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Letter

SARS-CoV-2: Viral Mechanisms and Possible Therapeutic Targets — What to Learn from Rheumatologists

To the Editor:

It was with great interest that we read the editorial by Drs. Cron and Chatham[1] linking the cytokine storm syndrome (CSS) seen in macrophage activation syndrome, common in the rheumatological setting, with a CSS postulated to be a background in the novel coronavirus (SARS-CoV-2) infection. Amid the high contagion of the virus, science was also infected by an infodemic, compelled to finish the race to find effective therapies, while physicians managed real-world patients.

Molecular evidence has shown that SARS-CoV-2, by using the angiotensin-converting enzyme 2[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 facilitates entry of coronaviruses into the host cell[3]. Once the coronavirus disease 2019 (COVID-19) enters the cell, it uses 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 antiinflammatory cytokines[2,4]. In addition to TLR, the enzyme AP-2–associated protein kinase 1 works in viral cellular entry with Janus kinase and signal transducer and activator of transcription (JAK-STAT) pathways, contributing to this process[2].

Those molecular interactions may result in the secretion of countless cytokines such as interleukin (IL)-6, IL-1β, and interferon-β, 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 such as lower white cell and platelet count, and high C-reactive protein, lactate dehydrogenase, and ferritin levels, all similar to hemophagocytic lymphohistiocytosis (HLH)[1]. In this stormy stage, drugs that reduce viremia may not be as effective[4], and minimizing the damage caused by the inflammatory process should be prioritized. We saw in previous pandemics[6] that immunosuppressed patients (e.g., rheumatic and post-transplant patients) did not evolve to the unfavorable outcome as frequently as expected, strengthening the rationale that immunosuppression may be the key. Yet it should be kept in mind that the inflection point between viremia and inflammatory response is a continuum. This signals that we may be able to, through molecular analyses 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 from among the different therapeutic strategies for different phases of the disease

Table 1. Biological plausibility and therapeutic options.

Viral Mechanism	Drug Rationale	Suggested Therapy	Current Research Status
The SARS-CoV-2 after entering the cell, uses the cellular machinery to synthesize and secrete a mature virion[2].	Inhibition of RNAP and protease	Inhibitors of RNAP (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[7].
The TMPRSS2 protease cleaves coronavirus fusion glycoproteins (called spike proteins), which induces virus–cell membrane fusion at the cell surface and facilitates entry of coronaviruses into the host cell[3].	Inhibition of TMPRSS2	Camostat mesylate	There are no clinical trials specifically testing these drugs as yet, although there are studies suggesting its off-label use[3].
The mature virion interacts with TLR to stimulate inflammatory pathways and regulate the production of proinflammatory cytokines[4].	Inhibition of endosomal TLR activation	Chloroquine and HCQ	Some studies showed no effectiveness[4] while others showed reduction in the recovery time for cough and fever[8].
JAK 1 and 2 are implicated in inflammation pathways, and the enzyme AAK1 works in viral cellular entry[2]. showed	Inhibition of JAK 1/2 (and consequently) AAK1	Baricitinib	A small, open-label, non-randomized pilot study with patients presenting moderate COVID-19 pneumonia that in the baricitinib-treated group, all clinical characteristics and respiratory function variables significantly improved when compared to baseline[9].
IL-6 production through TLR. IL-6 induces lung inflammation, fever, and fibrosis[10].	IL-6 inhibition	TCZ, sarilumab	A small retrospective study observed that symptoms, hypoxemia, and CT opacity changes were improved shortly 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[10].

RNAP: RNA polymerase; TLR: Toll-like receptors; HCQ: hydroxychloroquine; JAK: Janus kinase; AAK1: AP-2–associated protein kinase 1; COVID-19: coronavirus disease 2019; IL: interleukin; TCZ: tocilizumab; CT: computed tomography.

(Table 1[7,8,9,10]). Thus, the study of inflammatory pathways seems to be an assertive choice in the pursuit of an efficient and safe target for SARS-CoV-2. It prevents the disposal of a possibly effective treatment simply because it has been tested at an unsuitable stage. Indeed, biological plausibility, despite its limited applicability in real life due to *in vivo* variables not considered *in vitro*, is still a good starting point for scientific development. When chaos exists 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 medical bedside care. This pandemic can rescue science from the fallacy that its function is to predict the future and be the owner of the truth. In fact, science is moved by 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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