Cytokine storm and colchicine potential role fighting SARS-CoV-2 pneumonia.

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Abstract

For some patients with SARS-CoV-2, the worst clinical damage is not caused by the virus itself, but by an overactive inflammatory state. In fact, in some people the immune system goes into overdrive and launches a large-scale assault on the tissue known as cytokine storm. This excessive immune reaction can damage tissue and eventually kill people.
Several tests show that blocking such cytokine storms can be effective, studies are underway to test drugs that act by reducing cytokine response, such as tocilizumab and sarilumab that bind interleukin 6 (IL-6) or anikinra which is the interleukin 1 receptor antagonist (IL-1). However, other drugs that block the cytokine cascade can also be considered. In this article we describe the scientific and molecular motivation for the use of drugs that act by modulating the inflammatory system in patients with SARS-CoV-2, considering in particular an old drug that has been in use for many years for other therapeutic indications such as colchicine, and that could be favorable its use to block the cytokine cascade in SARS-CoV-2 patients, with low cost and good tolerability.

Introduction

In December 2019, an excessive number of cases of pneumonia caused by a newly identified coronavirus (SARS-CoV-2) occurred in Wuhan, China. This coronavirus quickly spread to China and other countries and received worldwide attention. SARS-CoV-2 is a β-coronavirus, which is surrounded by a non-segmented positive RNA virus and can lead to serious and potentially fatal respiratory tract infections. It has been found that the genomic sequence of SARS-CoV-2 shares 79.5% of the identity with SARS-CoV. The mechanism of virus penetration seems quite clear, using the angiotensin 2 conversion enzyme (ACE2), the same receptor as SARS-CoV, to infect humans.

Clinical characteristics of patients infected with SARS-CoV-2

Based on current evidence, the incubation period of the virus is 1-14 days, mostly 3-7 days. SARS-CoV-2 is contagious during the incubation period of the virus and probably even after it has been cured. It is highly transmissible in humans, and especially dangerous in the elderly and people with underlying diseases, and the European Sars Cov 2 virus is suspected to be even more aggressive than the Asian virus due to the mutations that have occurred. In most patients the symptoms are only a mild flu, while a smaller percentage rapidly develop acute respiratory distress syndrome, respiratory failure, multiple organ failure and, in the worst case scenario, death. (1-12)
The most common clinical manifestations are fever, cough, dyspnea. In addition, few patients have experienced gastrointestinal symptoms such as diarrhea and vomiting.
The elderly, immunodepressed or with pre-existing diseases (BPCO, heart disease, etc.) are more likely to rapidly develop acute respiratory distress syndrome, difficult to correct, more often associated with clotting dysfunctions, and multi-organ dysfunctions that eventually lead to death.
In severe patients, inflammatory factors such as IL-6, IL-10, IL-1, TNF-α increase, indicating the patient's compromised immune status.

In addition, in patients with worse outcomes, evidence has shown that patients have higher plasma levels especially of proinflammatory mediators such as IL-2, IL-7, IL-10 and granulocyte colony stimulation factor (GCSF) (13-43).

Inflammatory cytokine storm in patients with severe SARS-CoV-2

Cytokinic storm (CS) refers to a sudden, excessive and uncontrolled release of pro-inflammatory cytokines. CS syndrome can have several causes, such as infectious diseases or therapeutic treatments (e.g. CAR-T treatment). Clinically, it presents as systemic inflammation and multi-organ failure with high levels of circulating pro-inflammatory cytokines.
In infectious diseases, CS usually originates from the infected focal zone, in a patient infected with Sars Cov2 for example, the respiratory tract is the most at risk, spreading later through the circulation in the rest of the body. The accumulation of evidence has revealed that a percentage of patients with severe SARS-CoV-2 have a high cytokinic profile similar to SARS and MERS. Studies have reported that the main CS mediators are cytokines, IL-1, IL-6, IL-7, IL-8, IL-9, IL-10, granulocyte-macrophage colony stimulating factor (GM-CSF), IFNγ, granulocyte colony stimulating factor (G-CSF) and TNFα. In addition, studies seem to have confirmed that in the most seriously ill patients an increase in IL-6 and IL-1 levels in particular has been found (44-72). It is also possible that CS aggravates lung damage and leads to other fatal complications, such as pulmonary embolism. In the CS phase, the markers of systemic inflammation therefore appear to be extremely high. Therefore, blocking CS and knowing when to start anti-inflammatory therapy is essential to reduce the mortality rate of SARS-CoV-2. (73-79)

Therapeutic approaches to reduce cytokine storm

On the basis of the above it is obvious that one of the therapeutic strategies to be implemented is that of attenuating inflammatory responses and therefore updating from CS.
Undoubtedly, antiviral treatments are very important in the treatment of patients with SARS-CoV-2, although at the moment there is still confusion in this class of drugs on which may have the greatest effects. However, since CS has been shown to be relatively common in severe cases, anti-inflammatory therapy can help prevent further complications, multi-organ dysfunction and patient death. As we know, there are a variety of anti-inflammatory drugs, including non-steroidal anti-inflammatory drugs, glucocorticoids, immunomodulators.
The use of glucocorticoids is still a matter of debate, especially at what dose to administer and when! In contrast, the use of cytokine inhibitors such as tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist) has shown good efficacy, and several studies are underway to test them. .
Overall, the prognosis for this critical phase of the disease, such as that of CS in the positive Sars cov 2 patient, is serious, and immediate recognition and efficacy of therapies that decrease its intensity can be effective.
However, as with glucocorticoids, there are still many open questions, when to use immunomodulators, which doses, which patients? Only valid clinical trial protocols can answer these questions. All these questions are still the subject of intense debate and an uncommon answer in scientific opinion. The main concern, of course, is that immunomodulating drugs can delay the elimination of the virus by the immune system and, worse still, increase the risk of secondary infections, especially of the respiratory tract. Second, biological agents that plan to quote pro-inflammatory cytokines may only be inhibiting a specific inflammatory factor, and therefore may not be very effective in stopping CS in SARS-CoV-2, where other cytokines use to be those Importance. During the SARS epidemic of 2003, glucocorticoid was the primary drug of immunomodulatory therapy, however, there is no evidence of randomized clinical trials to support glucocorticoid treatment for SARS-CoV-2, although some evidence has shown that the benefit of using glucocorticoids is likely to outweigh the risks.

The Tocilizumab is a monoclonal antibody that blocks IL-6 and its mediated inflammatory response, and is widely used in rheumatic diseases, such as rheumatoid arthritis with an excellent efficacy profile. On August 30, 2017, Tocilizumab was approved in the United States for life-threatening cytokine release syndrome caused by chimeric T-cell antigen receptor (CART) immunotherapy. Recent evidence suggests the use of Tocilizumab in the treatment of severe or critically ill patients with SARS-CoV-2, with ongoing CS, also in combination with antiviral treatment. To date, several clinical safety studies and controls of Tocilizumab have been recorded in the treatment of the SARS-CoV-2 pneumonia tomb in hospitalized adult patients.
Sarilumab shares the same mechanism of action as Tocilizumab and has the same therapeutic indication for the treatment of rheumatoid arthritis, and they also share the same risk-benefit profile in the treatment of rheumatoid arthritis. It should be noted and stressed that the common side effects that occur in 1-10% of patients treated with these drugs are secondary upper respiratory tract infections, which could pose a major problem in positive SARS-CoV-2 patients. Emapalumab is an anti-interferon-gamma antibody (IFNγ) used for the treatment of hemophagocytic lymphohistiocytosis (HLH). Emapalumab binds and neutralizes IFN-γ, preventing it from inducing pathological effects, studies are underway to demonstrate its efficacy in patients with SARS-CoV-2.
Anakinra is a biopharmaceutical drug used to treat rheumatoid arthritis. It is a human interleukin 1 receptor antagonist. It also appears to be effective in the treatment of macrophage activation syndrome (MAS), a form of cytokine storm similar to CS. A study is currently underway to study the efficacy and safety of Emapalumab and Anakinra in reducing hyperinflammation and breathing difficulties in patients with SARS-CoV-2 infection. Chloroquine (CQ) and hydroxychloroquine (HCQ) are first-line drugs for the treatment and prophylaxis of malaria and are also used for the treatment of autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (LES). Studies have reported that QC / HCQ has a broad spectrum of antiviral effects on a variety of different viruses, such as human immunodeficiency virus (HIV), Marburg virus, Zika virus, dengue virus, Ebola virus. and the SARS-CoV-1. (79-97)

Colchicine

Colchicine is used for the treatment of gout, Behçet's disease, prevention of pericarditis and familial Mediterranean fever, Sweet's syndrome, scleroderma, amyloidosis. It is taken orally for the treatment of these pathologies. Probably the most effective results of colchicine treatment have been obtained in the prophylaxis of familial Mediterranean fever.
The scientific hypothesis of the use of colchicine in SARS-CoV-2 is based on the anti-inflammatory properties of the drug. Recently published data on colchicine seem to suggest a potential synergy in the treatment of the cytokine storm cascade at different levels. In fact, colchicine works by decreasing inflammation through multiple mechanisms. The main mechanism of action is to bind the tubulin molecule and therefore inhibit its polymerization into microtubules.
In particular, its anti-inflammatory effect has been attributed to its breakdown of microtubules into neutrophils, thus inhibiting their migration. Furthermore, it can alter the distribution of adhesion molecules on the surface of neutrophils and endothelial cells, leading to a significant inhibition of the interaction between white blood cells and endothelial cells that interfere with their transmigration. Therefore, there is growing evidence that colchicine's anti-inflammatory effect is multifaceted. Probably the main mechanism of action for the reduction of the cytokine cascade in patients with SARS-CoV-2 is the inhibition of IL-1, IL-6 and IL-18 which interfere with the inflammatory protein complex NLRP3,6-8 which it is increasingly recognized for its role in acute coronary syndrome, in crystal-induced gout and especially in recurrent idiopathic pericarditis (**Figure** 1).

Figure 1: *mechanism of action of colchicine*

Colchicine then accumulates in white blood cells and affects them by decreasing motility, loosening chemotaxis and adhesion. It also inhibits the production of superoxide anions, stops the degranulation of mast cells. It is important to note that previous studies have shown that viroporin E, a component of coronavirus associated with SARS (SARS-CoV), forms ion channels permeable to Ca2C and activates inflammation of NLRP3. In addition, another viroporin 3a was found to induce the activation of NLRP3 inflammation. The mechanisms are unclear. Colchicine counteracts the increased inflammation of NLRP3, thereby reducing the release of IL-1b and a number of other interleukins, including IL-6, which form in response to warning signs. Several clinical trials are currently underway to study the efficacy of colchicine in patients with SARS-Cov-2 infection, as shown in Table 1. (97-137)

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	-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)*

Conclusion

Inflammation is an indispensable part of an effective immune response, without which it is difficult to successfully eliminate an infectious agent. The inflammatory response begins with the initial recognition of a pathogen, which then mediates the recruitment of immune cells, eliminates the pathogens and ultimately leads to tissue repair and return to homeostasis. However, some viruses such as SARS-Cov-2 induce an excessive and prolonged cytokine response, known as "cytokine storms", which results in high morbidity and mortality. Therefore, therapeutic interventions targeting these pro-inflammatory cytokines could be useful to improve undesirable inflammatory responses. In addition, since high viral titers in the early and later stages of infection are strongly related to the severity of the disease in humans, strategies to control viral load and attenuate the inflammatory response may be useful. In conclusion, SARS-CoV-2 is a viral infectious disease that mainly manifests itself in fever and pneumonia, and antiviral therapies are certainly the mainstream, but we believe that treatments that reduce the cytokinic response may be effective especially for more severe cases. In this way, biological agents targeting pro-inflammatory cytokines can only inhibit a specific inflammatory factor, and therefore may not be very effective in stopping CS in SARS-CoV-2 where other cytokines may be of significant importance. The colchicine could result in a therapeutic treatment that acts upstream of the cytokine cascade IL6 and IL 1, bringing more benefits, it is also a low cost and if used at the right doses with a good tolerability profile. In addition there is a fundamental aspect to add, biological drugs (such as tocilizumab, sarilumab etc..) can, with reference to the RCP of the drugs, cause with a 'common' frequency secondary infections of the respiratory tract and therefore compromise paradossally the clinical situation of patients infected SARS-CoV-2, therefore clinical evidence is needed to clarify their possible use and on

which target of SARS-CoV-2 patients. For colchicine, however, with reference to the RCP and the clinical and pharmacovigilance data, the risk of upper respiratory tract infections may not be an issue. However, given the viral nature of SARS-CoV-2, and considering a substantial impairment of the host's immune system in severe cases, it is essential to balance the risk/benefit ratio before starting anti-inflammatory therapy. In addition, early anti-inflammatory treatment initiated at the right time is of paramount importance and should be tailored to the individual patient to achieve the most nevertheless, this would be an interesting area for future research favourable effects from clinicians derived from ongoing trials will answer our questions.

Main statements

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

- I 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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