Clinical and phamacological analysis of Sars Cov 2: how combination therapy makes checkmate

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Abstract

Objectives:Literature data have shown that decreasing the SARS-CoV-2-induced hyperinflammatory state is essential for fighting the virus in an emergency and avoiding death. Many authors have divided the SARS-CoV-2 infection into three phases, of which the second and third are purely inflammatory. For this reason, while the development of antiviral drugs and vaccines is increasing, the best pharmacological goal is the decrease in proinflammatory molecules. Design: In phase 3, the most serious, there is an overdrive state of the immune system with consequent assault against all tissues and lung damage. Sars cov 2 pneumonia is characterized by "cytokine storm" and can lead to death. Acting in advance and with combination therapy aimed at blocking the inflammatory cascade can be effective. Results: Many drugs are being tested in evaluating these effects such as IL-6 or IL-1 inhibitors, chloroquine / hydroxycloroquine and colchicine which is proving its effectiveness especially in association in the last two stages of SARS-CoV-2 infection. modulating the inflammatory state and allowing to use an effective combined terepia with drugs at non-lethal dosages. Colchicine is considered safe and effective for the treatment and prevention of the cytokine storm in patients suffering from SARS-CoV-2 infection and is certainly an added remedy to other therapeutic agents with a safety profile superior to that provided by others. drugs. Conclusion:The aim of this study is to explain the pharmacological rationale behind the use of a combination therapy as an effective and safe remedy to decrease pneumonia and the consequent death from Sars CoV 2.

Summary box

1) What is already known on this subject? It has been shown that uncontrolled inflammation and cytokine storm can cause death from SARS-Cov-2. Blocking the release of cytokines and reducing inflammation in stages two and three of the infection can be curative for the patient.

2) What are the new findings? Colchicine blocks the upstream inflammatory cascade compared to IL6 and IL1 inhibitors such as tocilizumab / sarilumab and anakinra / canakinumab. It could also be considered as monotherapy or in combination with these drugs. 3) How could it have an impact on clinical practice in the near future? Using anti inflammatory and immunomodulatory drugs in the right doses and timing, avoiding drug interactions can control the delicate inflammatory/immune balance of the SARS-Cov-2 patient.

Keywords : colchicine, sars-cov-2, cytokine, interleukin, coronavirus, pneumonia

Introduction

The spread of SARS-CoV-2 has rapidly spread all over the world generating a pandemic that the whole world is fighting to stem it as soon as possible. The researchers studied the SARS-CoV-2 virus and it was discovered

that not all exposed people are infected and not all infected patients develop serious respiratory diseases. SARS-CoV-2 infection has been shown to be divided into three phases: phase 1, asymptomatic or mildly symptomatic incubation period that does not require hospitalization with or without detectable virus; phase 2, period not severely symptomatic with presence of the virus; phase 3, severe respiratory symptomatic phase with high viral load and generalized hyperinflammatory state. Phase 3 is the most serious and dangerous phase; generalized hyperinflammatory was caused by a sudden release of cytokines in the circulation defined as "cytokine storm" (CS) which leads to death from pneumonia.

These are three phases with increasing gravity and for each phase a specific treatment can be indicated or avoided, always personalized for the clinical characteristics of each individual patient.

1. *Phase 1 (or non-severe phase):* A non-serious phase lasting about 7 days and the immune system begins to react against the virus. If the immune response is not specific for breaking down the virus, disease progression occurs in the severe stages. Increasing immune responses could certainly be important together with the use of an antiviral to prevent virus replication. The antivirals used in this phase are remdesivir, lopinavir / ritonavir, chloroquine and hydroxychloroquine. If the infection is contained in this phase and the virus is defeated, it does not go to the next more serious phases.
2. *Phase 2 (moderate):* The second stage of infection begins when the immune system has been unable to defeat the virus and this has repercussions on the respiratory tract and lungs. In this phase, hospitalization begins and the administration of oxygen with probable heart problems and coagulation with a moderate increase in pro-inflammatory markers. The treatment that could be indicated is a continuous use of antiviral drugs, oxygen support and / or the use of anti-inflammatory drugs, antibiotics and the administration of LMWH- (Low-partial-weight-heparin) to prevent thromboembolic events.
3. *Phase 3 (severe):* The third stage is the most serious and pruned to the patient's death. At this stage there is a hyperactive and systemic inflammatory state called Cytokine Storm (CS) with limited respiration. In this phase the values of the inflammation markers (IL-2, IL-6, GCSF, TNF-alpha, D-dimer, ferritin, etc.) are very high. The patient may have severe respiratory failure and heart shock. Immunological therapies such as corticosteroids, anti-interleukin 6 (tocilizumab and sarilumab), IL-1 receptor antagonists (anakinra or canakinumab), JAK inhibitors are required at this stage. The prognosis for patients at this stage of the disease is very serious (1-13)

Colchicine and combination therapy

Colchicine is the drug of choice for family Mediterranean fever prophylaxis (FMF), in addition to its traditional use as a first-line anti-gout treatment. Its use in SARS-CoV-2 infection is based on the anti-inflammatory properties of the drug. Many studies indicate its powerful synergistic action in the treatment of the cascade of cytokines at different levels by decreasing inflammation through multiple mechanisms. The main mechanism of action is to inhibit its polymerization as tubulin microtubules in neutrophils. Furthermore, colchicine leads to a significant inhibition of the interaction between white blood cells and endothelial cells that interfere with their transmigration. However, the main mechanism of action for CS reduction in patients with SARS-CoV-2 is probably the inhibition of IL-1, IL-6 and IL-18 due to its interference with the inflammatory protein complex NLRP3. Upstream inhibition of inflammation NLRP3 can be considered as a new approach for the prevention or treatment of SARS-CoV-2 infection. Several clinical trials are currently moving to investigate the efficacy of colchicine in patients with SARS-Cov-2 infection, as detailed in Table 1.

	Study Reference	**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)

	Study Reference	Conditions
3	Colchicine Efficacy in COVID-19 Pneumonia	-Coronavirus Infections -Pneumonia, Viral
4	The ECLA PHRI COLCOVID TRIAL	- SARS-Cov-2

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

Based on the knowledge of colchicine and its tolerability profile known in other therapeutic areas, the use of this drug could be considered as monotherapy or in combination in all three phases of coronavirus infection, in the first phase as prophylaxis, in the second and third phase as block CS as shown in Table 2 and described below.

Figure 1 : *Hypothetical timing of clinical pharmacological management of the inflammatory state in the SARS-Cov-2 patient*

In phase 1, colchicine can be used in low initial doses (0.5 mg / day) as a preventive method to avoid going to phase two and / or three. The combined use with antivirals can lead to a synergy with a reduction in the viral load and wait for the reaction of the immune system against the infection. Used at standard doses, colchicine shows a good tolerability profile.

The second phase is the critical moment of the pathology. With the increase of proinflammatory markers, colchicine can be increased up to 0.5 mg twice a day if the patient is an adult with a body weight greater than 70 kg by monitoring the health of the liver and kidneys. Another approach is the use of a 0.5 mg dose of colchicine (as phase 1) in combination with hydroxychloroquine or interleukin inhibitors or heparin (for possible presence of thrombi) according to the patient's condition.

In the third phase, in full CS, the goal is to slow down or block the uncontrolled inflammatory response and avoid the patient's death. The use of cytokine inhibitors such as tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist) has demonstrated good efficacy and numerous studies are underway to test them even if they expose the patient to the risk of further infections.The choice of giving colchicine (0.5 mg once or twice a day) may still be the most appropriate choice, alone or in combination with IL6 inhibitors to control CS. The advantage of colchicine is that it acts upstream of the cytokine cascade and not only on a particular cytokine and has a higher safety profile. The synergy of action with IL-6 inhibitors and other drugs could be the solution to checkmate the virus by ending the patient's death (14-27).

CONCLUSIONS

The SARS-CoV-2 infection is characterized by three phases and the third leads to the death of the patient due to a strong inflammatory state that leads to lung collapse. This is due to a sudden release of cytokines in the circulation referred to as "cytokine storm" (CS). To date, there are still no effective antivirals that can prevent the evolution of this clinical picture and, pending better solutions, it is good to avoid the patient's death with the blockage of inflammation. This is shown by several studies that save the patient. Correctly managing the inflammatory / immune status of the infected patient takes on a priority role. The combined use of multiple anti-inflammatory and antiviral drugs can help in the three stages of SARS-CoV-2 infection, especially in patients at risk. The use of colchicine, for its good tolerability and safety, could be a winning move. In addition, the combined use of multiple drugs allows a safe and non-risky dosage compared to monotherapy and is certainly the most effective and tolerable solution to manage the patient's inflammatory state without leading to death.

MAIN STATEMENTS

I, the undersigned, Francesco Ferrara and any other author, declare that:

- We have no conflict of interest;
- We have not received funding;
- There are no sensitive data and no patients were recruited for this study;
- The document does not conflict with ethical legislation.

Regards

The authors

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