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Potential Effect of Colchicine in the Prevention of Acute Respiratory Distress Syndrome (ARDS) In Patients with Covid-19 Infection

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Perspective

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Abstract

This work presents the theoretical basis for the use of Colchicine in the prevention of Acute Respiratory Distress Syndrome (ARDS) associated with COVID-19 infection. Several reports show that the common final event that increases mortality from COVID-19 infection is ARDS, which occurs due to an unmodulated inflammatory response, which leads to respiratory failure and death. For many years we have used colchicine, anti-inflammatory and antimitotic, for the management of symptoms associated with modeling disease, iatrogenic allogenosis, or Schoenfeld's syndrome, obtaining control of the inflammatory or autoimmune process that occurred in these patients. Colchicine is an alkaloid extracted from the plant "Genus Colchicum" and works by modulating the inflammatory response in patients with gout, gouty arthritis and familial Mediterranean fever. We observed that a group of patients consuming colchicine, 5 patients, diagnosed with COVID-19 infection and within the age group with the highest risk, presented only minor symptoms and did not develop ARDS. This clinical observation motivates us to describe as an incidental finding the possible prophylactic effect of colchicine in the prevention of acute respiratory distress syndrome (ARDS) in patients with COVID-19 infection. Early detection of patients who may have ARDS and the use of colchicine, a very low-cost drug, in these patients may decrease the mortality associated with COVID-19 infection.

Keywords: Colchicine; Acute Respiratory Distress; Inflammatory; Cytokines; Covid-19; Mortality

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; Ang-2: Angiopoietin-2; RAGE: Receptor For Advanced Glycation End Products; TNF-A: Tumor Necrosis Factor-A; VEGF: Vascular Endothelial Growth Factor; CASPASE: Cysteine Dependent Aspartate-Directed Proteases; CCF: Crystal-Induced Chemotactic Factor; MSU: Monosodium Urate Crystals (Gout); MICL: Myeloid Inhibitory C Type-Like Lectin; NALP3: NACHT-LRRPYD Containing Protein 3; TLR: Toll-Like Receptors; Myd88: Myeloid Differentiation Primary Response Gene 88; ROS: Reactive Species Of Oxygen; NO: Nitric Oxide; MDR1: Multi-Drug Resistance Protein 1; ABCB1: ATP-Binding Cassette Subfamily B Member 1; RA: Rheumatoid Arthritis; TNF: Tumor Necrosis Factor; CKDL: Chronic Kidney Disease ; HBP: High Blood Pressure; DM: Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease; PT: Prothrombin Time; CHD: Coronary Heart Disease.

Introduction

Coronavirus (COVID-19) infection and the mortality associated with the Acute respiratory distress syndrome (hereafter referred to as ARDS) poses a global public health problem [1,2]. To date, it exceeds one million infections worldwide, with a mortality greater than 60,000 cases [3]. The increase in the spread and associated mortality poses a scenario where cost-effective therapeutic options to control and reduce the epidemic and even to decrease the number of deaths are urgently and effectively proposed to the international scientific community.

In this scenario, new therapeutic options such as remdesivir and hydroxychloroquine have been reported and tested [4-7]. This last medicine shows promising results due to its immunomodulatory and antiviral effect. For more than 10 years, we have used colchicine in the symptomatic treatment of patients with modeling disease, iatrogenic allogenosis, or Schoenfeld' syndrome. In these patients, colchicine decreases the symptoms associated with the inflammatory response, manifestations such as arthralgia, headache, and pulmonary infiltrates are significantly reduced, and patients experience clinical improvement, reducing the frequency of appearance of these manifestations.

The first case of COVID-19 infection was reported in Colombia on March 2, 2020. To date, more than 1600 cases have been diagnosed, drawing attention 5 patients on colchicine treatment, 3 of these cases presented diagnosis of infection, and in the other 2, infection was diagnosed in their close family environments. All 5 patients showed minimal or non-existent clinical manifestations. These findings make us think about the "protective role" that the ingestion of colchicine could have, especially in patients at risk of developing ARDS.

In the light of current information, in this document, we will present a summary of recent knowledge about the mechanisms of action of colchicine, how through different ways, it could act in modulating or preventing the development of ARDS associated with COVID-19 infection, and its possible effects on viral replication and antigen presentation.

In the current global health crisis triggered by the Sars-Cov2 / Covid 19 pandemic, multiple research groups are working on the development or implementation of drugs both to prevent and treat patients infected with Covid-19 and offer from science a wellness opportunity by improving the complication and mortality rates caused by the pandemic.

In one of the searches in pubmed, a research proposal that involves the drug Colchicine in the protocol called GRECCO-19 study of a prospective, randomized, controlled and open type was found. It will be carried out in Greece to evaluate the prevention of complications in patients with Covid-19 treated with Colchicine [8] This gives our study proposal investigative consistency in accordance with the medical literature and a greater biological plausibility for the use of Colchicine as a prophylactic proposal or therapeutic alternative of the drug in individuals at risk or affected by Covid-19.

The therapeutic role of Colchicine in other pathologies triggered by viral infections is well known [9]. In patients suffering from acute and recurrent pericarditis, the 2015 guidelines of the European Society of Cardiology bestow Colchicine a recommendation 1A (indicated based on clinical trials or meta-analyzes) given its known and safe anti-inflammatory effect as first-line therapy, complementing the action of NSAIDs (nonsteroidal anti-inflammatory drugs) in this group of patients and decreasing the recurrence of Pericarditis, which in many cases its etiology is post viral infectious [10,11] therefore, it would not be the first time that Colchicine was used to treat patients affected by inflammatory processes triggered by a viral infection, reinforcing our research proposal in the current scenario of Sars-Cov2// Covid -19 affection.

Colchicine is also indicated in a wide group of inflammatory diseases that in its pathophysiology involve various mechanisms of innate immunity and inflammasome activation. Probably the best known disease for the use of the drug is Acute Gout Attack, which administration regimen has changed historically, from high doses to lower current doses with similar effectiveness and better safety profile, avoiding its use in patients with impaired renal function and

those who have been receiving inhibitors of P-glycoprotein (Cyclosporine, Verapamil) or of the liver enzyme CYP3A4 (Clarithromycin) [12]. Another group of diseases in which Colchicine is used are autoinflammatory or periodic fever syndromes such as Familial Mediterranean Fever (FMF), in which the medicine is indicated as prophylaxis of the attacks of this disease and in the prevention towards the progression to Amyloidosis. This is justified in its mechanism of action on microtubular polymerization that affects the mobility and migration of the neutrophil by reducing its cytoplasmic elasticity and increasing the viscosity of the cell membrane [13]. Additionally, Colchicine is also prescribed in the prophylaxis and treatment of Pseudogout crises triggered by articular deposition of Calcium Pyrophosphate Crystals, a scenario whose clinical evidence is extrapolated from the treatment of Gout attacks [14,15]. Another indication for Colchicine is the prevention of recurrences of both oral and genital ulcers and Erythema Nodosum in Behçet's disease [16]. Given the above, the indications for the drug involve multiple clinical scenarios with proven efficacy and an appropriate safety profile following the respective recommendations for use, precaution and contraindication of the drug [17].

The Development of Ards in Patients With Covid-19 Infection

Studies showing the behavior of COVID-19 infection indicate that between 70-80% of the infected population will have mild or moderate symptoms, 15% will have severe infections manifested by severe dyspnea with hypoxemia and pulmonary infiltrates and 5% will have critical conditions with respiratory failure, septic shock and multi-organ dysfunction [6]. Patients with higher age groups (over 60 years old) and associated comorbidities such as hypertension and diabetes have the highest mortality rates [18]. Among the predictors of worse prognosis are the presence of dyspnea, lymphopenia, elevated neutrophils, and decreased monocytes and platelets. The CD4 and CD8 T lymphocyte count are decreased, as well as the ureic nitrogen and creatinine elevated. In other words, a suppression of cellular immunity is evidenced but with a severe inflammatory reaction that can lead to death. Dyspnea as a symptom occurs in a greater proportion in patients who die versus survivors with a $p < 0.001$, which does not happen with fever, headache and other symptoms [10]. Other prevalent factors in patients who die from COVID-19 are a decrease in albumin, an increase in lactate, a slight decrease in the number of red cells and hemoglobin, and an increase in lactic dehydrogenase [11]. Among the predictors with the best prognosis are the high level of lymphocytes and female gender, characteristics that appear in a greater proportion in the group of survivors.

Acute respiratory distress syndrome (ARDS) appears to be the common final path leading to the death of the patient.

All patients die of respiratory failure, indicating that the lung is the target organ, calling attention to the fact that when multiorgan failure occurs, after the lung, the most compromised organ is the heart, followed by the kidney and liver. 0.5% of patients show elevated procalcitonin, probably as an indicator of bacterial infection. Patients who die have a severe inflammatory cascade, reflected in increased C-reactive protein and serum amyloid A [19,20].

ARDS is believed to be the result of an injury to the alveolar epithelium and capillary endothelium with abnormalities in the immune system. Neutrophils are recruited to the lungs by cytokines, toxic mediators such as oxygen free radicals and proteases are activated and released [21]. Extensive production of free radicals exceeds the capacity of endogenous antioxidants and causes oxidative cell damage. Factors such as endothelin-1, angiotensin-2, NF-kappa B and phospholipase A-2 increase vascular permeability and destroy microvascular architecture, increasing inflammation and lung damage. This results in an influx of protein-rich fluid into the airspaces caused by increased permeability of the alveolar-capillary barrier. Increased alveolar fluid reduces gas exchange through the alveolar-capillary membrane, resulting in hypoxemia and respiratory failure.

To determine which patients are at risk of developing ARDS, attempts are being made to establish algorithms and mathematical models. An interesting study carried out in China, using artificial intelligence and mathematical models shows 3 critical elements: 1. Liver enzyme levels alanine aminotransferase (ALT). Although these increase dramatically when diseases cause liver damage, they were only slightly higher in COVID-19 patients, however, these slight variations were key in predicting severity; 2. Deep muscle pains (myalgia), related to increased generalized inflammation and; 3. Higher hemoglobin levels, were also associated with succeeding respiratory distress [22]. Many biomarkers have been found for the diagnosis of ARDS, such as the receptor for advanced glycation end products (RAGE), angiopoietin-2 (Ang-2), surfactant protein D (SP-D), inflammatory factors [interleukin (IL) -6, IL-8 and tumor necrosis factor-α (TNF-α) [23]. However, no sensitive and specific clinical biomarkers for ARDS have been found. Dyspnea is also a predictive element.

Efforts should focus on preventing the development of ARDS in patients with COVID-19 infection, since once it occurs, mortality is very high and our health systems do not have the capacity to care for as many critically ill patients as has been seen in Italy, Spain and currently, the USA.

For this reason, we propose that colchicine could be

potentially use in patients who are at risk of developing ARDS, and who meet clinical and laboratory criteria that predict the appearance of ARDS.

Mechanisms of Action of Colchicine

Colchicine acts as a potent inhibitor of tubulin polymerization, it is an alkaloid extracted from the genus colchicum (autumn crocus) plant, commonly used in the treatment of gout and familial Mediterranean fever, but with multiple uses in other pathologies such as Behcet's disease, pericarditis, coronary heart disease, and other inflammatory and fibrotic conditions [5].

The most studied mechanism is related to the ability of colchicine to bind to tubulin and block the assembly and microtubules polymerization [24]. Microtubules are the key piece of the cytoskeleton and are involved in multiple cellular processes such as maintaining the shape of the cell, transfer of intracellular substances, secretion of cytokines and chemokines, cell migration, regulation of ion channels and cell division [24]. Colchicine is an antimitotic that blocks cell division during metaphase. At low concentrations it slows the growth of microtubules and at high concentrations it promotes microtubular depolymerization [25,26]. The role in the inhibition of cancer cells and their metastatic potential has been studied.

The anti-inflammatory effect in question is related to the decrease in the activity of leukocytes and the blocking of the autoimmune response by at least 5 ways:

1. At low doses, it inhibits the appearance of E-selectin from endothelial cells and prevents the adhesion of neutrophils. At high doses, it promotes the elimination of L-selectin from neutrophils, preventing further recruitment of these.
2. Colchicine inhibits the activation of innate immunity, the activation of the NALP3 inflammasome, the activation of CASPASE-1; it inhibits the release of chemotactic factor from neutrophils and then the recruitment of neutrophils [25].
3. Colchicine inhibits the activation and release of neutrophils from interleukins: IL1, IL8 and superoxide [27].
4. Colchicine promotes dendritic cell maturation to act as antigen-presenting cells.
5. Colchicine inhibits vascular endothelial growth factor (VEGF) and endothelial proliferation. CASPASE=cysteine dependent aspartate-directed proteases, CCF = crystal-induced chemotactic factor, MSU =monosodium urate crystals (gout), MICL = Myeloid inhibitory C type-like lectin, NALP3 = NACHT-LRRPYD containing protein 3, TLR = Toll-like receptors, MyD88 = Myeloid differentiation primary response gene 88, VEGF = Vascular endothelial growth factor [5].

A lot of attention has been put into the effects of colchicine on macrophages (Figure 1). It was shown that Colchicine modulates lipopolysaccharide-induced secretion of tumor necrosis factor (TNF) by liver macrophages in a rat model [5]. In a mouse brain macrophage cell line, colchicine inhibited ATP-induced IL1β release by preventing microtubule rearrangement and constraining activation of the Ras homolog gene family, member A (RhoA) associate, which contains the protein kinase (ROCK) pathway [27]. In the presence of colchicine, mouse peritoneal macrophages showed less ATP-induced permeability to ethidium bromide and less formation of reactive species of oxygen (ROS), nitric oxide (NO), and IL1β release. [5].

All these compounds intervene in the magnification of the inflammatory process and are responsible for alveolar damage, interstitial infiltration and lung collapse. By different ways, colchicine can minimize such damage.

In summary, colchicine has been the first-line therapy for the treatment of acute gouty arthritis and Familial Mediterranean Fever. However, due to anti-inflammatory and antifibrotic activities, the therapeutic use of colchicine has spread beyond arthritis. The exact mechanisms of action underlying its efficacy are not fully understood and remain under active investigation. Current results suggest that colchicine downregulates multiple inflammatory pathways and modulates innate immunity. If we recognize that the heart is the second target organ in Covid-19 infection and that organic damage is caused by a fulminant inflammatory response, colchicine could be considered as a prevention agent. Colchicine works by limiting myocardial damage and necrosis and the development of pneumonia with fulminant lung inflammation, inhibiting the NLRP3 inflammasome and endocytosis in the myocardial cell and respiratory endothelial cell.

As this brief review demonstrates, there are many potential therapeutic uses for colchicine or its analogs, and if an unmodulated inflammatory response is found in the etiology of ARDS associated with COVID-19 infection, its potential use in preventing these clinical manifestations should not be ignored. On the other hand, we know the unwanted effects of using this medicine, which can be controlled with alternative medicines. The low cost and ease of administration and bioavailability of this substance allows therapeutic levels to be obtained quickly, which also facilitates its use.

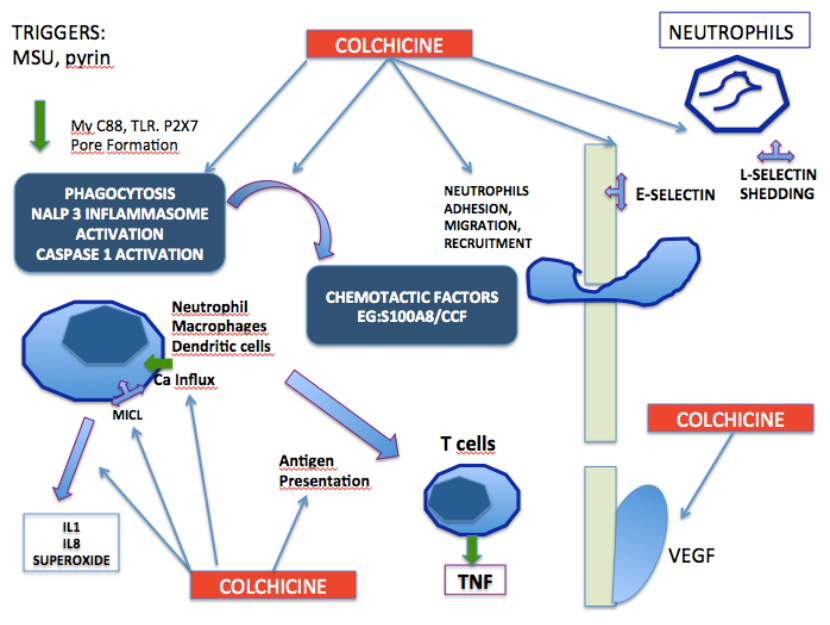

Figure 1: Modified from Leong Y, Yao L, Kraus V. Colchicine: Update on mechanism of action and therapeutic uses. Semin Arthritis Rheum 2015 (Dec) 45 (3): 341-350 [28]

Metabolism and Elimination of the Colchicine

Colchicine is mainly eliminated from the body through transport by P-glycoprotein [P-gp, also known as multi-drug resistance protein 1 (MDR1) or ATP-binding cassette subfamily B member 1 (ABCB1)], expressed in hepatocytes (biliary excretion), proximal renal tubules (renal excretion), enteric cells (intestinal excretion), monocytes, and blood-brain barrier cells. The P glycoprotein is encoded by the MDR1 gene, and certain MDR1 polymorphisms are associated with increased P-gp expression / activity and decreased serum colchicine concentrations. [29] A smaller, however, significant quantity of absorbed colchicine is metabolized by hepatic P450 cytochrome CYP3A4, or directly eliminated by the kidneys through glomerular filtration. All of these mechanisms are vulnerable to drug interaction, which can affect bloodstream levels [29].

Among the pathophysiological mechanisms of biological plausibility for the use of Colchicine in the group of patients at risk or affected by infection caused by Sars-Cov2 / Covid 19, we can mention works that involve the Inflammasome activation of the NLRP3 through extracellular histones that are produced by Acute Lung Injury (ALI) and ARDS promoting the recruitment of neutrophils and the spread of inflammatory mechanisms in this group of diseases [30] enabling to theorize the inactivation via the inflammasome as a probable therapeutic target for drugs of this class.

The NLRP3 inflammasome has also been implicated in the pathophysiology of ALI by observing the inhibition of its activity by blocking TREM-1 (Triggering receptor expressed on myeloid 1) can attenuate polysaccharide-induced ALI by creating an overview of possible therapeutic targets in this condition of the critical patient [31].

In animal models, there are experimental data showing that the inflammasome activation of the NLRP3 and the production of IL-1B have an important role in the development of hypoxemia in ALI induced by Lipopolysaccharides and mechanical ventilation [32].

Discussion

The global medical community does not know whether rheumatic disease or immunosuppression increases the initial risk of COVID-19 infection. In an Italian study during the 2009-2010 influenza season, 160 patients diagnosed with Rheumatoid arthritis (RA) and who took biological medications had a higher infection rate than controls, but complications and hospitalizations did not increase. It is not clear, based upon current information, whether the ingestion of colchicine in healthy patients may place the patient in immunosuppressed condition.

Despite concerns that immunosuppressive drugs may increase the risk of complications for infected patients, there is hope that the anti-inflammatory properties of these drugs

may mitigate lung injury. COVID-19 infection can give rise to what has been called "a cytokine storm" as seen in rare diseases such as macrophage activation syndrome. In such situations, there is a massive release of various cytokines, particularly interleukins. Therefore, some of the biological immunosuppressive drugs used by rheumatologists may be effective in treating serious COVID-19 infections.

For instance, interleukin blockers (IL-1 and IL-6) have been effective in ARDS, and IL-6 blocker, tocilizumab, is being used in clinical trials of COVID-19 in China and Italy. There is also evidence that tumor necrosis factor (TNF) inhibitors may be effective, and a study using adalimumab for COVID-19 infection is ongoing in China. A double-blind trial launched in the USA in March 2020 regarding the IL-6 inhibitor, sarilumab in patients with severe COVID-19 infection may be useful, as well.

In this sense, in the balance risk-benefit and cost-effectiveness, the administration of colchicine in healthy patients or at risk of complicating with an ARDS should be evaluated. The benefits exceed the risks of its use, thus, in an emergency situation caused by the current pandemic, we hypothesize that colchicine could have a potential use in this disease.

In this context, the properties of colchicine, previously described, could be potentially used to decrease the risk of patients with COVID-19 infection of developing ARDS. Also, the proposed scheme is to achieve that patients reach therapeutic blood levels of colchicine, a dose similar to that implemented for the management of acute gout attack, but that requires further research and clinical studies [22].

Side or undesirable effects include nausea, vomiting, or diarrhea, all of which should be managed symptomatically. Intravenous use of colchicine is not recommended due to the many complications it produces, such as bone marrow suppression, liver damage, acute kidney failure, disseminated intravascular coagulation, seizures, and even death [7]. On the other hand, it should be borne in mind that severe colchicine toxicity appears mainly in patients with simultaneous administration of cytochrome P450 inhibitors (CYP3A4) or of the glycoprotein P (P-gp), specifically macrolides, cyclosporine, statins and calcium antagonists (verapamil and diltiazem). In fact, colchicine toxicity is probably more related to concomitant medication than to the drug itself. Nevertheless, it should be noted that statin treatment is currently recommended for all patients with chronic kidney disease (CKD) due to its tendency to accelerated atherogenesis, which increases the risk of rhabdomyolysis in this group if colchicine is used simultaneously.

Conclusions

Colchicine is one of the medicines known since ancient times, originally described for the treatment of acute gout attacks, however, there is still much to learn about its mechanisms of action. Studies continue to discover its benefits in a growing variety of diseases. In addition to its well-established role in treating gout and Familial Mediterranean Fever, colchicine has recently shown benefits in a variety of heart conditions, including pericarditis and Coronary heart disease (CHD). New uses of colchicine and its anti-inflammatory effect are continuously being explored in at least 5 known ways. These findings, in a pressing situation for humanity, indicate that we could use it to reduce the risks of the development of ARDS in patients with COVID-19 infection. Given its relatively good safety and tolerability profile when used carefully and appropriately, we consider that its use should be implemented once protocols from other research groups are defined and proposed, resulting in an opportunity to decrease the results of the infection through clinical observation. We considered important to share the incidental findings we describe in the present manuscript and to invite the scientific groups to further analyze and research about the relationship and clinical adequate results that colchicine could have in preventing acute respiratory distress syndrome in patients with covid-19 infection.

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