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.

INTRODUCTION

At the end of 2019, a new coronavirus identified as SARS-CoV-2 was contracted in China and caused thousands of pneumonia results 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 asymptomatic 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 different3,4.

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 recovery2.

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 pneumonia3,4. This is also called the hypoxic phase with urgent hospitalization. Heart and
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 use. 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 action. The beneficial effects in SARS-CoV-2 are probably due to the inhibition of IL-1 beta, 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 cytokinin 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 prophylaxis. Extending the use of colchicine to SARS-CoV-2 is closely related to its main indication. FMF is an inherited autoimmune 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 attacks. 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 1: Trials on going with colchicine in SARS-CoV-2 patients. (Clinicaltrials.gov)

| Row | Study Title | Conditions |
|-----|-------------|------------|
| 1   | Colchicine Coronavirus SARS-CoV-2 Treatment (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 Countering Inflammation in COVID-19 Pneumonia (CoCOVID-19) | SARS-Cov-2 |
| 6   | Treatment with colchicine of patients affected by Covid-19: a pilot Study* | SARS-Cov-2 |

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 pathalogy. 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.

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 2. (Figure 1) The use of anti IL6 or anti IL1 or glucocorticoids should be considered based on the patient’s clinical picture.

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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