Colchicine for COVID-19: targeting NLRP3 inflammasome to blunt hyperinflammation

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Received: 30 July 2021 / Revised: 14 November 2021 / Accepted: 13 January 2022 / Published online: 3 February 2022
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Abstract
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is capable of inducing the activation of NACHT, leucine-rich repeat, and pyrin domain-containing protein 3 (NLRP3) inflammasome, a macromolecular structure sensing the danger and amplifying the inflammatory response. The main product processed by NLRP3 inflammasome is interleukin (IL)-1β, responsible for the downstream production of IL-6, which has been recognized as an important mediator in coronavirus disease 2019 (COVID-19). Since colchicine is an anti-inflammatory drug with the ability to block NLRP3 inflammasome oligomerization, this may prevent the release of active IL-1β and block the detrimental effects of downstream cytokines, i.e. IL-6. To date, few randomized clinical trials and many observational studies with colchicine have been conducted, showing interesting signals. As colchicine is a nonspecific inhibitor of the NLRP3 inflammasome, compounds specifically blocking this molecule might provide increased advantages in reducing the inflammatory burden and its related clinical manifestations. This may occur through a selective blockade of different steps preceding NLRP3 inflammasome oligomerization as well as through a reduced release of the main cytokines (IL-1β and IL-18). Since most evidence is based on observational studies, definitive conclusion cannot be drawn and additional studies are needed to confirm preliminary results and further dissect how colchicine and other NLRP3 inhibitors reduce the inflammatory burden and evaluate the timing and duration of treatment.

Keywords SARS-CoV-2 · COVID-19 · Colchicine · NLRP3 inflammasome · IL-1β · IL-6

Introduction
Coronavirus disease 2019 (COVID-19)—the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—is caused by a dysregulated hyperinflammatory response of the host during the late phase of immune response against SARS-CoV-2 [1, 2]. This occurs in a small portion of patients with COVID-19, as the disease has an asymptomatic or paucisymptomatic course in most patients [3]. Progression towards severe and critical COVID-19 leading to multi-organ failure is mainly driven by increasing levels of pro-inflammatory mediators, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), IL-18, granulocyte–macrophage colony-stimulating factor (GM-CSF), among others [4–8]. In light of this, anti-cytokine agents targeting IL-6 and IL-1β have been tested with encouraging results [9–13]. Recently, SARS-CoV-2 has been shown to activate the NACHT, leucine-rich repeat, and pyrin domain-containing protein 3 (NLRP3) inflammasome both in vitro and in vivo [14–17].
Colchicine is an anti-inflammatory drug currently used for gout, Adamantiaides-Behçet’s disease, acute and recurrent pericarditis, and other autoinflammatory diseases, such as familial Mediterranean fever [18, 19]. Apart from its effect on neutrophil activity, colchicine can indirectly block the NLRP3 inflammasome [20, 21], a macromolecular complex that senses danger and triggers a local or systemic inflammatory response by releasing pro-inflammatory cytokines, such as IL-1β [22]. Indeed, colchicine has been tested in COVID-19 both in the outpatient and inpatient setting [23–31].

We herein summarize currently available evidence about the involvement of the NLRP3 inflammasome in the pathophysiology of COVID-19 and studies testing colchicine as a targeted therapeutic approach.

Search strategy and selection criteria

A literature search has been performed using MEDLINE (Pubmed database) including original articles, reviews, systematic reviews, and meta-analyses published over the past months (from January 1st 2021 until December 31st 2021). Additional articles were identified from the reference list of the searched articles and from medRxiv and bioRxiv (i.e. pre-prints). For ongoing trials, we searched using ClinicalTrials.gov. Only articles published in English language were included. The search strategy included the following terms or their combination: “colchicine”, “NLRP3 inflammasome”, “NLRP3 inhibitors”, “IL-1β”, “COVID-19”, “SARS-CoV-2”, “hyperinflammation”, “cytokine storm”.

Inflammasomes as masters of inflammation

Inflammasomes are high-molecular-weight structures located in the cytosol of stimulated immune cells responsible for caspase-1 activation and processing of pro-inflammatory cytokines, such as IL-1β and IL-18 [32, 33]. Based on the activation of different pattern-recognition receptors (PRRs)—NLRP1, NLRP3, NLRC4, and absent in melanoma 2 (AIM2), —in response to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), several inflammasomes have been recognized [33]. Following the recognition of ligands, the sensor protein activates, oligomerizes, and binds the scaffold protein—apoptosis-associated speck-like protein containing a carboxy-terminal containing a caspase recruiting domain (ASC)—and pro-caspase-1. Importantly, the presence of ASC through the visualization of micron-sized structures through immunofluorescence staining, namely puncta or specks, is considered as a read-out of active inflammasomes in the cells [34]. After the autocatalytic cleavage of pro-caspase-1 to active caspase-1 [35], the final step is the processing of pro-IL-1β, pro-IL-18, pro-IL-33, and pro-IL-37 to their mature, active forms [36]. Along with the abovementioned canonical pathway, additional caspases may be activated through a non-canonical pathway, i.e. caspase-4 and caspase-5 in humans and caspase-11 in mice [37–40].

Inflammasomes are now recognized to be crucially involved in host defense against pathogens [41] and also in sterile inflammation [22], however, a dysregulated activation is responsible for development of autoimmune, autoinflammatory, and metabolic diseases and cancer [42–44].

NLRP1, NLRC4, and AIM2 inflammasomes have been widely studied for their role in infections, but less in non-infectious, inflammatory conditions [33, 45]. The NLRP3 inflammasome has been found in most infectious and non-infectious diseases and largely studied in the cardiovascular field [22, 46–48].

NLRP3 inflammasome and SARS-CoV-2

Previous reports about SARS-CoV described viral proteins ORF3a, ORF8b, and viroporin 3a to trigger the activation of the NLRP3 inflammasome [49–52]. As SARS-Co-V and SARS-CoV-2 appear similar (they share 82% of nucleotide sequence homology [53] and the same receptor—angiotensin-converting enzyme 2 (ACE2) [54]), evidence is being accumulated about the ability of SARS-CoV-2 to activate the NLRP3 inflammasome [55]. Indeed, the observation of cell death and increased levels of IL-1β and IL-18 and lactate dehydrogenase (LDH)—a classic marker of cell death—in the serum of COVID-19 patients prompted the attention on the potential involvement of the inflammasome [4–7, 56]. A clear evidence, therefore, is needed as some of these products may derive from inflammasome-independent pathways [57–60].

Xu et al. showed that SARS-CoV-2 induces preferentially NLRP3 inflammasome through ORF3a, but neither NLRP1 nor NLRC4 inflammasomes [61]. In particular, ORF3a increased caspase-1 and pro-IL-1β levels, as occurs during inflammasome activation [61]. The inflammasome priming provided by ORF3a increases the expression of IL-1β mediated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the activation of gasdermin D, the latter being responsible for pore formation leading to pyroptosis [61]. NIMA-related kinase 7 (NEK7) appears to be fundamental for inflammasome activation as NLRP3 associates with its catalytic domain. In fact, activated macrophages formed a NLRP3-NEK7 complex together with ASC oligomerization, that is abrogated in the absence of NEK7 [62]. In addition, Xu et al. found that blockade of potassium efflux blocks ORF3a-mediated caspase-1 cleavage [61].
Rodrigues et al. showed that SARS-CoV-2 is able to stimulate NLRP3 inflammasome activation in primary human monocytes, that was blocked by MCC950, a selective inhibitor of NLRP3 inflammasome [63]. In COVID-19 patients, authors found increased serum concentrations of active caspase-1 and IL-18 as well as an increased activation of NLRP3 inflammasome in peripheral blood mononuclear cells (PBMCs) through the visualization of ASC specks [14]. Rodrigues et al. also investigated whether NLRP3 inflammasome activation correlated with disease severity and clinical outcomes. They showed positive associations of caspase-1 and/or IL-18 levels with C-reactive protein (CRP), LDH, IL-6, and ferritin [14], that in turn correlated with COVID-19 severity [64–70]. With regard to clinical outcomes, IL-18 concentration was higher in patients needing mechanical ventilation compared with those who did not and in survivors compared with non-survivors. Considering 37 patients followed from the time of hospital admission up to 45 days, caspase-1 and IL-18 levels both decreased over time, but IL-18 levels remained higher in patients who died and never reached the levels of patients who recovered, irrespective of the need of mechanical ventilation [14]. The presence of the NLRP3 inflammasome has also been described in tissues from patients with COVID-19 [14, 15]. Importantly, the analysis of lung tissues from deceased COVID-19 patients showed the presence of active NLRP3 inflammasome in CD14+ cells (monocytes) [14] and was confirmed also by our group [15] (Fig. 1).

These findings strongly support a role for NLRP3 inflammasome in driving the early pathologic manifestations of COVID-19, leading to progressively worsening respiratory failure culminating with ARDS. According to this evidence, it appears reasonable to therapeutically target the NLRP3 inflammasome to reduce the burden of hospitalization and morbidity.

**Therapeutic effects of colchicine**

Colchicine is an old anti-inflammatory drug derived from the plant *Colchicum autumnale* [18]. Currently, colchicine is approved for acute flares of gout and familial Mediterranean fever and used off-label for several diseases, like Adamantides-Behçet’s disease, pericarditis, and other inflammatory and auto-inflammatory conditions [18].

The main anti-inflammatory effect of colchicine is mediated by its ability to dissolve microtubules within immune cells [71]. By intercalating into free α/β tubulin and inhibiting microtubule extension, the movement of adhesion molecules on cell surface is limited and this is especially seen in neutrophils, where colchicine concentration is much higher as compared with other immune cells. This latter effect depends on a reduction in the activity of P-glycoprotein membrane efflux pump that is responsible for energy-dependent colchicine efflux [72]. Colchicine is also able to reduce expression of L- and E-selectin, that mediate rolling and adhesion of neutrophils on the endothelium [73]. Microtubule breakdown also blocks neutrophil movements through blood vessels [74]. In addition, colchicine was found to negatively impact on neutrophil signaling and response during phagocytosis [75, 76].

In recent years, colchicine was found to inhibit NLRP3 inflammasome, although the exact mechanism of action is not fully understood yet. The putative step through which colchicine blocks NLRP3 inflammasome formation may rely on microtubule breakdown, that interferes with the oligomerization of the inflammasome [20, 21]. The result is a reduced production of IL-1β, that in turn decreases the production of IL-6 and tumor necrosis factor (TNF), leading to a reduction in the recruitment of neutrophils and macrophages [77, 78] (Fig. 2).

Colchicine was also demonstrated to play a role in the crosstalk between inflammation and thrombosis, although most evidence on this derives from pre-clinical studies. Colchicine can inhibit the release of α-defensin from neutrophils in mice, thus reducing the size of thrombi [79, 80]. Colchicine was also found to deform platelets through its effect on microtubules and block calcium entry into platelets [81], thus reducing platelet activity. An in vitro study showed that colchicine may blunt neutrophil-platelet interactions at physiological doses [82], suggesting a role in interfering with the inflammation/thrombosis interface.

**Colchicine to treat COVID-19: what is the rationale?**

Based on the pathophysiological premises previously mentioned, colchicine might have a positive impact on the natural history of SARS-CoV-2 infection [83, 84]. Since SARS-CoV-2 activates the NLRP3 inflammasome, this leads to an increased production of pro-inflammatory cytokines [1]. Differently from other repurposed anti-rheumatic agents used in COVID-19 patients (anakinra, tocilizumab, or sarilumab targeting either IL-1β or IL-6), colchicine has a pleiotropic mechanism of action with diverse effects on the inflammatory cascade. Although less potent when compared with glucocorticoids (dexamethasone in particular), colchicine has the great advantage to be available for oral administration. Moreover, colchicine has an extremely favorable safety profile and since it does not exert any overt immunosuppressive activity, it does not interfere with the effective viral clearing nor is associated with the occurrence of secondary infections [83]. Additionally, compared with anti-cytokine agents, colchicine is less immunosuppressive and cheaper.
By taking in mind the pathophysiology of SARS-CoV-2, the use of colchicine should be considered in the early inflammatory phase (i.e. phase 2 according to the clinical-therapeutic staging proposal [85]) in order to prevent progression towards phase 3 or hyperinflammatory stage. This may be the case of non-hospitalized patients with symptoms dating back a few days or also hospitalized patients not progressing to critical disease. As for other agents, the optimal timing of administration of colchicine is still a matter of debate and warrants future investigation.

To date, few randomized clinical trials (RCTs) have been conducted with colchicine given on top of standard-of-care [23, 26, 30, 31, 86, 87] (Table 1). Recruitment to the colchicine arm of the RECOVERY trial was interrupted for futility, as preliminary data showed no convincing evidence for a mortality benefit [31, 88]. This might either depend on a limited anti-inflammatory power of colchicine in the advanced stages of COVID-19. In addition, the concurrent administration of dexamethasone in the majority of patients should be considered as its anti-inflammatory property is much larger compared with that of colchicine. However, the latter is not fully supported by data from this trial, as colchicine was not found beneficial in patients not receiving glucocorticoids [31], probably suggesting a limited utility of colchicine in the hyperinflammatory phase of COVID-19. In the trial by Deftereos et al., colchicine reduced the primary clinical endpoint (time from baseline to clinical deterioration defined as a 2-grade increase on World Health Organization ordinal clinical scale) compared with control (odds ratio [OR] 0.11, 95% confidence interval [CI] 0.01–0.96, p = 0.046) in hospitalized COVID-19 patients [23]. Lopes et al. found that among hospitalized patients, those treated with colchicine suspended supplemental oxygen use before those treated with placebo (median 4 vs. 6.5 days, p < 0.001) and reduced their hospital stay (median 7 vs. 9 days, p = 0.003). In addition, after 1 week of treatment, colchicine markedly reduced C-reactive protein levels compared with placebo [26]. The ColCORONA trial was conducted among non-hospitalized patients in Canada treated with colchicine or placebo. The primary endpoint (a composite of death or hospitalization due to COVID-19 in the 30 days after randomization) was not met (OR 0.79, 95% CI 0.61–1.03, p = 0.08) [30]. In the pre-specified analysis of the study including 4,159 patients with a polymerase chain reaction-confirmed diagnosis, the primary endpoint occurred less frequently in colchicinetreated than in placebo-treated patients (OR 0.75, 95% CI 0.57–0.99, p = 0.04) and the risk for hospitalization was decreased (OR 0.75, 95% CI 0.57–0.99) [30]. For all of these trials, the most common adverse event was diarrhea, especially among patients treated with colchicine, while no safety concerns with regard to infections were recorded. Several other observational studies reported encouraging results, with few, tolerable side effects [24, 25, 27–29, 89–92] (Table 2). Piantoni et al. also reported about long-term results, describing an improved survival in patients treated with colchicine compared with standard-of-care (mortality rate at 270 days: 20% vs. 44%, p = 0.0001) [91].

There are ongoing clinical trials testing whether colchicine may reduce the rate of clinical worsening in hospitalized patients with moderate disease (Treatment with COLchicine of patients affected by COVID-19: a Pilot Study [COLVID-19], EudraCT number: 2020–001,475–33; Colchicine Counteracting Inflammation in COVID-19 Pneumonia [ColCOVID-19], NCT04322565) or hospitalization in outpatients (CHOICE-19, EudraCT number: 2020-001,806-42). A complete list can be found online (https://clinicaltrials.gov/ct2/results?cond=Covid19&term=colchicine&cnty=&state=&city=&dist=).

Recent meta-analyses, although based on few available studies, have shown encouraging signals of benefit for mortality [84, 94–96] and reduced progression towards severe COVID-19 [95]. However, the benefit was not confirmed in the subgroup analysis including RCTs [97]. A Cochrane meta-analysis including three RCTs (11,525 hospitalized patients and 1 RCT with 4,488 non-hospitalized subjects) concluded that colchicine has little or no effect on mortality or clinical progression compared with placebo or standard-of-care alone in patients hospitalized with moderate-to-severe COVID-19 [98]. Indeed, available findings from RCTs are certainly influenced by different sample size, different endpoints, and different follow-up. Importantly, a variable time of administration might represent an additional bias as the only common evidence for colchicine starting was hospitalization for COVID-19, except for the ColCORONA trial. It is then plausible that administration in a later phase of disease may not be as useful as when administered earlier. However, this is not fully understood based on current studies. It appears that, at present time, colchicine cannot be recommended as a first agent to treat hospitalized COVID-19 patients. However, it could be considered on a case-by-case basis for home patients with early presentation of mild symptoms.
TNF tumor necrosis factor. acute respiratory syndrome coronavirus 2. PRRing protein 3. CoV-2 severe pattern recognition receptor. cell.

Future perspectives

Colchicine has the ability to block NLRP3 inflammasome oligomerization and prevent the processing and release of active IL-1β, thus blocking the subsequent upregulation of downstream cytokines, that are responsible for detrimental effects (Fig. 2). Colchicine, however, is a nonspecific inhibitor of the NLRP3 inflammasome as it has multiple mechanisms of inhibition, either upstream and downstream of NLRP3 inflammasome [99]. For this reason, a specific inhibition might have increased advantages in reducing the progression of the inflammatory burden and its related clinical manifestations through a selective blockade of different steps preceding NLRP3 inflammasome oligomerization and reduced release of IL-1β and IL-18. To this end, different experimental NLRP3 inflammasome inhibitors (BAY 11–7082, MCC950, OLT1177 [dapansutrile], INF4E, 16,673-34-0) were tested in animal models of acute myocardial infarction and are summarized in detail elsewhere [99]. Among these compounds, OLT1177 (dapansutrile) is the only orally active specific NLRP3 inhibitor [100] that has been studied in patients with acute flares of gout [101] and heart failure [102], showing positive results. An RCT is currently ongoing to test the safety and efficacy of dapa-sutrile in moderate COVID-19 (NCT04540120). Based on current evidence, it is reasonable that the downregulation of NLRP3 inflammasome might blunt the inflammatory cascade elicited by SARS-CoV-2 infection, especially in high-risk patients (i.e., those with obesity, diabetes, cardiovascular or pulmonary diseases). This could depend by the fact that most of these patients have an IL-1β-mediated inflammation related to their underlying conditions, further exacerbated by viral infection.

Importantly, when considering colchicine for COVID-19 patients, it is important to consider the ground-breaking results provided by the RECOVERY trial testing dexamethasone [103]. Dexamethasone is more powerful compared with colchicine in terms of anti-inflammatory efficacy and suppression of the hyperinflammatory syndrome. The latter, indeed, is responsible for progression of COVID-19 towards severe and critical stages, often fatal. However, dexamethasone is also associated with poor prognosis when administered too early in the course of the disease [103]. For this reason, attention should be paid on the timing of administration of colchicine, that is still a matter of debate. Based on current, limited evidence, it might be hypothesized that colchicine should be administered (i) in very early phases of disease (when dexamethasone is contraindicated) or (ii) in patients with low-grade inflammation and on low-flow oxygen on top of glucocorticoids or (iii) as a long-term therapy (i.e. 1 to 3 months) after hyperinflammation has been controlled. For the latter case, colchicine may be considered as a good choice for patients with persistently increased levels of pro-inflammatory cytokines and persisting symptoms (i.e. Long COVID patients), allowing to switch off inflammation without the long-term side effects of glucocorticoids. This may also be the case of pericarditis, that has been described in patients with COVID-19 [104] and may benefit from colchicine [105]. However, dedicated studies testing colchicine, dapansutrile and dexamethasone in different phases of COVID-19 may help better understand the efficacy of these drugs and the best timing of administration.

While considering hyperinflammation and the role of NLRP3 inflammasome/IL-1β axis in COVID-19, results from the SAVE-MORE (suPAR-guided Anakinra treatment for Validation of the risk and Early Management Of severe respiratory failure by COVID-19) trial showed a significant
| Authors | Design | Study population | Colchicine dose | Main findings |
|---------|--------|------------------|-----------------|--------------|
| **Hospitalized patients** | | | | |
| Deftereos et al. GRECCO-19 Randomized Clinical Trial [23] | Prospective, open-label, RCT | 50 hospitalized patients in the SOC group  55 hospitalized patients in the SOC + colchicine group | Loading dose: 1.5 mg followed by 0.5 mg of colchicine after 1 h (loading dose 1 mg in case of azithromycin co-administration)  Maintenance: dosage: 0.5 mg twice daily (once daily if body weight < 60 kg) until hospital discharge or a maximum of 21 days | The primary clinical endpoint (time from baseline to clinical deterioration based on WHO ordinal clinical scale) occurred more frequently in the SOC vs. colchicine group (14% vs. 1.8%; OR 0.11, 95% CI 0.01–0.96, \( p = 0.046 \))  Event-free 10-day survival was 83% vs. 97% in the control vs. interventional group (\( p = 0.03 \))  Similar AEs were observed in the 2 groups, except for diarrhea that was more frequent in the colchicine arm (45.5% vs. 18.0%, \( p = 0.003 \)) |
| Lopes et al. [26] | Double-blind, placebo-controlled RCT | 37 hospitalized patients in the placebo group  37 hospitalized patients in the colchicine group | 0.5 mg three times daily for 5 days, then 0.5 mg twice daily for 5 days  If weight ≥ 80 kg, first dose was 1.0 mg  If eGFR < 30 mL/min/1.73 m², 0.25 mg three times daily for 5 days, then 0.25 mg twice daily for 5 days | Patients treated with colchicine stopped using supplemental oxygen before those in the placebo group (median 4 vs. 6.5 days, \( p < 0.001 \)) and had a reduced length of hospital stay (median 7 vs. 9 days, \( p = 0.003 \))  Across 1 week, patients treated with colchicine experienced a marked reduction in CRP levels compared with those in the placebo group (\( p < 0.001 \))  Common AEs like diarrhea and pneumonia were more frequent in the colchicine and placebo groups, respectively |
| RECOVERY Collaborative Group RECOVERY Trial [31] | Investigator-initiated, open-label RCT | 5730 hospitalized patients in the SOC group (dexamethasone, HCQ, lopinavir/ritonavir, azithromycin, tocilizumab, and convalescent plasma)  5610 hospitalized patients in the colchicine group | 1 mg after randomization, then 0.5 mg 12 h later, followed by 0.5 mg twice daily for 10 days or until discharge, whichever came first, or 0.5 mg once daily for patients receiving a moderate CYP3A4 inhibitor or with eGFR < 30 mL/min/1.73 m² or estimated body weight < 70 kg | No difference in the proportion of patients meeting the primary outcome (all-cause mortality) was found (1173 patients in the colchicine group vs. 1190 patients in the SOC group; RR 1.01, 95% CI 0.93–1.10, \( p = 0.77 \))  No secondary outcome (time to discharge, need for MV, or death) was met  Two AEs probably related to colchicine were recorded (AKI and rhabdomyolysis) |
Table 1 (continued)

| Authors                        | Design                                      | Study population                                                                 | Colchicine dose                                                                 | Main findings                                                                                                                                                                                                 |
|-------------------------------|---------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mareev et al. COLORIT study [86] | Prospective, comparative, quasi-randomized trial | 22 hospitalized patients in the control group (no anti-inflammatory therapy) 21 hospitalized patients in the colchicine group | 1 mg daily up to day 3, then 0.5 mg daily up to 14 days | The primary endpoint (SHOCS-COVID score reduction after treatment) was met by the colchicine group (8 vs. 2, \( p = 0.017 \)), but not by control group                                                                 |
| Pascual-Figal et al. [87]     | Prospective, randomized, controlled, open-label RCT | 51 hospitalized patients without MV receiving standard treatment 52 patients without MV receiving colchicine on top of standard treatment | Loading dose of 1.5 mg (1 mg followed by 0.5 mg 2 h later), then 0.5 mg twice daily for the next 7 days, and then 0.5 mg once daily until day 28 | Colchicine was associated with a lower risk of clinical deterioration (OR 0.11, \( p = 0.03 \)) At day 28, all patients treated with colchicine were discharged alive, while 2 patients died in the standard treatment arm and one was still hospitalized |
| Outpatients                   |                                             |                                                                                  |                                                                                  | No difference in the occurrence of the primary endpoint (a composite of death or hospitalization within 30 days from randomization) was observed between groups Among those with a PCR-confirmed COVID-19 diagnosis, the primary endpoint occurred less frequently in colchicine-treated patients vs. placebo (OR 0.75, 95% CI 0.57–0.99, \( p = 0.04 \)). The risk for hospitalization was decreased (OR 0.75, 95% CI 0.57–0.99), but no effect on death was seen Serious AEs were 4.9% in the colchicine group and 6.3% in the placebo, with pneumonia occurring less frequent and diarrhea more frequent in the colchicine arm |

Where available, SOC therapy was included

AE adverse event. AKI acute kidney injury. CI confidence interval. COVID-19 coronavirus disease 2019. CRP C-reactive protein. CYP3A4 cytochrome P450 3A4. eGFR estimated glomerular filtration rate. MV mechanical ventilation. OR odds ratio. PCR polymerase chain reaction. RCT randomized clinical trial. RR rate ratio. SHOCS-COVID Symptomatic Hospital and Outpatient Clinical Scale for COVID-19. SOC standard-of-care. WHO World Health Organization
### Table 2: Observational studies that investigated colchicine in patients with COVID-19

| Authors            | Design                                      | Study population                                      | Colchicine dose                                              | Main findings                                                                                                                                 |
|--------------------|---------------------------------------------|-------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Scarsi et al. [29] | Case–control study                          | 140 hospitalized patients in the SOC group (antivirals, HCQ or glucocorticoids) | Colchicine: 1 mg once daily                                 | A reduced proportion of patients died among those treated with colchicine on top of SOC vs. SOC alone (16% vs. 37%, \( p < 0.001 \))  |
| Piantoni et al. [91]| 122 hospitalized patients treated SOC + colchicine | Colchicine 0.5 mg once daily in case of severe diarrhea | Treatment with colchicine on top of SOC was independently associated with a lower mortality risk (HR 0.15, 95% CI 0.06–0.37, \( p < 0.0001 \)) |
| Sandhu et al. [28] | Case–control study                          | 78 hospitalized patients in the SOC group (HCQ, glucocorticoids, LMWH) | Colchicine 0.6 mg twice a day for 3 days, then 0.6 mg once daily for 12 days; discontinued if discharge occurred before completing 15 doses |
| Brunetti et al. [24]| Single-center propensity score matched, open-label cohort study | 33 hospitalized patients treated with colchicine on top of SOC (HCQ, azithromycin, remdesivir, tocilizumab, glucocorticoids) | Not specified                                                | Patients in the SOC + colchicine group experienced a reduced rate of death (47% vs. 81%, \( p < 0.001 \)) and intubation (47% vs. 87%, \( p < 0.001 \)) and an increased discharge rate (53% vs. 19%, \( p < 0.001 \))      |
| Pinzón et al. [92] | Cross-sectional study                       | 145 hospitalized patients treated with colchicine and glucocorticoids | Colchicine 0.5 mg twice daily for 7 to 14 days               | No statistically significant difference was observed in patients treated with colchicine + glucocorticoids vs. glucocorticoids alone (9.6 vs. 14.6%, \( p = 0.179 \)) |

**Hospitalized patients**

**Authors**
- Scarsi et al. [29]
- Piantoni et al. [91]
- Sandhu et al. [28]
- Brunetti et al. [24]
- Pinzón et al. [92]
### Table 2 (continued)

| Authors                        | Design                      | Study population                                                                 | Colchicine dose                                                                                     | Main findings                                                                                          |
|--------------------------------|-----------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| **Outpatients**                |                             |                                                                                  |                                                                                                     |                                                                                                        |
| Della-Torre et al. [25]         | Observational study         | Nine patients treated with colchicine at home                                    | Loading dose 1 mg twice on the first day, then 1 mg once daily until third day of axillary temperature < 37.5 °C | Colchicine led to prompt resolution of fever within 72 h in all patients. One patient was hospitalized and discharged after 4 days. Diarrhea was the most frequent AE without any need to interrupt the treatment. |
| **Hospitalized patients and outpatients** |                             |                                                                                  |                                                                                                     |                                                                                                        |
| Manenti et al. [27]             | Observational, retrospective | 71 patients (either hospitalized patients or outpatients in the SOC group (antivirals, HCQ or azithromycin)) 70 patients (either hospitalized patients or outpatients) taking colchicine on top of SOC | Colchicine 1 mg once daily from day 1 up to clinical improvement or to a maximum of 21 days.  
Colchicine 0.5 mg once daily in case of severe diarrhea or eGFR < 30 mL/min/1.73 m².  
Colchicine 0.5 mg once every other day in case of hemodialysis or liver impairment. | The 21-day cumulative incidence of death was lower in patients treated with colchicine vs. SOC (adjusted HR 0.24, 95% CI 0.09–0.67).  
Clinical improvement across a 21-day period occurred more frequently in colchicine-treated patients (adjusted RR 1.80, 95% CI 1.00–3.22).  
Common AEs were skin rash and diarrhea (7% of patients taking colchicine). |

Where available, SOC therapy was included.

AE: adverse event. CI: confidence interval. CRP: C-reactive protein. eGFR: estimated glomerular filtration rate. HCQ: hydroxychloroquine. HR: hazard ratio. LMWH: low-molecular-weight heparin. OR: odds ratio. OSCI: ordinal scale for clinical improvement. PCR: polymerase chain reaction. RR: relative rate. SOC: standard-of-care. WHO: World Health Organization.
reduction in mortality and hospital stay using anakinra, a recombinant human IL-1 receptor antagonist [106]. The SAVE-MORE study is a phase 3, double-blind RCT that investigated early start of anakinra in hospitalized patients with moderate-to-severe COVID-19 at risk for respiratory failure (defined by an elevated serum level of soluble urokinase-type plasminogen activator receptor [suPAR]). Importantly, nearly 90% of patients were receiving dexamethasone. After 28 days, anakinra reduced clinical deterioration by 64% as compared to placebo. In addition, 28-day mortality was reduced by 55% as well as hospital stay [106]. These findings definitely consolidate previous findings from observational studies about the use of anakinra in COVID-19 patients [10, 11, 107–109] and a recent meta-analysis [110]. It is likely that the positive effect of anakinra in COVID-19 patients might depend on a selective blockade of IL-1 differently from colchicine. Indeed, colchicine is an indirect NLRP3 inflammasome inhibitor and this may explain the limited efficacy observed in RCTs.

Conclusions

SARS-CoV-2 can induce the activation of the NLRP3 inflammasome that leads to the activation of several pro-inflammatory pathways. This suggests that pharmacological blockade of the NLRP3 inflammasome is of interest in COVID-19. Indeed, colchicine is known to block the NLRP3 inflammasome and has many advantages, such as a limited immunosuppression, oral administration, and few side effects. As few randomized studies have been published to date and our knowledge of COVID-19 is evolving, additional studies are warranted to unravel how colchicine and other NLRP3 inhibitors reduce the inflammatory burden caused by SARS-CoV-2 and to evaluate the best timing and duration of treatment, either in hospitalized patients and outpatients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00011-022-01540-y.

Acknowledgements Figure 1 has been reproduced with permission from Toldo et al., “Inflammasome formation in the lungs of patients with fatal COVID-19” [15]. Figure 2, Panel A has been reproduced with permission from “NLRP3 Inflammasome in Acute Myocardial Infarction” by Mauro et al. [48]. Figure 2, Panel B has been partially created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com.

Author contributions AB is responsible for conceptualization and first draft of the manuscript. AV contributed to first draft and figure design. LD, FT, AA, and FD critically reviewed the manuscript. All authors approved the final version of the manuscript.

Funding None.

Declarations

Conflict of interest Aldo Bonaventura received a travel grant from Kiniksa Pharmaceuticals Ltd. to attend the 2019 AHA Scientific Sessions and receive honoraria from Effetti s.r.l. (Milan, Italy) to collaborate on the medical website www.inflammology.org. Alessandra Vecchii received a travel grant from Kiniksa Pharmaceuticals Ltd. to attend the 2019 AHA Scientific Sessions and receive honoraria from Effetti s.r.l. (Milan, Italy) to collaborate on the medical website www.inflammology.org. Lorenzo Dagna received consultation honoraria from Abbvie, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Galapagos, GlaxoSmithKline, Kiniksa, Novartis, Pfizer, Roche, Sanofi-Genzyme, and SOBI. The Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR) received unrestricted research/educational grants from Abbvie, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Kiniksa, Merk Sharp & Dohme, Mundipharma Pharmaceuticals, Novartis, Pfizer, Roche, Sanofi Genzyme, and SOBI. Antonio Abbate has received research support from Kiniksa, Novartis, Olatec, R-Pharm, Serpin Pharma, and has served as an advisor to Abiomed, Cromos Pharma, Effetti, Eli Lilly, Implicit Bioscience, Novo-Nordisk. The remaining authors have nothing to disclose related to this study.

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