The side effect profile of colchicine is widely known, with gastrointestinal symptoms occurring in up to 17% of patients, while severe organ manifestations being rare.[13]

Based on the identification of HIS in patients with COVID-19 pneumonia and the anti-inflammatory properties of colchicine, we postulated the rationale of use of colchicine in patients admitted to the hospital for COVID-19.

METHODS

Patients

In the interval between 5 March and 5 April 2020, 272 patients affected by COVID-19 were admitted to the Valcamonica Hospital in Esine, Lombardy, Italy. Patients were treated according to local guidelines,[14] with antiviral drugs, and/or hydroxychloroquine (HCQ) and/or corticosteroids. This protocol will be referred to as 'standard-of-care' (SoC). The combination of these drugs depended on physician's indication and drug availability. HCQ and lopinavir/ritonavir antiviral treatment were not constantly used for intermittent drug availability due to the emergency. HCQ was given orally 200 mg two times per day. Intravenous dexamethasone was administered at 20 mg/day for 5 days, followed by 10 mg/day for 5 days. Patients received antibiotics and supportive care when required.

Since 19 March, colchicine was proposed to the patients as off-label treatment, according to the notification provided to the local ethics committee. After written informed consent, 122 consecutive patients were treated with colchicine 1 mg/day (reduced to 0.5 mg/day, if severe diarrhoea). In these patients, antiviral drugs were stopped because of the potential interaction with colchicine.

A control group of 142 patients affected by COVID-19 pneumonia treated with SoC, admitted before 19 March, was retrieved by clinical charts analysis. In two cases, colchicine was used as a rescue therapy; these patients were excluded from the treatment group and were considered only for the safety analysis. Eight patients who had a glomerular filtration rate less than 30 mL/min were not eligible for colchicine treatment and excluded from the study (see online supplementary figure 1).

Statistical analysis

Continuous variables were compared by Mann-Whitney test and categorical variables by χ^2 or Fisher's exact test.

Table 1 Comparison of baseline demographic, clinical and laboratory features between patients treated with colchicine plus (+) standard-of-care (SoC) or with SoC only

Clinical features	Colchicine + SoC, n=122	SoC, n=140	P value
Male (%)	77 (63)	90 (64)	0.84
Age (years), mean (SD)	69.3 (9.6)	70.5 (13.8)	0.12
Period of observation (days), mean (SD)	21.3 (6.8)	25.0 (14.8)	0.012
Smokers or previous smokers (%)	21/96 (22)	18/113 (16)	0.37
Cardiovascular comorbidities* (%)	65/101 (64)	85/115 (74)	0.22
Chronic obstructive bronchopneumonia (%)	17/103 (17)	24/111 (22)	0.34
History of malignanicies (%)	9/104 (9)	24/116 (21)	0.013
Ever treated with hydroxychloroquine (%)	46/102 (45)	78/138 (57)	0.08
Ever treated with lopinavir/ritonavir (%)	10/106 (9)	53/139 (38)	<0.0001
Ever treated with dexamethasone (%)	62/107 (58)	44/139 (32)	<0.0001
PaO_2/FiO_2 (mm Hg/%), mean (SD)	176.6 (81)	244.9 (106)	<0.0001
Ferritin (ng/mL), mean (SD)	1987 (1983)	1130 (1104)	0.0005
C reactive protein (mg/L), mean (SD)	159.0 (92.9)	112.5 (82.6)	0.0003
Neutrophil count (cell/µL), mean (SD)	6859 (4070)	5844 (3786)	0.022
Lymphocyte count (cell/µL), mean (SD)	921 (427)	1016 (660)	0.75

*Cardiovascular comorbidities: any history of cardiovascular disease, including coronary heart disease (ie, myocardial infarction, angina and coronary revascularisation), cerebrovascular disease (ie, stroke and transient ischaemic attack) and/or peripheral arterial disease, diabetes mellitus and arterial hypertension.

Survival rates were computed by the Kaplan-Meyer analysis and the difference between survival curves by the Mantel-Cox (log-rank) test. Survival data were censored at 16 April 2020.

Cox proportional hazards regression survival analysis was performed by selecting covariates based on the research question (effects of treatment with colchicine) and plausible independent variables that were *a priori* selected among demographical (gender and age), clinical and laboratory parameters (PaO_2/FiO_2 ratio, ferritin and C reactive protein), comorbidities (history of malignancies, cardiovascular disease or chronic obstructive pulmonary disease) and other treatments (HCQ, antivirals and dexamethasone).

Statistical analysis was performed using GraphPad Prism V.7.0 and Statview V.5.0.

RESULTS

Colchicine was administered to 122 consecutive inpatients with COVID-19. The dosage of colchicine was reduced from 1 to 0.5 mg/day in nine patients (7.4%) due to diarrhoea; no other significant adverse events were reported. Survival data were compared with those of 140 inpatients admitted before the initiation of the protocol with colchicine and treated with SoC. SoC patients had more frequently a history of malignancies ($p=0.013$), and of treatment with antiviral drugs ($p<0.0001$), whereas received less frequently corticosteroids ($p<0.0001$), if compared with patients treated with colchicine (plus SoC). On the contrary, no difference was observed with regard to sex and age between the two groups (table 1). At baseline, serum levels

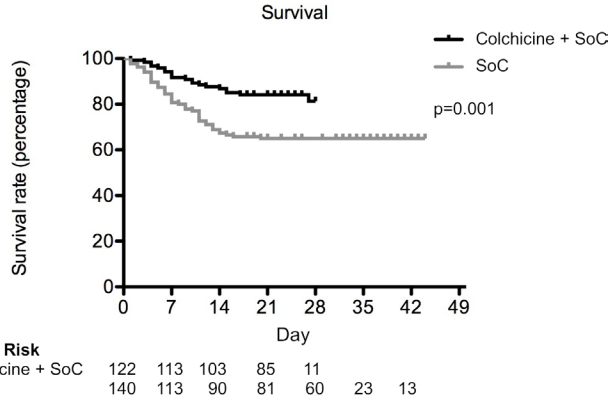

Figure 1 Survival rate in patients treated with colchicine as compared with the 'standard-of-care' (SoC) group.

of C reactive protein and ferritin, as well as neutrophil count, were lower, and PaO_2/FiO_2 ratio was higher in the SoC group (table 1).

Up to the 16 April 2020, 20 patients treated with colchicine (16.3%) and 52 patients in the SoC group (37.1%) died for complications related to COVID-19 (p<0.001). Kaplan-Meyer analysis demonstrated a better survival in the colchicine group than in the SoC group (figure 1; log-rank test; p=0.001). Survival rate at 21 days of follow-up was estimated to be 84.2% (SE=3.3%) in the colchicine group and 63.6% (SE=4.1%) in the SoC group (figure 1). Among the colchicine group, there was no difference between patients who were treated or not with dexamethasone (p=0.37), or with HCQ (p=0.34).

Cox proportional hazards regression survival analysis indicated that a lower risk of death was independently associated with colchicine treatment (HR=0.151 (95% CI 0.062 to 0.368), p<0.0001), whereas older age, worse PaO_2/FiO_2, and higher serum levels of ferritin at entry were associated with a higher risk (table 2).

DISCUSSION

To the best of our knowledge, case reports but no case–control studies have been published so far about the use of colchicine for the treatment of COVID-19.[15] This is the first study on a large series of consecutive hospitalised patients. The rationale of using colchicine resides on both experimental evidence and the long-standing experience in the management of autoinflammatory diseases. It is known that colchicine can inhibit the NLRP3 inflammasome,[7] which is activated by the transport of calcium ions through the envelope protein of SARS-CoV.[16] Moreover, there is no evidence that colchicine may worsen the course of a disease induced by a virus.[17]

Practical advantages of the use of such an old anti-inflammatory drug are: (1) a well-known safety profile, (2) widespread availability and (3) low cost. Colchicine was therefore considered as a possible valuable treatment option in the context of an unprecedented emergency that posed the healthcare system at risk of collapse in Lombardy. It soon became clear that many patients could rapidly evolve into ARDS, unravelling the insufficient resources for ICU and posing dramatic dilemmas in ethics, logistics and therapeutics.[1] In the medium-sized Hospital of Esine, located in the middle of an alpine valley and serving a population of nearly 100 000 adult inhabitants, a treatment protocol with colchicine was proposed to consecutive patients admitted for COVID-19 as adjunct treatment to the SoC,[14] (HCQ—intermittently available, due to national shortage—and/or dexamethasone; antiviral drugs—also intermittently available—were stopped because of possible interaction with colchicine). We can assume that bias selection can be considered as minimal, as only patients with formal contraindications to the drug (ie, renal failure) were excluded.

The safety profile of colchicine was good, as no patient had to stop the drug for severe adverse events. Diarrhoea occurred in 7.4% of treated patients, which is in line with data reported in the systematic review of the literature.[13]

The main finding of this study was that patients treated with colchicine had a better survival rate as compared with SoC. We acknowledge that this result might be affected by a survival bias deriving from the inclusion in the colchicine group of patients who were 'survivors' at the moment of initiating the treatment with this drug. However, this bias is likely to be minimal, since the interval between hospital admission and colchicine initiation was very short in most cases (mean of 1 day), and mortality in the first days after admission was anyway limited (figure 1). Baseline differences between patients treated with colchicine and SoC must be acknowledged: patients in the SoC group were older and received less frequently corticosteroids. However, these patients received more often other treatments (HCQ and antivirals) and seemed to suffer from a less severe disease (better $PaO_2/$

Table 2 Univariable and Cox proportional hazards regression analysis of variables associated with survival

	Univariable analysis			Cox proportional hazards regression survival analysis	
Features	**Non-Survivors, n=72**	**Survivors, n=190**	**P value**	**HR (95% CI)**	**P value**
Colchicine treatment (%)	20/72 (28)	102/190 (54)	0.0002	0.151 (0.062 to 0.368)	<0.0001
Male (%)	49 (68)	118 (62)	0.37	1.220 (0.586 to 2.543)	0.59
Age (years), mean (SD)	78.4 (7.5)	66.6 (13.4)	<0.0001	1.049 (1.007 to 1.093)	0.021
Cardiovascular comorbidities* (%)	46/52 (88)	120/166 (72)	0.017	0.637 (0.211 to 1.920)	0.42
Chronic obstructive bronchopneumonia (%)	11/50 (22)	30/164 (18)	0.56	1.164 (0.519 to 2.611)	0.71
Neoplastic comorbidities (%)	15/52 (29)	18/168 (11)	0.0014	0.549 (0.261 to 1.157)	0.11
Hydroxychloroquine treatment (%)	34/66 (52)	90/174 (52)	0.98	1.359 (0.530 to 3.486)	0.52
Lopinavir/ritonavir treatment (%)	19/67 (28)	44/178 (25)	0.56	1.037 (0.350 to 3.074)	0.94
Dexamethasone treatment (%)	39/67 (58)	68/179 (38)	0.0044	0.870 (0.414 to 1.828)	0.71
PaO_2/FiO_2 (mm Hg/%), mean (SD)	155.8 (76.7)	229.8 (100.8)	0.50	0.994 (0.990 to 0.998)	0.0048
Ferritin (ng/mL), mean (SD)	1839 (1561)	1450 (1679)	0.50	1.002 (1.001 to 1.004)	0.010
C reactive protein (mg/L), mean (SD)	178.3 (86.7)	121.5 (87.8)	0.16	1.002 (0.998 to 1.006)	0.27

*Cardiovascular comorbidities: any history of cardiovascular disease, including coronary heart disease (ie, myocardial infarction, angina, coronary revascularisation), cerebrovascular disease (ie, stroke, transient ischaemic attack) and/or peripheral arterial disease, diabetes mellitus, arterial hypertension.

FiO_2, lower CRP, ferritin and neutrophil count). Indeed, Cox proportional hazards regression survival analysis showed the independent association of colchicine treatment with survival and that of older age, higher serum levels of ferritin and more severe hypoxaemia at admission with death.

In conclusion, our report can be considered as a proof-of-concept study supporting the possible use of colchicine in the treatment of the early phase of COVID-19 with the purpose of preventing the host's autoinflammatory response. Properly designed trials will determine the efficacy and safety of colchicine and the best protocol in terms of dosage and timing of administration in patients with COVID-19. Such trials have been approved in Greece,[18] Italy[19] and Canada.[20]

Author affiliations
[1]Internal Medicine Department – Hospital of Esine, ASST della Valcamonica, Esine, Lombardia, Italy
[2]COVID Unit – Hospital of Esine, ASST della Valcamonica, Esine, Lombardia, Italy
[3]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Lombardia, Italy
[4]Rheumatology and Clinical Immunology Unit, ASST Spedali Civili di Brescia, Brescia, Lombardia, Italy
[5]Neurology Unit – Hospital of Esine, ASST della Valcamonica, Esine, Lombardia, Italy
[6]Pneumology Unit – Hospital of Esine, ASST della Valcamonica, Esine, Lombardia, Italy
[7]Hospital Pharmacy – Hospital of Esine, ASST della Valcamonica, Esine, Lombardia, Italy
[8]Department of Biomedical and Clinical Sciences "Sacco", University of Milano, Ospedale Fatebenefratelli, Milano, Italy

Twitter Silvia Piantoni @piantoni_silvia and Laura Andreoli @lauraandreoli80

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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.

Ethics approval The off-label use of colchicine was supported by the hospital administration as the emergency situation of COVID-19, which was particularly severe in Lombardy with dozens of new patients on a daily basis, had to be managed quickly and amidst shortage of 'standard of care' treatments such as antiviral drugs and hydroxychloroquine.

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ORCID iDs
Silvia Piantoni http://orcid.org/0000-0003-0913-0197
Paolo Airó http://orcid.org/0000-0001-5241-1918
Antonio Brucato http://orcid.org/0000-0002-7566-5600
Franco Franceschini http://orcid.org/0000-0003-3678-6124
Laura Andreoli http://orcid.org/0000-0002-9107-3218

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