Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The "Perfect Cytokine Storm" of COVID-19

To the Editor: I have read with great interest the recent article by Vijayvargiya et al,[1] which was published in *Mayo Clinic Proceedings*. Many of the deaths caused by severe acute respiratory syndrome coronavirus 2 are in patients older than 55 years of age, who develop acute respiratory distress syndrome (ARDS).

At the histological level, ARDS is characterized by an intense inflammatory response occurring in the lungs of patients.[2] Human aging is associated with an up-regulated inflammatory response.[3]

Inflammation is involved in the mechanisms underlying the pathogenesis of several age-associated diseases such as cardiovascular disease, type 2 diabetes, Alzheimer disease, Parkinson disease, rheumatoid arthritis, and osteoporosis.

Elderly individuals have lost the ability to control and contain inflammatory processes to the same degree of which younger individuals are capable. The innate immune system plays a central role in inflammation and is also key in its ability to slow down and arrest inflammatory processes. Interleukin-10 (IL-10) and C1-esterase inhibitors are 2 molecules that help contain and slow down inflammatory processes, whereas IL-6 promotes and intensifies inflammation (though it also has some anti-inflammatory properties in muscle cells). Given the up-regulation of inflammatory processes with aging, it is not surprising that ARDS is usually more severe and more lethal in the elderly. COVID-19 triggers a "cytokine storm" that involves multiple organ systems. In the kidneys, it leads to renal insufficiency and failure, and in the vascular system, it causes a vasculitis, which is at first visible as pernio or chilblain lesions in the toes ("coronavirus toes") but that can involve also large blood vessels. The central nervous system is not spared, resulting in headaches, altered mental status, confusion, or inability to arouse, as well as the loss of the sense of smell, which is reportedly one of the early symptoms of the disease. Thirty-six percent of patients had some type of neurological symptom. On the mild end of the spectrum, people commonly had the loss of taste and smell. Headache was reported in 13% of patients; dizziness was observed in about 17%; and muscle inflammation and nerve pain occurred in about 19%. Autopsy reports have revealed brain tissue edema and partial neuronal degeneration in deceased patients. To effectively treat the cytokine storm, tocilizumab (Actemra) has been used to block the proinflammatory action of IL-6 and seems to have been helpful in anecdotal cases (3 patients treated in Italy). C1-esterase inhibitor (Berinert, Cinryze, and Ruconest) could also be tested to see whether it is capable of slowing down the inflammatory response. But these are expensive medications and difficult to produce rapidly in quantities. Using them to treat tens of thousands of patients may prove impossible because of cost and logistics. Interleukin-10 is another anti-inflammatory molecule that could be tested, and it could be administered via a gene therapy approach using naked plasmid DNA vectors[4] engineered to produce IL-10 inside the recipient cells, thus reducing cost and simplifying production. It would be more cost-effective for treating many thousands of patients.

COVID-19 infection involves multiple organs and systems, with symptoms developing rapidly over 2 to 14 days. Most infections however produce mild or minimal symptoms, and up to 80% of persons infected may have mild disease or even be asymptomatic. Reports from Italy indicate that some individuals continue to have positive nasal swab tests for COVID-19 for at least 50 days after their initial positive test and after having apparently recovered from the illness. There is one case of a person who has had positive nasal swab test results for 57 days. This raises the possibility that some individuals, after recovering from their illness, may become asymptomatic carriers of the virus for extended periods of time, further complicating efforts to contain the pandemic and requiring that patients be tested after their recovery to make sure they clear the virus. This means that antiviral therapies and vaccines will be needed. Countries need to invest in technologies such as DNA vaccines[5] and antiviral gene therapy strategies such as RNA Interference (RNAi) technology, which is an ideal tool to inhibit viral replication in host cells as small interfering RNA can interact with certain viral genes and silence their expression.[6] DNA-based therapeutics can be developed immediately after a virus DNA sequence becomes known. Modular plasmid vectors could be created that allow to switch one viral sequence for another and produce a new vaccine with minimal manipulation. The same applies to RNAi vectors. These strategies are also likely to be much more cost-effective than other methods, a consideration that becomes important as the population needing treatment expands.

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We need to develop detailed protocols now on how to quickly produce vaccines and antiviral therapies that can be adapted to future viral pandemics. We also need to develop protocols for the most effective containment and mitigation strategies so that they can be implemented without hesitation in future emergencies.

Alessandro Testori, MD, PhD
Immunoe Health Centers
Longmont, CO

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ORCID
Alessandro Testori: https://orcid.org/0000-0002-3259-7695

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In reply—The "Perfect Cytokine Storm" of COVID-19

We read with great interest the letter by Testori regarding our review article.[1] Testori pointed out the important association of proinflammatory cytokines in the pathogenesis of coronavirus disease 2019 (COVID-19), which could account for the worse outcome in older individuals. Strategies to combat the proinflammatory state, using multiple investigational compounds, are in the pipeline as potential treatment modalities for COVID-19.

In France, the Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients (CORIMUNO-19) platform was designed and set up as a series of multicenter randomized controlled trials (RCTs) to evaluate the efficacy of immunomodulators and other treatments of COVID-19. As part of this platform, one open-label RCT, CORIMUNO-TOCI, found that the use of tocilizumab, an interleukin-6 receptor inhibitor, was associated with a lower ventilation requirement (invasive or noninvasive) or death at day 14. However, the final report of this RCT has not yet been released for peer review.[2] As mentioned in our review article, there are several other RCTs that are currently being conducted to assess interleukin-6 inhibition in COVID-19.

An artificial intelligence platform, BenevolentAI, identified baricitinib, a Janus kinase inhibitor, as another potential option to battle the cytokine storm associated with COVID-19.[3,4] In addition to its anti-inflammatory properties, baricitinib can have antiviral properties by preventing the adaptor-associated protein kinase 1 and cyclin G-associated kinase–mediated endocytosis of the virus. Baricitinib will be tested as one of the drugs in the National Institute of Allergy and Infectious Diseases Adaptive COVID-19 Treatment Trial (ACTT). As we emphasized in our review article, the appropriate timing for the use of these anti-inflammatory agents will be critical. It is important to reiterate that the host inflammatory response plays a vital role in the immune defense against the infection, and curbing the inflammatory state may decrease the response mounted by the host's immune system.

Since the online publication of our review, the investigational RNA-dependent RNA inhibitor remdesivir has been granted emergency use authorization by US Food and Drug Administration on the basis of preliminary data obtained from the ACTT. The press release of this trial stated a 31% faster time to recovery in the remdesivir arm compared with placebo (11 days vs 15 days, respectively; $P<.001$).[5] The scientific community is eagerly awaiting the release of the clinical trial results. Interestingly, another study, conducted in China, did not find any clinical benefit with remdesivir use. There was no difference in 28-day mortality between the 2 groups, and the degree of viral decline was similar. However, this study was underpowered to detect significant differences because of low accrual as a result of the decline in severe acute respiratory syndrome coronavirus 2 infection rates.[6]

The author highlighted the recent reports of prolonged detection of severe acute respiratory syndrome coronavirus 2 in some individuals. However, the presence of viral nucleic acid in respiratory samples can be a reflection of nonviable genetic material. The viability of the virus material in these patients has not been conclusively established. Nonetheless, we agree with his comment that there is an urgent need for the development of antiviral therapies and vaccines. Indeed, there are many parallel and collaborative efforts to advance this goal, at an extraordinary pace, and some using novel RNA interference- and plasmid DNA–based approaches. In the meantime, multicenter trials such as World Health Organization's Solidarity Trial, National Institute of Allergy and Infectious Diseases ACTT, and European CORIMUNO-