NARRATIVE REVIEW

Colchicine in the management of Covid-19: With or lieu of evidence

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Abstract

Coronavirus disease 2019 (Covid-19), leads to global calamitous effects. Covid-19 is caused by a novel coronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Covid-19 is associated with development of hyper-inflammation and/or cytokine storm that together with high viral load trigger tissue damage and multi-organ failures (MOF). Colchicine (CN) is a lipophilic tricyclic alkaloid used for treatment of gout since ancient time. In Covid-19 era, CN is repurposed for treatment of SARS-CoV-2 infection depending on its anti-inflammatory and broad-spectrum antiviral effects. Therefore, a recent clinical trial recommends use of CN in treating Covid-19 patients. It has been confirmed that inhibition of neutrophil chemotaxis, lysosomal degranulation, and release of pro-inflammatory cytokines is the main mechanism by which CN produces anti-inflammatory effects. CN attenuates generation of free radicals and reactive oxygen species (ROS) with consequent inhibition release of pro-inflammatory cytokines. Different studies illustrate that microtubule network is necessary and important for replication of different viruses including SARS-CoV-2 since; intracellular transport of viral particles is mediated through cytosolic microtubules. Therefore, CN therapy is effective in the management of Covid-19 patients when timely administrated through reduction of tissue damage and hyper-inflammations. Thus, the anti-inflammatory, antiviral, and immunomodulatory properties of CN might be the potential mechanisms of CN therapy against Covid-19. The review concludes that CN is a potent anti-inflammatory agent for the management of Covid-19; it inhibits SARS-CoV-2-induced-acute lung injury(ALI) due to its anti-inflammatory and anti-viral effects.

Keywords: Covid-19, Colchicine, SARS-Co-V-2, Cytokine storm.

(DOI)

Introduction

The present pandemic coronavirus disease 2019 (Covid-19) leads to global calamitous effects affecting more than 183 million with 4 million confirmed deaths till the fist of July 2021. Covid-19 is caused by a novel coronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).1 SARS-CoV-2 is a single-strand; RNA virus contains spike protein, enveloped protein and nucleocapside protein similar to that found in other beta corona viruses like SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV).[1] At present, with exception of dexamethasone there is no approved drug for treatment of SARS-CoV-2 infection, however, different drugs are used in the management of this disease in light of different published researches in lieu of evidence.[2]

Covid-19 is associated with development of hyper-inflammation and/or cytokine storm that together with high viral load trigger tissue damage and multi-organ failures (MOF). Thus, lessening of cytokine storm and amelioration of inflammatory reactions could be an essential base in the management of Covid-19.[3] Notwithstanding of the initial prodigious propaganda for using chloroquine as antiviral and anti-inflammatory agent in the management of Covid-19, currently there is disappointing clinical data to advocate the use of chloroquine for Covid-19.[3] Therefore, diverse case-controlled studies endorse the use of colchicine in the management of Covid-19.[4]

Colchicine (CN) is a lipophilic tricyclic alkaloid from (Figure-1) Cochicum autumnale plant, used for treatment of joint painful gout since ancient times. At present, CN is an effective agent in the management of crystal arthropathy, pericarditis, and Familial Mediterranean Fever (FMF).[5]

In Covid-19 era, CN is repurposed for treatment of SARS-

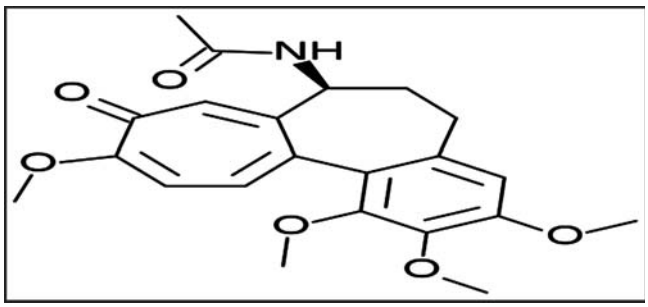

Figure-1: Chemical structure of colchicine.

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CoV-2 infection depending on its anti-inflammatory and broad-spectrum antiviral effects. Therefore, a recent clinical trial recommends use of CN in treating Covid-19 patients.[6]

Conversely, CN therapy might be harmful in the Covid-19 as it could escalate danger of MOF and acute respiratory distress syndrome (ARDS).[7]

Therefore, the aim of this contemporary review was to appraise the possible role of CN in the management of Covid-19 concerning its anti-inflammatory and antiviral properties.

Pharmacology of Colchicine: CN acts as an inhibitor of tubulin polymerisation due to higher affinity to the cellular β-tubulin subunit leading to powerful inhibition of cytoplasmic microtubule polymerisations with suppression of cell division at metaphase. Microtubules are intricate in cell integration, migration, ion channel regulation, chemokines and cytokines release.[8] Also, CN unconventionally prevents association of microtubule and initiation of tubulin heterodimers.[9] Furthermore, CN suppresses mitochondrial metabolism through inhibition of voltage gated ion channels with subsequent reduction of cellular activity. These changes lead to inhibition of chemotaxis of inflammatory cells chiefly monocytes and neutrophils via inhibiting the activity of cellular endosomes. In addition, CN inhibits extracellular adhesion molecules such as E-selectin by which it blocks neutrophils migration and chemotaxis.[10] It has been reported that CN has an effective anti-inflammatory effect through inhibition of neutrophil free radical productions and inflammasome activation with succeeding suppression release of pro-inflammatory cytokines.[11]

CN is well absorbed orally and reaches the peak plasma concentration within one hour, and its supreme anti-inflammatory effect happens within 24-48 hours. CN is highly concentrated in the monocytes and neutrophils about 16 times more than plasma for several days after the last oral intake.[12] The selective accumulation of CN in the neutrophils is due to lack of P-glycoprotein in the neutrophils, which is involved with efflux of CN. CN elimination is chiefly through biliary and renal routes and this type of elimination is the P-glycoprotein dependent pathway.[13] Hence, CN is exposed for drug interaction mainly when co-administrated with P-glycoprotein inhibitors such as verapamil and diltiazem causing CN toxicity.[14]

Anti-inflammatory Effects of Colchicine: It has been confirmed that inhibition of neutrophil chemotaxis, lysosomal degranulation, and release of pro-inflammatory cytokines is the main mechanism by which CN produces anti-inflammatory effects.[15] Further, CN constrains the interaction between adhesion molecules and endothelial cells thus reduce neutrophil migration to the site of inflammation and tissue injury through selective inhibition of neutrophil microtubules. These physical changes reduce neutrophil elasticity and extravasations from blood stream.[16]

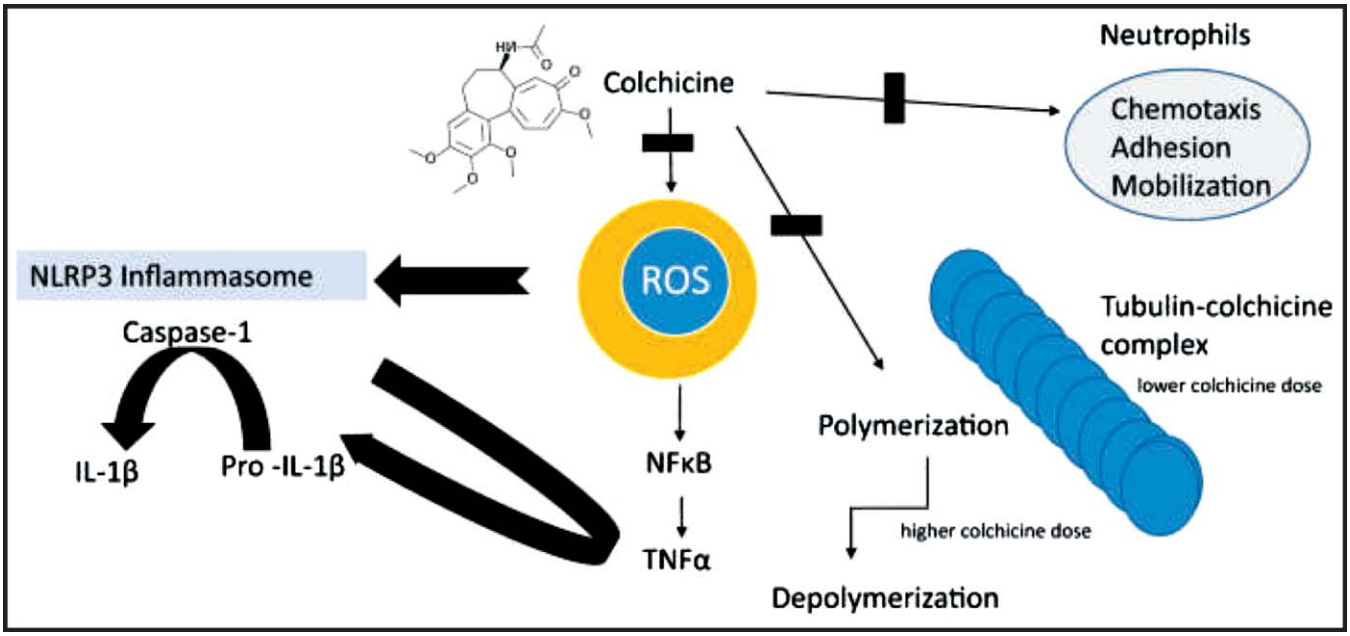

Figure-2: Anti-inflammatory effect of colchicine: colchicine blocks neutrophil chemotaxis, adhesion and mobilization. Colchicine-tubulin complex blocks tubulin polymerization, reactive oxygen species (ROS)-dependent NF-κB and TNF-α activations as well as nod-like receptor pyrin 3 (NLRP3) inflammasom.

Instead, CN attenuates generation of free radicals and reactive oxygen species (ROS) with consequent inhibition release of IL-1β and IL-6 at a lower dose before inhibition of neutrophil migrations. Both TNF-α and ROS interact mutually and upstream each other, therefore CN disrupts this vicious cycle and prevents the deleterious effect of ROS.[17] In addition, CN indirectly reduces stability of neutrophil microtubules through reticence the synthesis and release of TNF-α with downregulation of TNF-α receptors at endothelial and neutrophil surfaces.[18]

Moreover, CN modulates function of nod-like pyrin 3 (NLRP3) inflammasome, which are cytosolic multi-protein oligomer complex expressed in macrophages, adipocytes, monocytes, and neutrophils. Activation of NLRP3 inflammasome increases maturation, proteolytic and release of pro-inflammatory cytokines such as IL-18 and IL-1β. It has been reported that a higher dose of CN inhibits neutrophil inflammasome products in experimental myocardial infarction.[19] Therefore, CN has pleiotropic anti-inflammatory actions with immunomodulatory effects (Figure-2).

Anti-viral effects of colchicine: Different studies illustrate that microtubule network is necessary and important for replication of different viruses since; intracellular transport of viral particles is mediated through cytosolic microtubules.[20] Richter et al., confirm that CN inhibits the replication of Flaviviruses by suppressing the polymerization of microtubules.[21] Besides, CN and its derivatives have potential broad spectrum antiviral effect with reduction of pro-inflammatory cytokines.[21]

Coronavirus (CoV) is a single strand positive-sense RNA virus and its replication and transport is dependant mainly on the formation of microtubules and vesicles in the infected cells. Coronaviruses interact with tubulin proteins, which facilitate the nuclear entry and assembly of viral proteins (Figure-3).[22] So, suppression formation of microtubules by CN may attenuate replication and transport of coronaviruses. Tschope et al., illustrated that CN reduces acute lung injury (ALI) and myocardial damage in infection with SARS-CoV due to suppression of NLRP3 inflammasome and inflammatory cytokines that are stimulated by SARS-CoV spike protein, with subsequent activation of IL-1β and Caspae-3 during ALI.[23]

Colchicine and SARS-CoV-2 infection: The dangerous hallmark of Covid-19 is ARDS and ALI, however systemic complications such as myocardial injury, acute kidney injury, stroke and cytokine storm can also develop even in absence of underlying cardiovascular disorders. Besides, endothelial dysfunction and inflammation are also provoked by SARS-CoV-2 viroporin E leading to acute coronary syndrome and acute ischaemic stroke.[24] CN reduces these complications via inhibition of NLRP3 inflammasome and cytokine activations thus it ameliorates systemic and local inflammatory disorders such as myocarditis, myocardial infarction, and pericarditis.[25]

The possible value of CN treatment in Covid-19 is evaluated by a Clinical Trial.gov Identifier: NCT04322565 that revealed the significant effect of CN therapy against Covid-19.[26]

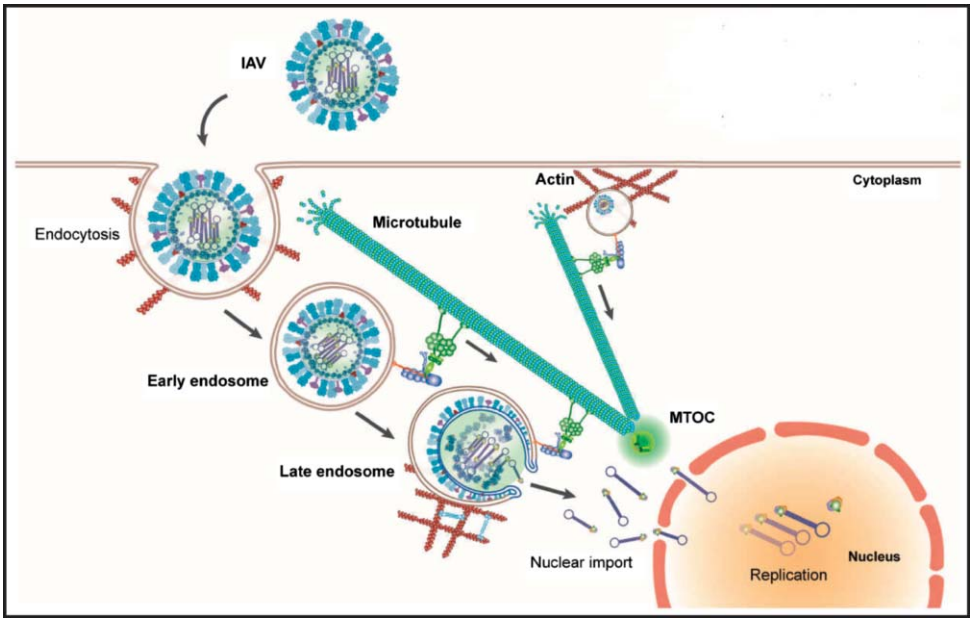

Figure-3: Microtubules and viral endocytosis.

Recently, administration of CN at the 8th day of the standard therapy in Covid-19 patients improves clinical outcome and severity through inhibition release of pro-inflammatory cytokines mainly IL-1β and IL-6 that are associated with progression of ALI/ARDS.[27] It has been shown that anti-cytokines such as IL-6 antagonist are effective in attenuating the development of a cytokine storm and ALI/ARDS.[28,29] Thus anti-inflammatory agents should be administered before the development of ALI. Immune stimulation in the early phase of SARS-Co-V-2 infection is linked with viral clearance;

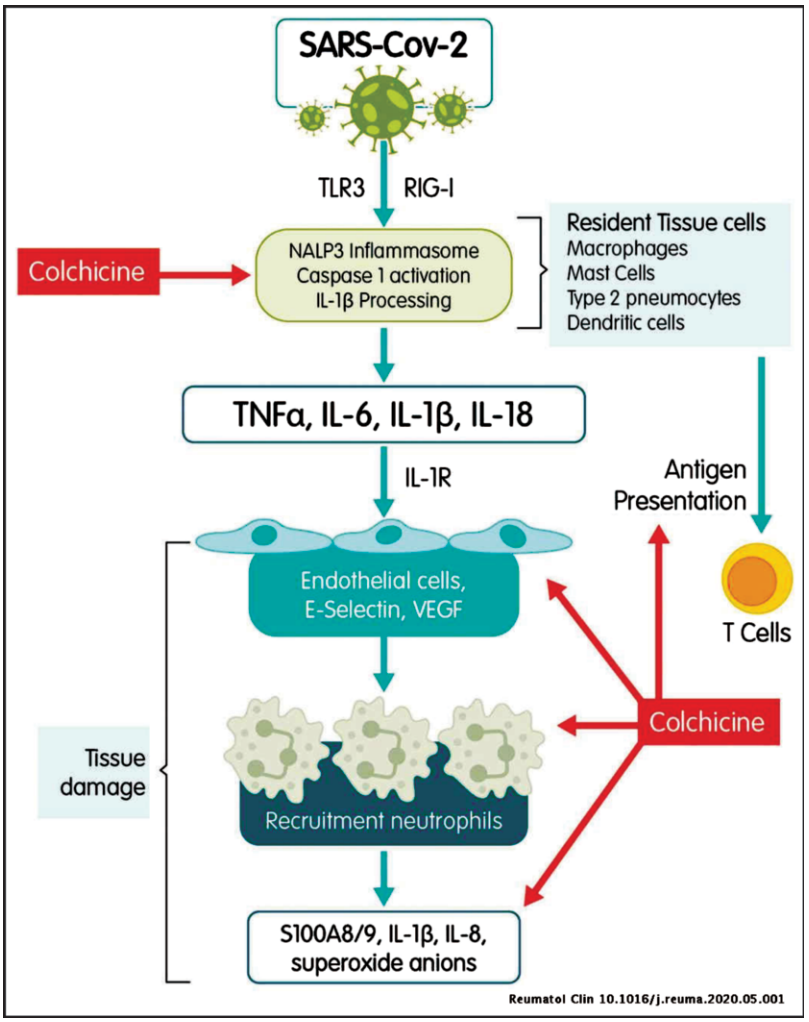

Figure-4: Role of colchicine in Covide-19.

however immunological stimulation in the late phase is associated with cytokine storm and tissue injury. Hence, administration of CN in the late phase of SARS-Co-V-2 infection reduces exacerbation of innate immune response.[4]

Therefore, appropriate direction of CN therapy at the 5th day of fever or 8th day of flu-like illness in Covid-19 patients suppresses the development of cytokine storm-induced ALI and MOF.[30] Though early CN therapy in Covid-19 could impair the beneficial immunological response against SARS-CoV-2 infection but sequential CN therapy was effective against the progression of ALI/ARDS as shown in the case series published by Al-Kuraishy et al.[4] Similarly, Deftereos et al., observed that CN therapy reduces risk of ALI and acute cardiac injury in Covid-19 patients.[31] Therefore, patients with FMF on CN therapy develop mild Covid-19 due to the potent anti-inflammatory effect of CN.[32]

On the contrary, CN therapy may be harmful due to the following reasons: 1-SARS-CoV-2 binds ACE2 at low cytosolic PH. CN inhibits microtubule H-ATPase leading to acidic cytosolic environment. 2-Therapeutic and toxic doses of CN might cause ARDS through inhibition the synthesis of alveolar surfactant from type II pneumocytes. 3- CN may increase risk of MOF through induction of coagulopathy.[33] These hypothetical findings were not dependent on animal studies or clinical findings and the author did not highlight the outstanding benefit of CN therapy in Covid-19 patients in a scientific manner. However, a prospective study by Piantoni et al., confirms that CN therapy is highly effective in reducing the pro-inflammatory biomarkers and ferritin in hospitalised patients.[34]

In addition, different researches illustrate that CN treatment is beneficial in anticipation of ALI and ARDS through improvement of pulmonary oxygenation and pulmonary oedema via suppression of neutrophil chemotaxis and migration.[35]

Therefore, the assorted view of preponderance concludes that CN therapy is effective in the management of Covid-19 patients when timely administrated through reduction of tissue damage and hyper-inflammation (Figure-4).

Conclusion

CN, a potent anti-inflammatory agent is an effective therapy in the management of Covid-19 infection. It inhibits SARS-CoV-2-induced ALI and ARDS due to its anti-inflammatory and anti-viral effects.

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