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.

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 lymphohistiocytosis.

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3.2 million confirmed deaths throughout the world. 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. The other two strains are SARS-CoV and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV). 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%. 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. 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. It is uncommon for animal coronaviruses to be transmitted from animals to humans and cross the species barrier in a phenomenon called spill-over. When considering the seasonal flu, reports on COVID-19 indicate that this virus is less virulent than influenza.
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 and its impact on the elderly population and those with chronic diseases. As the pandemic continues, acquired experience summarizes COVID-19 and its impact on the elderly population and those with chronic diseases.

ACS contains a rich content of anti-inflammatory cytokines and anti-inflammatory molecules from the blood. According to this hypothesis, the preparation of ACS may be used in COVID-19 patients as a nebulized therapy. If this hypothesis holds true, it can be administered via a nebulizer. If this hypothesis holds true, it can be administered via a nebulizer.

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.\(^16\) 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 mm² surface area) that were exposed to chromium sulphate as

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a method to attach the blood monocytes and other adherent cells to stimulate the production of an anti-inflammatory cocktail (Fig. 1). Subsequently, the syringes are incubated aseptically at 37°C with 5% CO2 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.

The nebulizer is held in an upright position until all ACS is gone from the reservoir. ACS is now deep within the lungs.

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). In contrast, the levels of pro-inflammatory cytokines, particularly IL-1β and tumor necrosis factor-alpha, do not substantially increase. 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. 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%. 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. 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.

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). In 2003, Baltzer et al. published the first clinical uses of ACS in a nonrandomized study on 1,000 patients for the treatment of osteoarthritis (OA) of the knee, 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). The results in both studies demonstrated that ACS considerably improved clinical signs and symptoms of OA. Yang et al. 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 OA.
### 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.  | Prospective, double-blind, reference-     | ACS vs Triamcinolone            | Eighty-four patients        | Epidural injections for patients with lumbar         | ACS showed a consistent pattern of superiority over both triamcinolone groups. ACS group was significantly different from triamcinolone 5 mg. |
|                | controlled                                | (5 mg and 10 mg)                | followed-up for six months  | radicular compression                               |                                                                         |
| Auw Yang et al.| Randomized, multi-center, double-blind,  | ACS vs Saline                   | One-hundred-sixty-seven     | Intra-articular injections for patients with         | ACS-treated patients consistently showed more improvement compared to   |
|                | placebo-controlled                        |                                 | patients followed-up for    | symptomatic knee osteoarthritis                      | placebo-treated patients, although none of these differences were       |
|                |                                           |                                 | 12 months                   |                                                      | statistically significant.                                              |
| Baltzer et al. | Prospective, double-blind, placebo-      | ACS vs HA vs saline             | Three-hundred-seventy-six   | Intra-articular injections for patients with knee    | ACS was significantly superior to HA and saline, no differences between |
|                | controlled                                |                                 | patients followed-up for    | osteoarthritis                                      | HA and saline. The frequency of adverse events was comparable in the ACS |
|                |                                           |                                 | two years                   |                                                      | and saline groups, but higher in the HA group.                         |
| Darabos et al. | Prospective, randomized, double-blind,   | ACS vs physiological solution   | Twenty patients followed-up | Intra-articular injections (on the day of surgery    | A decrease in the synovial fluid IL-1β concentrations appeared to be    |
|                | placebo-controlled                        |                                 | for 10 days                  | and postoperative days one, six, and 10) for patients| more pronounced in absolute terms in the ACS group when compared to    |
|                |                                           |                                 |                             | who underwent surgery of a traumatic rupture of the  | control group. A correlation between IL-1β in the peripheral circulation |
|                |                                           |                                 |                             | knee joint ligament                                 | and synovial fluid persisted in ACS group patients.                    |
| Darabos et al. | Prospective, randomized, double-blind,   | ACS vs saline                   | Sixty-two patients          | Intra-articular injections (on the day of surgery    | IL-1β synovial fluid concentration dropped off significantly in both     |
|                | placebo-controlled                        |                                 | followed-up for one year    | and postoperative days one, six, and 10) for patients| groups and reached approximately normal values by day six. In the ACS  |
|                |                                           |                                 |                             | who underwent surgery of a traumatic rupture of the  | group, the values continued to decline until day 10, whereas in the   |
|                |                                           |                                 |                             | knee joint ligament                                 | 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. | Retrospective, non-blinded, non-randomized| ACS vs ACS+cortisone vs         | One-hundred-nineteen patients| Intra-articular injections for patients with hip    | Neither cortisone nor cortisone+rIRAP increased the beneficial         |
|                | intervention study                         | ACS+cortisone+rIRAP              | followed-up for 14 months   | osteoarthritis                                      | 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.| Retrospective, uncontrolled, case series  | ACS                             | Forty-seven patients        | Knee injections for patients with heterogeneous      | Significant improvement in MRI-based meniscus morphology over all       |
|                |                                           |                                 | followed-up for six months  | knee meniscus lesions                               | patients.                                                              |
| Tassara et al. | Retrospective case series                 | ACS                             | Twenty-eight patients       | Intra-articular injections for patients with         | Treatment with ACS produced a rapid decline in pain, accompanied by a   |
|                |                                           |                                 | followed-up for six months  | symptomatic knee or hip osteoarthritis               | large improvement in range of motion.                                  |
| Damjanov et al.| Prospective, randomized, double-blind,   | ACS vs betamethasone vs saline  | Thirty-two patients         | Injections into the enthesis and paratenon of the   | Compared with betamethasone, ACS therapy improved joint function and   |
|                | placebo-controlled                        |                                 | followed-up for 24 weeks    | supraspinatus tendon for chronic tendinopathy       | 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)
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. 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. 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. attempted to answer this question. The authors investigated ACS from horses with and without OA. 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. Besides that, there was no correlation between the serum IL-1Ra concentrations in an individual horse before and after incubation, nor was there a correlation between the serum IL-1Ra concentrations and the strategy of inhibiting the IL-1 pathway has been an important area in the treatment of such diseases since the early 1980s.

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. 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 cer-\textsuperscript{tain} types of surface.<sup>15</sup> The products released by mononuclear cells and platelets through ACS production are partly derived from intracellular reservoirs and partly synthesized de novo.<sup>11</sup> 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. Frisbie et al.<sup>14</sup> 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 pa-
tients are asymptomatic or mild cases that usually recover, ap-
proximately 15% of infected adults develop severe pneumonia that requires treatment with supplemental oxygen, and an addi-
tional 5% progress to critical illness with hypoxemic respiratory failure, ARDS, and multi-organ failure that necessitates ventilator support, often for several weeks.<sup>40</sup> Studies propose that cytokine release syndrome plays a crucial role in the pathogenesis of severe COVID-19.<sup>41</sup> In a study from a hospital in Wuhan, it was reported that pa-
tients with COVID-19 had higher concentrations of IL-1β, inter-
feron-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 pa-
tients than non-ICU patients.<sup>42</sup> Huang et al.<sup>42</sup> also noted that the cytokine storm was associated with disease severity.<sup>43</sup> 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. In patients with COVID-19, when 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.<sup>43</sup> 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. 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.<sup>44</sup> 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.<sup>44</sup> 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.<sup>44</sup> This extremely severe hyper-cytokineremic inflammatory state variously termed as a cytokine storm, macrophage activation syndrome, or secondary haemophagocytic lymphohistiocytosis (sHLH) may be the underlying cause in COVID-19 patients that become critical.<sup>43</sup> In adults, sHLH is under-recognized worldwide. The leading cause of sHLH is viral infections and the cytokine release, with sHLH including unifying features of fever, cytopenia, and hyperferritinemia as well as pulmonary involvement (including ARDS) resembling COVID-19.<sup>43,45</sup> 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.<sup>46</sup>

The effects of COVID-19 on children and immunosuppressed adults

It is obvious that COVID-19 itself is not highly aggressive and dam-
aging to the respiratory system.<sup>4</sup> The cytokine storm is held respon-
sible for the tissue damage, possibly due to a failure of the immune system or a hyperimmune response.<sup>5</sup> 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.<sup>5</sup> Likewise, contrary to expectations, immunosuppressed adults without any other comor-
bidities appear to have no increased risk of more severe disease, and they present a favorable outcome compared to patients with other comorbidities.<sup>5,13</sup> 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.<sup>5</sup> 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 recommend-
ed 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.<sup>47</sup> Although corticosteroids show a temporary recovery period in COVID-19 patients, they might exacerbate COVID-19-associated lung injury likely due to the nonspecific blockade of the entire inflammatory process, including cellular effects.<sup>45</sup> It has also been reported that corticosteroids will impair host defense against bacteria and fungi making pa-
tients more susceptible to secondary infections, which are a major cause of death due to complicated viral pneumonitis.<sup>5</sup> To control the hyperinflammatory state and attenuate the detrimental host immune response without increasing adverse events, the use of immunomodulators have been proposed.<sup>41</sup> 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 antagon-
ist) was suggested to increase survival and be used for COVID-19 patients with sepsis accompanied by hyperinflammation.<sup>5,48</sup> 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 with-
out any obvious adverse reactions.<sup>49</sup> Although the use of biologics is a relatively new field, these therapies could be promising mo-
dalities to treat COVID-19-induced sHLH.<sup>41</sup>
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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