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Hypothesis

COVID-19-associated Cytokine Release Syndrome and Autologous Conditioned Serum: A Hypothesis

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Abstract

Coronavirus disease 2019 (COVID-19) is a rapidly progressing pandemic causing death worldwide, particularly in individuals with comorbidities or in the elderly population. The increased pro-inflammatory cytokines in patients with severe COVID-19 can be considered macrophage activation syndrome or a cytokine storm. It has been reported that an autocrine loop of interleukin (IL) 1 beta (IL-1β) over-secretion leads to a cytokine storm of IL-6, IL-18, ferritin, interferon-gamma, *etc.* from macrophages. Several features of COVID-19, such as the cytokine profile including pro-inflammatory cytokine levels, subsets of immune cells, serological markers, and clinical symptoms resemble a cytokine storm commonly triggered by viral infections. Although the pathophysiology and management of severe COVID-19 remains uncertain, the use of an easily obtained autologous anti-inflammatory cocktail, termed autologous conditioned serum (ACS), can be hypothesized. ACS consists of a variety of anti-inflammatory cytokines, including mainly IL-1 receptor antagonist (IL-1Ra; as much as 140-fold greater than plasma), and several growth factors. Post-mortem findings of COVID-19 patients reveal that the main pathological events are localized to the alveoli. Therefore, administering ACS via the same pathway as the viral trigger may have a positive impact on treatment. ACS should be discussed for the management of COVID-19 to target and lessen the overactive immune response while still allowing time for the host immune system to clear the virus. To balance the cytokine storm, it could be suggested to administer ACS by the same pathway as the viral trigger, using a nebulizer to directly reach the most intensely affected location: the alveoli.

Introduction

The novel coronavirus disease defined as COVID-19 by the World Health Organization was first seen in Wuhan, a city in the Hubei Province of China.[1] It has spread rapidly, and by early May 2021 there were nearly 153 million confirmed cases and nearly 3.2 million confirmed deaths throughout the world.[1] COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to the β-coronavirus group and is the third coronavirus strain discovered to date that can cause zoonotic diseases.[2] The other two strains are SARS-CoV and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV).[2] SARS caused by SARS-CoV first occurred in China in 2002, and spread to 29 countries in 2003 through a travel-related global outbreak, with 8,098 cases and a fatality rate of 9.6%, whereas MERS first occurred in Middle East with a case fatality rate close to 35%.[3] The mortality rates of MERS and SARS are higher than COVID-19; however, MERS and SARS are not as easily transmitted from person to person as COVID-19.[2] Despite the low case mortality rate, the number of deaths caused by COVID-19 has already exceeded the sum of the deaths due to SARS and MERS.[2] It is uncommon for animal coronaviruses to be transmitted from animals to humans and cross the species barrier in a phenomenon called spill-over.[4] When considering the seasonal flu, reports on COVID-19 indicate that this virus is less virulent than influenza

Keywords: COVID-19; Biological products; Anti-inflammatory agents; Interleukin 1 receptor antagonist protein.

Abbreviations: ACS, autologous conditioned serum; IL, interleukin; IL-1β, interleukin 1 beta; IL-1Ra, interleukin 1 receptor antagonist; OA, osteoarthritis; SARS-CoV, severe acute respiratory syndrome coronavirus; sHLH, secondary haemophagocytic lymphohistocytosis.

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viruses. However, we need to take into consideration that human beings have a long history of exposure to influenza viruses, which has ensured that the majority of humans possess a certain degree of immunity against influenza viruses, but this is not the case with COVID-19.[4] So, unlike common viral agents, SARS-CoV-2 does not seem to cause greater disease severity, but the lung tissue damage during infection seems to be worsened by the host innate immune response.[5]

COVID-19 can affect all age groups but is more severe in the elderly population and those with chronic diseases. As the pandemic months pass, acquired experience summarizes COVID-19 as a serious, highly variable and often extremely persistent disease, and optimal therapeutic approaches inevitably require the pathogenesis to be understood.[6] A cytokine storm caused by a failure in the host immune system is held responsible for the disease severity in certain patients with an unknown cause.[5] In particular, based on post-mortem pathologies, the main cause of lung tissue damage has been reported to be caused by excessive inflammation, rather than the direct damaging effect of the virus itself.[4] In other words, it may be an exaggerated overactive response of the immune system to protect the host that is responsible for severe pneumonia, and consequently the development of acute respiratory distress syndrome (ARDS).[4,7] Aside from inflammation, COVID-19 has a clear vascular component, and endothelitis has been observed in the lungs of patients who died. This is a unique feature of the disease, underscoring that SARS-CoV-2 can infect and inflame endothelial cells, which can increase blood vessel permeability.[8] During this COVID-19 pandemic, many drugs and therapeutic modalities have been used in an attempt to treat the particularly severe forms of the disease. Until now, many studies have demonstrated the importance of anti-inflammatory therapies in severe COVID-19. Various approaches are currently being used to treat the observed cytokine storm associated with COVID-19, and expectations are particularly high for new cytokine-targeted therapies, such as tocilizumab (recombinant humanized anti-human IL-6 receptor monoclonal antibody), anakinra (recombinant human IL-1 receptor antagonist), and baricitinib (selective inhibitor of Janus kinase).[9] Although a number of studies have been conducted with anti-inflammatory treatments for severe COVID-19, there are still no specific recommendations regarding which drugs should be used for which patients and when they should be administered.[9] Due to the cytokine storm, which includes the disease mechanism and the steps involved in treatment, it is a complicated network of factors. In fact, it is still not known exactly why the immune deficiency occurs or what causes it.

Autologous conditioned serum (ACS) is obtained through the incubation of whole blood for a certain period of time, which is then taken into a tube containing sterile medical grade glass beads and centrifuged. ACS was developed by Wehling *et al*.[10,11] in the mid-1990s as an expeditious, practical, and relatively inexpensive means of generating interleukin (IL) 1 receptor antagonist (IL-1Ra) for local, therapeutic application in musculoskeletal diseases. ACS is based on studies that found that macrophages and monocytes are major endogenous sources of IL-1Ra, and production of IL-1Ra can be enhanced by a variety of stimuli, including adhesion to certain surfaces such as glass beads.[10,11] Therefore, the prepared ACS contains a rich content of anti-inflammatory cytokines and growth factors, particularly IL-1Ra.[12] It is well known that IL-1 is a key component that stimulates the synthesis and upregulation of prostaglandins, oxygen radicals, and cytokines that initiate and mediate the inflammatory cascade. ACS has a fairly rich concentration of IL-1Ra that competitively binds to the IL-1 cytokine receptor without triggering any cellular effects, unlike steroids.[12]

Hypothesis: use of an anti-inflammatory biological cytokine cocktail to balance the overactive inflammatory response of COVID-19

The data obtained during past and present outbreaks suggest that SARS-CoV-2 tends to infect lower parts of the respiratory system (bronchioles and alveoli), unlike other common human coronaviruses, and causes severe pneumonia in 15–20% of cases.[4,13] The concern behind COVID-19 is the absence of memory cells in the immune system, which leads to an inability to turn off the innate inflammatory response, eventually causing pro-inflammatory molecules to flood into the lungs. For reasons that remain unclear, in a subset of the population this cytokine storm results in alveolar pneumonitis and/or interstitial pneumonia, which can be severe enough to damage most of the lung tissue and cause hypoxia and respiratory disturbance.[4]

Physicians in China and other countries have started to administer potent cortisone-based anti-inflammatory drugs to critically ill patients. It has been observed that this strategy is not effective to stop the progression of the tissue-damage due to pneumonia because of the systemic cellular effects of steroids.[4] Importantly, what we need is to prevent or balance the excessive inflammatory response without impeding the protective cellular activity of the host immune system via the blood. This may be achieved by administering an anti-cytokine mixture through the same passageway as the virus to accomplish optimal penetration at the location most needed, where the virus-cell encounter is most intense and without disturbing the protective cellular effects of the immune system.

Incubation of human whole blood samples with medical-grade glass beads exposed to chromium sulfate stimulates the production of IL-4, IL-10, and IL-1Ra as well as fibroblast growth factor-1, hepatocyte growth factor, and transforming growth factor-beta 1, resulting in higher concentrations of those cytokines and factors in human ACS.[14] The increase in these anti-inflammatory mediators does not appear to be accompanied by an increase in the pro-inflammatory cytokines IL-1β or tumor necrosis factor-alpha.[14] ACS is administered locally to treat conditions in which IL-1 is thought to be an important mediator of the pathological condition.[15]

ACS, an inexpensive and easily prepared material obtained from the patient's own blood, may provide those same effects if administered via a nebulizer. If this hypothesis holds true, it can be postulated that the management of critically ill COVID-19 patients with marked pro-inflammatory changes may include the administration of a serum rich in anti-inflammatory cytokines, obtained from the patient's own blood and following simple steps of incubation and centrifugation, via the airway by aid of a jet nebulizer.

It may be hypothesized that the immunomodulatory properties of ACS may be used in COVID-19 patients as a nebulized therapeutic strategy to balance the excessive immune response in the respiratory system via the same route as the causative virus.

Evaluation of the hypothesis

The preparation of ACS

The history of ACS began when Meijer *et al*.[16,17] first developed a novel method for increasing the production of IL-1Ra and other anti-inflammatory molecules from the blood. According to this method, fresh blood (60 mL) is drawn into a syringe containing 200 medical grade borosilicate glass beads (2.5 mm in diameter; 21 mm^2 surface area) that were exposed to chromium sulphate as

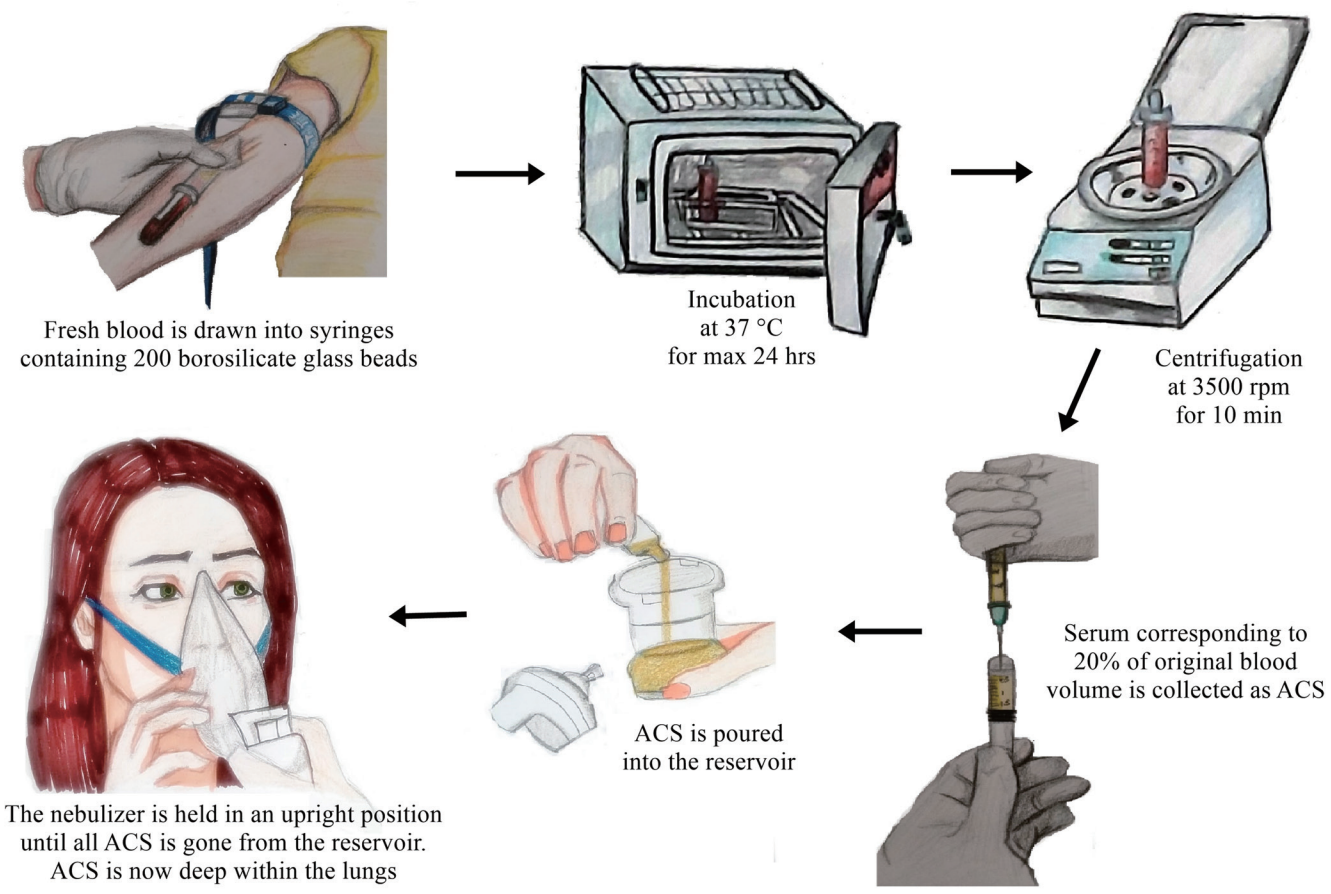

Fig. 1. A diagram for the preparation and administration of autologous conditioned serum (ACS).

a method to attach the blood monocytes and other adherent cells to stimulate the production of an anti-inflammatory cocktail (Fig. 1).[15,16] Subsequently, the syringes are incubated aseptically at 37°C with 5% CO_2 for a maximum of 24 hours. After incubation, the serum is retrieved for centrifugation at 3,500 rpm for 10 minutes. Next, the serum (approximately 10 mL; ~20% of the total original blood volume) is collected as ACS.[16]

The content of ACS

During the whole blood incubation period, platelets begin to secrete preformed granules and mononuclear cells synthesize and secrete IL-1Ra along with a variety of additional anti-inflammatory cytokines (IL-4, IL-10, IL-13) and growth factors (epidermal growth factor, vascular endothelial growth factor, hepatocyte growth factor, insulin-like growth factor 1, and platelet-derived growth factor).[15,18,19] In contrast, the levels of pro-inflammatory cytokines, particularly IL-1β and tumor necrosis factor-alpha, do not substantially increase.[15] Exposure of the blood to processed glass beads provides a vigorous and rapid increase in the synthesis of various anti-inflammatory mediators. The concentration of IL-1Ra has been reported to increase 140-fold after a 24 h incubation, whereas IL-4 and IL-10 were only slightly induced.[16] In another study, it was reported that ACS increased the concentration of fibroblast growth factor-2 by 750% compared to baseline, whereas the concentration of IL-1Ra was increased by 600%.[20] Barreto and Braun reported that a short incubation period of 30 m resulted in a 32-fold increase in IL-1Ra between baseline and ACS.[21] These concentration values are of great importance since it has been reported that IL-1Ra concentrations must exceed IL-1β levels by 10-100-fold to competitively inhibit the interaction of IL-1β and its receptors.[22]

Evidence-based data regarding ACS

ACS has mainly been used as a local treatment in musculoskeletal diseases for many years as a relatively inexpensive way to create an anti-inflammatory environment (Table 1).[17,23–34] In 2003, Baltzer *et al*.[35] published the first clinical uses of ACS in a nonrandomized study on 1,000 patients for the treatment of osteoarthritis (OA) of the knee,[17] and subsequently reported the outcomes of 376 patients with knee OA in a prospective, randomized trial in which the clinical effects of ACS were compared to standard of care (hyaluronic acid) and placebo (saline).[23] The results in both studies demonstrated that ACS considerably improved clinical signs and symptoms of OA.[17,23,35] Yang *et al*.[24] reported that ACS clearly induced a biological response different from placebo in a randomized, placebo-controlled trial that included 167 patients with symptomatic knee OA who received six intra-articular injections, either with ACS or saline. The same clinical efficacy results were confirmed by Garcia-Escudero and Trillos in a two-year prospective observational study of 118 patients with highly symptomatic

Table 1. Clinical trials reported in the literature on the use of autologous conditioned serum (ACS)

Study	Study design	Comparison	Method	Model	Outcome
Becker *et al.*[25]	Prospective, double-blind, reference-controlled	ACS *vs* Triamcinolone (5 mg and 10 mg)	Eighty-four patients followed-up for six months	Epidural injections for patients with lumbar radicular compression	ACS showed a consistent pattern of superiority over both triamcinolone groups. ACS group was significantly different from triamcinolone 5 mg.
Auw Yang *et al.*[24]	Randomized, multi-center, double-blind, placebo-controlled	ACS *vs* Saline	One-hundred-sixty-seven patients followed-up for 12 months	Intra-articular injections for patients with symptomatic knee osteoarthritis	ACS-treated patients consistently showed more improvement compared to placebo-treated patients, although none of these differences were statistically significant.
Baltzer *et al.*[23]	Prospective, double-blind, placebo-controlled	ACS *vs* HA *vs* saline	Three-hundred-seventy-six patients followed-up for two years	Intra-articular injections for patients with knee osteoarthritis	ACS was significantly superior to HA and saline, no differences between HA and saline. The frequency of adverse events was comparable in the ACS and saline groups, but higher in the HA group.
Darabos *et al.*[26]	Prospective, randomized, double-blind, placebo-controlled	ACS *vs* physiological solution	Twenty patients followed-up for 10 days	Intra-articular injections (on the day of surgery and postoperative days one, six, and 10) for patients who underwent surgery of a traumatic rupture of the knee joint ligament	A decrease in the synovial fluid IL-1β concentrations appeared to be more pronounced in absolute terms in the ACS group when compared to control group. A correlation between IL-1β in the peripheral circulation and synovial fluid persisted in ACS group patients.
Darabos *et al.*[27]	Prospective, randomized, double-blind, placebo- controlled	ACS *vs* saline	Sixty-two patients followed-up for one year	Intra-articular injections (on the day of surgery and postoperative days one, six, and 10) for patients who underwent surgery of a traumatic rupture of the knee joint ligament	IL-1β synovial fluid concentration dropped off significantly in both groups and reached approximately normal values by day six. In the ACS group, the values continued to decline until day 10, whereas in the placebo group the IL-1β concentrations tended to increase until day 10. ACS-treated patients scored consistently better with the lowest pain scores and the largest reduction in bone tunnel widening compared to the placebo-treated patients.
Baltzer *et al.*[28]	Retrospective, non-blinded, non-randomized intervention study	ACS *vs* ACS+cortisone *vs* ACS+cortisone+rIRAP	One-hundred-nineteen patients followed-up for 14 months	Intra-articular injections for patients with hip osteoarthritis	Neither cortisone nor cortisone+rIRAP increased the beneficial treatment effect over and above ACS alone. The sole application of ACS can be even more beneficial than the combination of ACS with steroids.
Strümper *et al.*[29]	Retrospective, uncontrolled, case series	ACS	Forty-seven patients followed-up for six months	Knee injections for patients with heterogeneous knee meniscus lesions	Significant improvement in MRI-based meniscus morphology over all patients.
Tassara *et al.*[17]	Retrospective case series	ACS	Twenty-eight patients followed-up for six months	Intra-articular injections for patients with symptomatic knee or hip osteoarthritis	Treatment with ACS produced a rapid decline in pain, accompanied by a large improvement in range of motion.
Damjanov *et al.*[30]	Prospective, randomized, double-blind, placebo-controlled	ACS *vs* betamethasone *vs* saline	Thirty-two patients followed-up for 24 weeks	Injections into the enthesis and paratenon of the supraspinatus tendon for chronic tendinopathy	Compared with betamethasone, ACS therapy improved joint function and reduced shoulder pain more effectively after four weeks of treatment; these improvements were sustained to week 24. Adverse events were reported in betamethasone patients.

(continued)

Table 1. *(continued)*

Study	Study design	Comparison	Method	Model	Outcome
Shirokova *et al.*[31]	Prospective, non-randomized, controlled, open label	ACS *vs* PRP	One-hundred-twenty-three patients followed-up for three months	Intra-articular injections for patients with knee osteoarthritis	ACS induced endogenous IL-1Ra expression, downregulated IL-1β and improved synovial fluid viscosity. ACS significantly reduced the concentration of conjugated dienes - interpreted as reactive oxygen species footprints- in synovial fluid, compared to PRP
Pishgahi *et al.*[32]	Randomized, controlled trial	ACS *vs* PRP *vs* dextrose prolotherapy	Ninety-two patients followed-up for six months	Intra-articular injections for patients with knee osteoarthritis	Both ACS and PRP treated patients showed improvement in pain intensity and knee function at the one and six month follow-up visit, but this progress was more significant in the ACS group.
Vitali *et al.*[33]	Uncontrolled, case series	ACS	Fifteen patients followed-up for six months	Intra-articular injections for patients with knee osteoarthritis	Improvement in all evaluation scales at six months follow-up.
Simon *et al.*[34]	Uncontrolled, observational, case series	ACS	Thirty-six patients followed-up for two years	Intra-articular injections for patients with shoulder osteoarthritis	ACS injections into the shoulder joint can improve clinical function and decrease pain in many cases and delay the need for surgery.

ACS, autologous condition serum; HA, hyaluronan; rIRAP, recombinant IL-1 receptor antagonist protein; IL-1β, interleukin 1 beta; IL-1Ra, interleukin 1 receptor antagonist; MRI, magnetic resonance imaging; PRP, platelet-rich plasma.

knee OA who received ACS in conjunction with physiotherapy,[36] and also by Barreto and Braun in a retrospective study of 100 patients with symptomatic knee OA who received a total of six ACS injections.[37] Following clinical trials, researchers have concluded that the overall safety profile of ACS, a biological material, is satisfactory for clinical use. As such, it has been used according to a standard protocol in muscle and joint diseases in recent years.

Importantly, ACS has not only been used in patients with OA. Wright-Carpenter *et al.*[38] conducted an experimental study in which mice were subjected to a contusion injury of their gastrocnemius muscle. One group received local injections of ACS at 2 h, 24 h, and 48 h after injury, and a control group received saline injections. The authors noted that ACS treatment appeared to be a powerful tool for the treatment of muscle contusion injuries, likely through conditioning the cellular systems and mechanisms responsible for regeneration and repair. Additionally, Wright-Carpenter *et al.*[20] conducted a clinical study on muscle strain injuries in professional athletes receiving ACS compared to Actovegin®/Traumeel® therapy, which was the standard therapy in their practice for muscle strains. Of note, Actovegin® is a deproteinised dialysate from bovine blood, and Traumeel® is a homeopathic anti-inflammatory drug with extracts of arnica, calendula, chamomile, *etc*. In this study, ACS was found to be a promising approach to reduce recovery time following muscle injury. Becker *et al.*[25] reported a prospective, double-blind study on lumbar radicular compression in which patients were treated by epidural perineural injections with either ACS or triamcinolone and noted that ACS was clinically remarkable, and potentially superior to the steroid injection.

Since ACS is a biomaterial prepared from the patient's own blood, it raises an important question. If there is already an inflammatory condition in the patient, and this situation will naturally manifest itself with inflammatory cytokines in the blood, will the blood taken from an affected individual create a treatment effect? Lasarzik de Ascurra *et al.*[39] attempted to answer this question. The authors investigated ACS from horses with and without OA.[39] They reported that there was no significant difference in the concentration of IL-1Ra or IL-1β in the ACS between OA horses and control horses with equal incubation times.[39] Besides that, there was no correlation between the serum IL-1Ra concentrations in an individual horse before and after incubation.[39] Therefore, the baseline values cannot predict the IL-1Ra concentration in ACS after incubation.[39]

ACS should not be seen as just an IL-1 receptor antagonist, since it also has a disease modifying effect. Evans *et al.*[15] noted that glycosylated, native IL-1Ra, as is presumably present in ACS, has approximately the same potency as the recombinant form, but it may have superior retention properties. It is clear that many other substances are induced, some of which do not even begin to address non-proteinaceous components that might be therapeutically important or may have therapeutic properties of their own.[15]

ACS is more than an anti-inflammatory agent

IL-1 has a key role in triggering the release of mediators leading to the formation of many inflammatory and degenerative diseases, and the strategy of inhibiting the IL-1 pathway has been an important area in the treatment of such diseases since the early 1980s.[16] Treatment regimens for blocking the biological activities of IL-1 involve the use of IL-1Ra, soluble forms of IL-1 receptors, and type 1 cytokines such as IL-4, IL-10 and IL-13 that inhibit the synthesis of IL-1, increase the synthesis of IL-1Ra, or do both.[16] The main sources of endogenous IL-1Ra are primarily macrophages and monocytes, and IL-1Ra production from these sources can be

increased by a wide variety of stimuli, including adhesion to certain types of surfaces.[15]

The products released by mononuclear cells and platelets through ACS production are partly derived from intracellular reservoirs and partly synthesized de novo.[11] Cytokines that exist in ACS are likely to be much more extensive than detected. Although ACS is rich in IL-1Ra, its clinical effects cannot be attributed to this single component. It has not been formally demonstrated that IL-1Ra is responsible for the therapeutic properties of ACS, but rather that the synergistic action of all factors present in the ACS contribute to its effect.[11] Frisbie *et al*.[14] commented that the administration of ACS may also stimulate the endogenous production of IL-1Ra. Consequently, ACS can be seen as a modulator with anti-inflammatory properties, comprised of a mixture of cytokines and growth factors.

The problem with COVID-19: the cytokine release

According to current knowledge, although most COVID-19 patients are asymptomatic or mild cases that usually recover, approximately 15% of infected adults develop severe pneumonia that requires treatment with supplemental oxygen, and an additional 5% progress to critical illness with hypoxemic respiratory failure, ARDS, and multi-organ failure that necessitates ventilator support, often for several weeks.[40] Studies propose that cytokine release syndrome plays a crucial role in the pathogenesis of severe COVID-19.[41]

In a study from a hospital in Wuhan, it was reported that patients with COVID-19 had higher concentrations of IL-1β, interferon-gamma, induced protein 10, and monocyte chemoattractant protein-1 in both intensive care unit (ICU) and non-ICU patients compared to healthy adults and, moreover, some inflammatory chemokines and cytokines were more commonly seen in ICU patients than non-ICU patients.[42] Huang *et al*.[42] also noted that the cytokine storm was associated with disease severity.[42] As is well known, the main role of regulatory T cells is to balance the immune response by suppressing the activation, proliferation, and pro-inflammatory function of lymphocytes.[43] In patients with COVID-19, helper T cells and regulatory T cells are below normal levels, while those in patients with severe disease are significantly lower than non-severe patients, suggesting that immune homeostasis is impaired towards inflammation.[43] Post-mortem pathology results suggest that primarily macrophages, monocytes and moderate multinucleated giant cells in the alveoli account for, at least in part, the severe immune-mediated injury in these patients.[44] In addition, harmful exogenous agents stimulate airway epithelial cells that act as immune effector cells to express adhesion molecules on their surface, and secrete various immune molecules that play a major role in cell-mediated immunity.[4] In COVID-19 patients, cell-mediated immunity begins to eradicate virus-infected cells at an extensive scale, along with a surge in local and systemic cytokines, leading to severe and devastating alveolar and interstitial inflammation, resulting in the damage of lung tissue and the filling of alveoli with inflammatory exudates.[4] At this point, it seems that this chaotic condition cannot be stopped for some people, especially the elderly and those with chronic diseases, for reasons that are still not clear. As a result, the release of inflammatory cytokines and mediators continues in the lung.[4] This extremely severe hyper-cytokinemic inflammatory state variously termed as a cytokine storm, macrophage activation syndrome, or secondary haemophagocytic lymphohistocytosis (sHLH) may be the underlying cause in COVID-19 patients that become critical.[43] In adults, sHLH is under-recognized worldwide. The leading cause of sHLH is viral infections and the cytokine profile, serological markers, and cardinal features of sHLH including unremitting fever, cytopenia, and hyperferritinaemia as well as pulmonary involvement (including ARDS) resemble COVID-19.[43,45] Importantly, sHLH is characterized by an inability to clear antigens from an infection, which leads to inappropriate immune stimulation in which innate immune system dysfunction is key, and IL-1 is central to this pathogenesis.[46]

The effects of COVID-19 on children and immunosuppressed adults

It is obvious that COVID-19 itself is not highly aggressive and damaging to the respiratory system.[4] The cytokine storm is held responsible for the tissue damage, possibly due to a failure of the immune system or a hyperimmune response.[5] Considering this explanation, children with fewer comorbidities present a different inflammatory response: it was reported that children had higher levels of T regulatory and B cells, which were involved in immune tolerance and lead to a less pronounced inflammatory immune response. Therefore, they have a more mild disease and do not develop any severe presentations of COVID-19, such as pneumonia.[5] Likewise, contrary to expectations, immunosuppressed adults without any other comorbidities appear to have no increased risk of more severe disease, and they present a favorable outcome compared to patients with other comorbidities.[5,13] Although it may seem like a paradox, this might be explained by a hypothetical protective role of a weaker immune response against COVID-19, which leads to a more mild disease presentation.[5] These reports reinforce the concept that COVID-19 may actually be the result of an unstoppable and exaggerated inflammatory process triggered by a virus.

Future directions

Corticosteroids, which first come to mind to stop the destruction caused by an excessive inflammatory response, were recommended as a part of the main treatment during the early phase of the COVID-19 pandemic; however, current interim guidance from World Health Organization regarding the clinical management of COVID-19 advises against the use of corticosteroids unless indicated for a different reason.[47] Although corticosteroids show a temporary recovery period in COVID-19 patients, they might exacerbate COVID-19-associated lung injury likely due to the nonspecific blockage of the entire inflammatory process, including cellular effects.[45] It has also been reported that corticosteroids will impair host defense against bacteria and fungi making patients more susceptible to secondary infections, which are a major cause of death due to complicated viral pneumonitis.[8] To control the hyperinflammatory state and attenuate the detrimental host immune response without increasing adverse events, the use of immunomodulators have been proposed.[41] From a study containing a re-analysis from a phase III randomized controlled trial of IL-1 blockade, anakinra (a recombinant human IL-1 receptor antagonist) was suggested to increase survival and be used for COVID-19 patients with sepsis accompanied by hyperinflammation.[45,48] It was also shown that tocilizumab (a recombinant humanized anti-human IL-6 receptor monoclonal antibody) immediately improved clinical outcomes in severe and critical COVID-19 patients without any obvious adverse reactions.[49] Although the use of biologics is a relatively new field, these therapies could be promising modalities to treat COVID-19-induced sHLH.[41]

Conclusions

We are still in an early stage of understanding of the management of COVID-19, and the outcomes of all treatment modalities currently applied in the world remain below expectations and are generally built on viral destruction and decreasing viral load. It is overlooked, perhaps, that in certain people (particularly the elderly population), the cause of death is not the virus itself, but the excessive inflammation; that is, the extreme immune response of the host. With these considerations, the idea of a treatment modality that can be easily obtained from the patient's own blood and can be applied with the help of a simple nebulizer may guide further studies and treatment strategies.

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Conflict of interest

The author declares no competing interests related to this publication.

Author contributions

K Ozer performed the manuscript writing, critical revision, technical and material support. K Ozer agreed to the submitted version of the paper, and bears responsibility for it.

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