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REVIEW ARTICLE

USE OF COLCHICINE TO COUNTERACT THE STRONG HYPERINFLAMMATORY STATE INDUCED BY SARS-COV-2

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ABSTRACT

Research in present time has been focusing on finding a specific SARS-CoV-2 vaccine or antiviral, which will probably be the therapeutic goal in the fight against the virus. In the meantime, scientific evidence shows that it is possible to have effective clinical improvements of infected patients in reducing the strong hyperinflammatory state. The SARS-CoV-2 infection is divided into three stages. The most serious phase is the third one where the immune system overdrives and launches an intense attack against itself. This is called "cytokine storm" and leads to tissue damage and often to death. Stopping the cytokine storm early is definitely an effective move; since March several studies have been evaluating how this can be an important pharmacological aspect. Blocking IL-6 or IL-1 inhibitors, for example, is already known to have wide efficacy, but they are not alone in being able to block the cascade of cytokines. This is a clinical pharmacology article and demonstrates how the use of colchicine, monotherapy or in combination in all three phases of SARS-CoV-2, controls inflammation and prevents patient death. Colchicine is safe and effective for treating SARS-CoV-2 patients in preventing inflammation and lung collapse and is certainly useful as an added remedy for other drugs. The advantage is certainly its safety profile much higher than that provided by other drugs, such as corticosteroids and immunosuppressive drugs. Note is the story of hydroxychloroquine: use has been banned due to its high toxicity.

Keywords: Colchicine, coronavirus, cytokine, interleukin, pneumonia, SARS-CoV-2.

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INTRODUCTION

At the end of 2019, a new coronavirus identified as SARS-CoV-2 was contracted in China and caused thousands of pneumonia resulting in deaths. It quickly spread all over the world. Much has been understood about SARS-CoV-2 and its pathogenesis. SARS-CoV-2 infection can be divided into three phases: phase 1, asymptomatic period that does not require hospitalization; phase 2, slightly symptomatic period with virus detection; phase 3, severe symptomatic phase and strong hyper inflammatory state. Phase 3 is most serious and dangerous because the strong inflammation causes lethal pneumonia due to a large release of cytokines defined as "cytokine storm" (CS)^{1,2}.

Phases of SARS-CoV-2 infection

For each pathological phase, a specific therapeutic treatment can be indicated or avoided. Every single phase must be well identified from patient to patient because the therapeutic approach is different^{3,4}.

Phase 1 (or non-serious phase)

At this stage the patient is infected and the immune system tries to counter it. This phase lasts between three and seven days. At this stage, an immune response is required that is suitable for breaking down the virus and avoiding progression in the later stages of the disease. The use of an antiviral to lower the viral load is definitely helpful and would stimulate the immune system to react effectively. Encouraging evidence of efficacy concerns remdesivir, lopinavir/ritonavir, chloroquine and hydroxychloroquine. If the virus is defeated at this stage there is an easy clinical recovery^{5,6}.

Phase 2 (moderate)

The second stage of infection occurs between the tenth and fourteenth days. The protective immune response has failed and the virus cannot be defeated. The deep respiratory tract is the tissue that is exposed to the greatest risk of pneumonia^{7,8}. This is also called the hypoxic phase with urgent hospitalization. Heart and

clotting problems they are frequent, leading the patient to aggravate his clinical picture. Laboratory tests show a marked increase in pro-inflammatory molecules. Co-combined treatment of antiviral, oxygen and anti-inflammatory drugs is the ideal solution to treat these patients, the administration of low molecular weight heparin should always be used to prevent thromboembolic events^{9,10}.

Phase 3 (severe)

The third stage leads to the patient's death and is therefore the most serious. The hyperactive inflammatory state called Cytokine Storm (CS) quickly

leads the patient to respiratory distress syndrome (ARDS)^{11,12}. In this phase the values of the proinflammatory molecules (IL-2, IL-6, GCSF, TNF-alpha, D-dimer, ferritin, etc.) are very high with severe respiratory insufficiency and cardiac shock. Immunological therapies (corticosteroids, anti-interleukin 6, such as tocilizumab and sarilumab, IL-1 receptor antagonists such as anakinra or canakinumab, JAK inhibitors, convalescent plasma) are needed in this phase to reduce the inflammatory response triggered by cytokines. The prognosis is obviously very serious^{13,14}.

Table 1: Trials on going with colchicine in SARS-Cov-2 patients.(Clinicaltrials.gov)

Row	Study Title	Conditions
1	Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA)	Corona Virus Infection
2	The GREEK Study in the Effects of Colchicine in Covid-19	Corona Virus Disease 19 (SARS-Cov 2)
3	Colchicine Efficacy in COVID-19 Pneumonia	Corona Virus Infections Pneumonia Viral
4	The ECLA PHRI COLCOVID TRIAL	SARS-Cov-2 infection
5	Colchicine Counteracting Inflammation in COVID-19 Pneumonia (ColCOVID-19)	SARS-Cov-2
6	Treatment with colchicine of patients affected by Covid-19:a pilot Study"	SARS-Cov-2

Colchicine

Colchicine is a well-known drug and used in various therapies such as family Mediterranean fever (FMF) in which it has the greatest clinical success, in addition to traditional anti-gout use¹⁵. The anti-inflammatory properties of the drug make it suitable for its use in SARS-CoV-2 infection by interfering in the cascade of cytokines at different levels with multiple mechanisms. Binding the tubulin molecule and therefore inhibiting its polymerization as microtubules in neutrophils is the main mechanism of action, thus migration is inhibited. In addition, the formation of adhesion molecules is altered, leading to a strong inhibition of the interaction between white blood cells and endothelial cells. For these reasons, the anti-inflammatory effect has multiple mechanisms of action¹⁶. The beneficial effects in SARS-CoV-2 are probably due to the inhibition of IL-1, IL-6 and IL-18 because colchicine can interfere with the inflammatory protein complex NLRP3 which is primarily responsible for the release of cytokines.

The NLRP3 inflammasome is activated in various ways and has a major role in the development of the cytokine storm from SARS-CoV-2. Its upstream inhibition can be considered as prevention or treatment of SARS-CoV-2. Many clinical trials are currently underway to investigate the use of colchicine in positive Covid patients, as detailed in Table 1.

Colchicine (at a dose of 0.5-2 mg/day) is the gold standard drug in FMF prophylaxis¹⁷. Extending the use of colchicine to SARS-Cov2 is closely related to its main indication. FMF is an inherited autoinflammatory disease with febrile episodes (attacks) and severe inflammation. The use of colchicine (max 3 mg / day) is proven to have an efficacy in preventing inflammatory attacks¹⁸. Based on its safe and known tolerability profile after many years of clinical practice, this drug can be used both as monotherapy and in

combination in all three stages of coronavirus infection as shown in Table 2.

Table 2: Hypothetical timing of clinical pharmacological management of the inflammatory state in the SARS-Cov-2 patient

	Phase 1	Phase 2	Phase 3
COL	Prophylaxis	Treatment	Treatment
HCQ		Treatment	Treatment
TCZ/SAR		Treatment?	Treatment

Colchicine as monotherapy in phase 1 and for complications prevention in phase 2 or 3

The drug used in common doses, according to the existing literature that narrates the effective treatments in FMF, is a good remedy in phase 1 of the positive covid pathology. Practically a low initial dose (0.5 mg / day) can be used as a preventive method to avoid going to the next stages. This therapy can also be used in combination with antivirals to reduce virus replication pending the immune system's reaction to the infection. At standard doses colchicine, unlike other drugs, has a good tolerability profile and this is very important to combat the first phase where you must avoid administering immunosuppressants or glucocorticoids because they depress the immune system^{19,20}.

Colchicine as monotherapy or in combination for phase 2 treatment

This phase is crucial and therapy should be carefully decided based on the patient's clinical condition. Antivirals at this stage could have their use even if therapeutic interactions and adverse effects need to be monitored. Based on clinical analyzes, the variation in doses of colchicine is an appropriate strategy to be put in place: bring the dose of 0.5 mg twice a day if the patient is an adult with a body weight greater than 70 kg. Another therapeutic approach is the combination of colchicine always at 0.5 mg with hydroxychloroquine

in low doses to avoid toxic effects. Colchicine and hydroxychloroquine have synergistic action on inflammation and in addition there is also the antiviral action of hydroxychloroquine to support it in phase 2²¹. (Figure 1) The use of anti IL6 or anti IL1 or glucocorticoids should be considered based on the patient's clinical picture²².

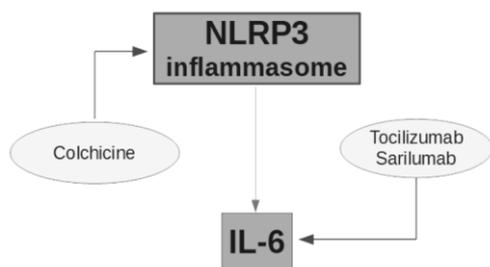


Figure 1: Pharmacological synergism of the association colchicine-chloroquine

Colchicine in association for phase 3 treatment

Slowing down or blocking the uncontrolled inflammatory response is the main objective of this pathological phase in which the release of cytokines occurs. Antiviral treatments are overshadowed and their benefits at this level are quite questionable as the risks of the benefits are high²³.

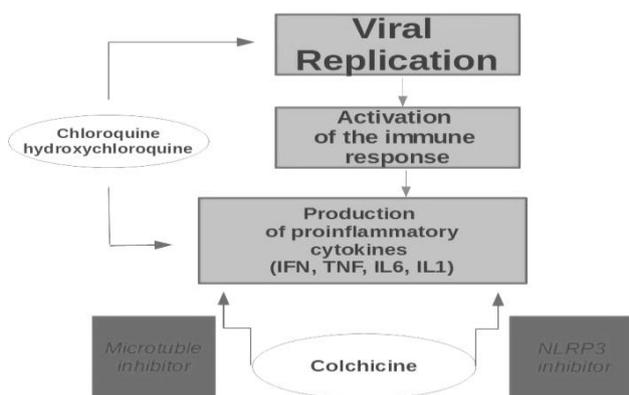


Figure 2: Pharmacological synergism of the association colchicine-inhibitors IL-6

Anti-inflammatory therapy must be further strengthened to avoid patient death. There are many anti-inflammatory drugs, including non-steroidal anti-inflammatory drugs, glucocorticoids, immunomodulators²⁴. While the use of glucocorticoids appears to be of little use also in relation to the dose to be used, the use of cytokine inhibitors such as tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist) have shown good efficacy in numerous studies even if precise efficacy doses have not been identified. The expert opinions of the past few months are constantly overlapping²⁵. The main concern, of course, is that immunomodulatory drugs increase the risk of infections and therefore there is the risk of delaying the elimination of the virus and risking the appearance of secondary infections. The IL-6 tocilizumab and sarilumab inhibitors have shown good anti-inflammatory efficacy and are therefore used in rheumatoid arthritis. In addition, on August 30, 2017, Tocilizumab was approved for cytokine release

syndrome in the United States and studies are underway to evaluate its use in FMF, just like colchicine²⁶. This we don't think is a coincidence. Colchicine (0.5 mg once or twice a day), alone or in combination with IL6 inhibitors to control CS, can make significant clinical progress²⁷. The advantage of colchicine compared to other drugs is represented by the inflammatory block upstream of all cytokines and not just one and also has a safe safety profile. The combination of colchicine and IL-6 inhibitors can show a synergistic action as shown in Figure 2 (15-28)²⁸.

CONCLUSION

SARS-CoV-2 infection can be divided into three phases, respectively: asymptomatic or slightly symptomatic incubation period with or without detectable viruses; slightly symptomatic period with the presence of viruses; severely symptomatic respiratory phase with high viral load and generalized hyperinflammatory state characterized by a sudden release of cytokines in the circulation defined as "cytokine storm" (CS). The combination of different drugs, at doses below monotherapy, may be the most effective and tolerable solution to change the patient's inflammatory state, particularly in the second and third phases.

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