SARS-CoV-2: Viral Mechanisms and Possible Therapeutic Targets – What to learn from Rheumatologists?

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Sources of support in the form of grants or industrial support

There were no grants or industrial support.

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Key Words

SARS-CoV-2, Cytokine Storm, COVID-19, coronavirus, macrophage activation syndrome, hemophagocytic lymphohistiocytosis

COVER LETTER:

All authors confirm that the article has not been published and is not under consideration for publication elsewhere;

All authors confirm that there are no financial or other relationships that could lead to a conflict of interest;

All authors confirm that the manuscript has been read and approved by all of them.

All authors declare that ethics approval for this type of study is not required.

All authors agree with the policy of this journal.

It was with great interest that we read the letter from Randy Cron and collaborators [1] linking the cytokine storm syndrome (CSS) seen in macrophage activation syndrome, common in the rheumatological setting, with the CSS postulated to be a background in the novel coronavirus (SARS-CoV-2) infection. Amid the high contagiousness of the virus, science was also infected by an infodemia, compelled to enter a race to find effective therapies studying mechanisms molecular aspects of SARS-CoV-2 concomitant to urgent bedside manage of patients.

Molecular evidence has shown that SARS-CoV-2, by using the angiotensin-converting enzyme 2 (ACE2) [2], enters in alveolar epithelial and endothelial cells, as well as macrophages. The TMPRSS2 protease induces virus-cell membrane fusion at the cell surface and facilitate entry of coronaviruses into the host cell [3]. Once the COVID-19 enters the cell, it utilizes the RNA polymerases and protease inhibitors to synthesize and secrete a mature virion [2]. After that, the virion interacts with toll-like receptors (TLR) causing an imbalance in the pro and anti-inflammatory cytokines [2,4]. In addition to TLR, the enzyme AP-2-associated protein kinase 1 (AAK1) works in viral cellular entry with JAK–STAT pathways, contributing for this process [2].

Those molecular interactions may result in the secretion of countless cytokines like IL-6, IL-1β and IFN-γ, depending on the patient's immune status. According to some studies [5], the severity of the disease can be signaled by identifying this storm of cytokines, suggested by laboratory characteristics like lower white cell and platelets count, and high C-reactive protein (CRP), lactate dehydrogenase (LDH) and ferritin levels, all similar to hemophagocytic lymphohistiocitosis (HLH)[1]. In this stormy stage, drugs that decrease viremia may not be as effective [4], and minimizing the damage caused by the inflammatory process should be prioritized. Although the inflection point between viremia and inflammatory response is a continuum process, the fact that immunosuppressed patients (e.g. rheumatic and post-transplant patients) in previous pandemics [10] did not evolve to the unfavorable outcome with a high frequency as we imagined, signals that we can, through molecular analyzes of the virus-cell relationship, identify specific therapeutic targets at different stages of the disease.

Therefore, understanding the virus-cell interaction and the binomial viral load and immune response, can help us to make better choices between the different therapeutic strategies for different phases of the disease (table 1). That´s why the study of inflammatory pathways seems to be an assertive choice on the pursuit of an efficient and safe target for SARS-CoV-2, avoiding discarding a possible effective treatment simply because it has been tested at an unsuitable stage. Indeed, biological plausibility, despite its little applicability in real life due to *in vivo* variables not considered *in vitro*, is still a good starting point for scientific development. When chaos is imposed and there is an urgent need for quick answers, the best evidence, with all its flaws, is usually intuition and prior

knowledge. Balancing them with the security required by the *primum non nocere* principle is the essence of the medical bedside care. This pandemic can rescue science from the fallacy of the idea that its function is to predict the future and be the owner of the truth. In fact, science is based on uncertainty. As the physicist Cesar Lattes wisely said "Science cannot predict what will occur. It can only calculate the probability of something happening". So, time will tell whether today's science is right or wrong.

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Table 1 – Biological Plausibility and Therapeutic Options

Viral Mechanism	Drug Rationale	Suggested Therapy	Current Research Status
The SARS-COV-2 after entering the cell, utilizes the cellular machinery to synthesize and secrete a mature virion [2].	Inhibition of RNA polymerase and protease.	inhibitors of RNA polymerase (e.g. remdesivir and favipiravir) and protease inhibitors (*e.g.* lopinavir and ritonavir)	Primary studies with lopinavir/ ritonavir did not show clinical improvement or reduction in mortality [2]. The use of Remdesivir in rhesus macaques infected with SARS-CoV-2 was effective in reducing clinical disease and lung damage [6].
The TMPRSS2 protease cleaves coronavirus fusion glycoproteins (called spike proteins) which induces virus-cell membrane fusion at the cell surface and facilitate entry of coronaviruses into the host cell [3].	Inhibition of TMPRSS2.	Camostat mesylate.	Although, there are studies suggesting its off-label use [3]. There are yet no clinical trials specifically testing these drugs.
The mature virion interacts with toll-like receptors (TLR) to stimulate inflammatory pathways and regulate the production of pro-inflammatory cytokines. [4]	Inhibition of endosomal TLR activation.	Chloroquine and hydroxychlo-roquine.	Some studies showed no effectiveness [4] while others showed reduction in the recovery time for cough and fever [7].
Janus kinases 1 and 2 are implicated in inflammation pathways, and the enzyme AP-2-associated protein kinase 1 (AAK1) works in viral cellular entry. [2]	Inhibition of JAK 1/2 (and consequently) AAK1.	Baricitinib.	A small, open-labeled, no randomized, pilot study with patients presenting moderate COVID-19 pneumonia showed that in the baricitinib-treated group, all clinical characteristics and respiratory function parameters significantly improved when compared to baseline [8].
IL-6 production through TLR. IL-6 induces lung inflammation, fever and fibrosis. [9]	IL-6 inhibition.	Tocilizumab, Sarilumab.	A small retrospective study observed that symptoms, hypoxemia, and CT opacity changes were improved short after the treatment with tocilizumab (IL-6 blocker), suggesting that inhibition of IL-6 pathway could be an efficient target for the treatment of COVID-19 [9].