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Annals of Vascular Medicine & Research

Review Article

The Role of Colchicine in the Treatment of COVID-19 Infection, an Ancient Medicine to Combat Current Coronavirus Pandemics?

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Submitted: 09 March 2021

Accepted: 25 March 2021

Published: 28 March 2021

ISSN: 2378-9344

Keywords

- COVID-19
- Colchicine
- TNF-a; Dexamethasone
- PCSK9
- c-IAP1
- LDLr

Abstract

Colchicine is a well-known ancient remedy to treat gouty and arthritis, more recently, to the Mediterranean fever. It also has a good efficacy in the treatment of some cardiovascular disease conditions. The role of colchicine in the treatment of the ongoing pandemic COVID-19 has been suggested to control of the COVID-19-induced cytokine storm. Recently, in several clinical trials, colchicine has been shown to reduce the length of the need for supplemental oxygen and the length of hospitalization and beneficial to the COVID-19 patients before hospitalization. It has been known that some health conditions with increased cholesterol level such as fat, obesity and diabetes making patients more vulnerable to death in the SARS-Cov-2-virus attack. We have discussed the possible mechanisms of colchicine in virus-induced TNF-a-mediated cytokine storm in crosstalk with the cholesterol regulation pathway.

ABBREVIATIONS

PCSK9: (proprotein convertases subtilisin/kexin 9); C-IAP1: Cellular Inhibitor of Apoptosis Protein1); TNF-a: (Tumor Necrosis Factor alpha); Traf2: (TNF receptor associate protein);] e.g., MCI: infection diseases, COVID-19; Sars-CoV-2, Cholesterol, Obesity, Diabetes

INTRODUCTION

Colchicine is a well-known ancient remedy that has been used to treat gouty and arthritis over 1,400 years (Alexander of Tralles during the 6th century) [1]. In recent years, FDA proved colchicine as a prescribing drug for treatment of acute gout flares and familial auto-inflammatory disease Mediterranean fever [2]. Recently, in our high-throughput screening of PCSK9(proprotein convertases subtilisin/kexin) inhibitors, we found that one of the lead compounds, colchicine, exhibited strong inhibition of PCSK9 biological activity in the human liver HepG2 cells and the result has been further validated by the Western blot assay for PCSK9-mediated LDLR degradation in dose-responsive assay [3]. Colchicine has also been shown to have a good efficacy in preventing cardiovascular adversary events in some of myocardial infarction patients [4].

Colchicine: the potential drug to treat COVID-19 infection

Since December, 2019, a new global pandemic disease, Covid-19 infection is spreading all over the world. The disease is caused by coronavirus-2 (SARS-CoV-2) infection, resulting in infecting over 114 million people, and caused over 2.5 million people death so far(WHO data, 01/03/2021). So far only very few limited drugs such as dexamethasone and remdesivir have been identified [5]. Given Colchicine has been used to treat fever infection disease syndromes such as familial Mediterranean fever., its possible role in treatment of the ongoing pandemic COVID-19 have been suggested [6] to control of the systemic inflammation. The rationale of its use for the treatment of COVID-19, is focused on the control of the systemic inflammation caused by SARS- CoV-2 infection. There were several clinical trials [7-9]. Lope et al presented data of a Randomized Controlled Trial (RCT) of colchicine for hospitalized patients with COVID-19, demonstrating that the drug reduced the length of the need for supplemental oxygen and the length of hospitalization [9]. In another small cohort of patients in Bogota, Colombia, colchicine has shown encourage result to treat covid-19 [10],

More recently, Dr. Jean-Claude Tardif et al in Montreal Heart Institute, Canada, has obtained significant positive result in larger scale clinical trials with over 4488 COVID-19 patients, in which 4159 patients have PCR positive diagnosis. They found that colchicine-treated patients have 25% less hospitalization (4.6% colchicine-treated patients in comparison of 6.0% in control placebo treated patients, P<0.05) in double-blind clinical trial.), indicating that among non-hospitalized patients with

COVID-19 infection, colchicine reduces the composite rate of death or hospitalization [11, medRxiv the preprint]. Currently, more colchicine clinical trials are in progress for the treatment of SARS-CoV-2 infection. If confirmed by other studies, colchicine is warrant to be pursued as an additional drug to be added in the drug arsenal in treating COVID-19 patients.

Cholesterol, Furin, PCSK9 in COVID-19

It has been known that some health conditions with increased cholesterol level, such as , such as fat, obesity and diabetes making patients more vulnerable to death in the SARS_ Cov-2-virus attack [12], medRxiv. The preprint]. One of the key cholesterol regulators-- ACE2 (Angiotensin Converting Enzyme 2) receptor, is known to be an entry point of the SARS- Cov-2 virus. Cholesterol increased receptor binding domains in the nasal endothelium cells [12]. Furthermore, Furin-mediated endothelial tropism seems to underlie the multi-organ system involvement of COVID-19[13]. Furin binds and cleaves PCSK9 (proprotein convertases subtilisin/kexin 9), one of the key regulator of LDL (low-density lipoproteins) receptors and cholesterol level inside the cells.

PCSK9 was initially discovered by a French group investing a raregeneticdisorderofautosomaldominanthypercholesterolemia [14]. PCSK9 has a wide spectrum of mutations in human population. PCSK9 gain-of-function variations are associated with hypercholesterolaemia, whereas loss-of-function variations are associated with hypocholesterolaemia [15]. Due to its direct binding to and degradation of LDLR, PCSK9 is regarded as a valid and novel target for the treatment of hypercholesterolemia. Recently, in a high throughout inhibitor screen of PCSK9, we found that colchicine exhibited strong inhibition of PCSK9 biological activity in the human liver HepG2 cells and the result has been further validated by the Western blot assay [3]. We propose that colchicine binds microtube, disrupting endocytic recycling of the LDL receptor returning to the plasma membrane depends on microtubule-dependent motility [16]. Interestingly, in a separate in vitro cell culture model of the Alzheimer's disease, increased APP expression and Aβ exposure alters microtubule function, leading to reduced transport of LDLR to the plasma membrane, moving it toward the Golgi apparatus and lysosomes [17]. PCSK9 is known forming a complex with LDLR in the early endosomes and lysosomes [15] that makes the PCSK9/LDLR complex is likely moving on the microtubules network, which is vulnerable to the disruption by colchicine. Frequently, elderly people are more susceptible to COVID-19 death, could be one of the mechanisms for LDLR involvement in the SARS-CoV-2 virus attack.

Colchicine and dexamethasone are both involved in TNF-a pathway in COVID-19 cytokine storm

Colchicine has also been shown to reduce the generation of TNF-a by macrophage and its receptors on the endothelial cell [18,19]. Interestingly, in recent large-scale study (involving in 1,484 COVID-19 patients), inflammatory cytokine signature that predicts COVID-19 severity and survival found that high serum IL-6 and TNF-α levels are strong and independent predictors of patient survival, indicating TNF-a apoptosis pathway could be involved disease development and therapeutical intervention [20]. It is noteworthy that in a large scale study involved in 2104 patients [5], dexamethasone, a potent inhibitor of the TNF-a-induced apoptosis [21], is so far one of the most potent therapeutic drugs to be used in treating severe mechanical ventilation treated COVID-19 patients, resulting in significant lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone [5]. Dexamethasone is known to inhibit the TNF-a-induced apoptosis and IAP protein downregulation in breast cancer cells MCF-7 and the bovine glomerular endothelial cells [21]. Treatment of MCF-7 cells with TNF-a will lead to apoptotic cell death within 24 h, while treat 100 nM dexamethasone can block 80±90% of TNF-a-induced apoptosis [21]. Interestingly, the mechanism that dexamethasone to blocking TNF-a-induced apoptosis is through inhibiting IAP (Inhibitors of Apoptosis Proteins) downregulation , which is a key feature of TNF-a-induced apoptosis. In mammalian cells, there are three types of IAP proteins: c-IAP (cellular Inhibitor of Apoptosis Protein1), c-IAP2 and X-linked IAP (XIAP) [22]. These IAP proteins are widely expressed and inhibit the apoptosis process in the TNF-a mediated inflammation cytokine storm. Dexamethasone has been shown to be able to protect full-length of the c-IAP1 protein in both MCF-7 and bovine glomerular endothelial cells [21]. In our previous study using the shotgun proteomic approach, we found that PCSK9 binds c-IAP1/Traf2 complex in TNF-a pathway [23]. We proposed that there is a novel cholesterol regulation pathway that links PCSK9/LDLR cholesterol uptake to the TNF-α-induced c-IAP1/TRAF2 regulatory pathway. Further explore this novel pathway (including c-IAP1-mediated ubiquitination) pathway, could provide anew medicine for COVID-19 treatment.

CONCLUSION

The role of colchicine in treatment of the ongoing pandemic COVID-19 has been suggested to control of the COVID-19-induced cytokine storm**.** Recently, in several clinical trials, colchicine has been shown to reduce the length of the need for supplemental oxygen and the length of hospitalization and beneficial to the COVID-19 patients before hospitalization.

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Cite this article

Xu W (2021) The Role of Colchicine in the Treatment of COVID-19 Infection, an Ancient Medicine to Combat Current Coronavirus Pandemics? Ann Vasc Med Res 8(1): 1127.