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COMMENTARY

Can Glycine Mitigate COVID-19 Associated Tissue Damage and Cytokine Storm?

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COVID-19, caused by the highly contagious RNA virus SARS-CoV-2, has infected over 8 million and killed over four hundred thousand worldwide as of June 2020. In response, the research community around the world is racing to develop treatments. The major thrust of the efforts appears to be three-pronged: antivirals, vaccines, and mitigators of tissue damage and cytokine storm. Here I propose the hypothesis that glycine, a non-essential amino acid, should be evaluated as a beneficial mitigator of tissue damage and cytokine storm in COVID-19 patients.

An increasing body of literature has documented that COVID-19 can attack multiple cell types throughout the body (*1*). These include cells in the lung, heart and blood vessels, liver, kidneys, intestines and brain. Tissue damage in one or more of these organs is associated with the severity and mortality of COVID-19 in patients. Although the exact cause of how COVID-19 kills remains unknown, there are some important clues. The first is the association of cytokine storms with mortality. Cytokine storms have been associated with acute respiratory distress syndrome (ARDS), a major cause of mortality (*2*). Elevated levels of pro-inflammatory cytokines, such as IL-2, IL-7, G-CSF, IP10, MCP1, MIP1A and TNF-α, were correlated with COVID-19 severity (*3*). Similarly, GM-CSF and IL6 were observed at significantly higher levels in COVID-19 patients needing ICU care compared to those who did not (*4*). Another potential cause of death was increased blood clotting, vessel constriction, and cardiac damage in COVID-19 patients. Possible reasons include: 1. SARS-CoV2-induced death of endothelial cells and constriction of blood vessels and ischemia; 2. secondary cardiac damage after lung damage, which leads to hypoxia; or 3. damage caused by cytokine storm. In addition to lung, heart and blood vessels, significant tissue damage has also been observed in the kidney, GI tract, liver and brain. Taken together, a scenario emerges in which tissue damage in the lung and other organs causes the release of an abundance of pathogen-associated molecular patterns (PAMPS) and damage-associated molecular patterns (DAMPS). The PAMPS and DAMPS subsequently lead to the onset of cytokine release syndrome (CRS), ARDS, and secondary hemophagocytic lymphohistiocytosis (sHLH) (*5*), which can cause multiple organ failure and COVID-19 mortality.

Given the prominent association of CRS with COVID-19 mortality, an important emerging treatment strategy that is being widely evaluated is the use of anticytokine or immunomodulatory drugs. One example is tocilizumab, a clinically-approved anti-IL6 receptor antibody, which showed some promise in reducing mortality in COVID-19 patients (*4*). Another anti-IL6R antibody being evaluated is sarilumab. In addition, inhibitors of the JAK1 and JAK2 kinases, such as baricitinib and ruxolitinib, which act downstream of IL6, are being evaluated for the treatment of severely ill COVID19 patients, and have shown some promise (*6, 7*). In addition to the above pharmaceutical-based approach, another recently proposed unorthodox treatment of COVID-19-associated ARDS and CRS is low-dose irradiation of the lung (*8–12*). This approach was proposed based on historical observations of successful control of virus or bacteria-induced pneumonia (*13*). Interestingly, a small clinical trial showed promising results in 4 of 5 COVID-19 patients who received radiotherapy (*14*). However, given the early stages of the trials, it is too soon to conclude whether any of the above strategies will be effective against COVID-19-induced CRS. Additional approaches/ideas are clearly needed.

I propose here that glycine, a non-essential amino acid, may be an effective mitigator for both the tissue damage and cytokine storm in COVID-19 patients. Previously reported studies have demonstrated both the cytoprotective and anti-inflammatory properties of glycine in human patients and animal models. Dietary intake of glycine significantly reduced endotoxin/ischemia-induced liver and lung tissue damage and extended overall survival in rats (*15*). Oral glycine prevented rat hemorrhagic shock and liver injury (*16*). Glycine also blunted endotoxin-induced superoxide

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and proinflammatory cytokine TNF-α production in alveolar macrophages (*17*). Glycine has been further shown to have anti-inflammatory and protective roles in experimental models of acute pancreatitis (*18*), gastric ulcer (*19*) and arthritis (*20*). Furthermore, glycine attenuated TNF-α and IL-6 production in obese mice (*21*), a very relevant finding since obesity has been linked with increased COVID-19 hospitalizations (*22*). In human cystic fibrosis patients, oral glycine at 0.5 g/kg/day reduced inflammatory cytokines TNF-α, IL-6 and G-CSF and improved clinical status (*23*). Importantly, no major untoward side effects were observed in human patients who had taken high doses of 0.5–1.0 g/kg for 8 weeks (*24, 25*) or 5 years (*26*).

Mechanistically, it has been suggested that the anti-inflammatory properties of glycine in macrophages and other leukocytes are dependent on the expression of a glycine-gated chloride channel in these cells (*27, 28*). Glycine caused hyperpolarization of macrophages, which blunted endotoxin-induced calcium influxes and membrane depolarization that were necessary for free radicals and TNF-α induction (*29*) Fig. 1. However, the precise mechanisms through which glycine attenuates inflammatory cytokines are still not well understood. One likely mechanism is its potent ability to inhibit pyroptosis (*30*), a pro-inflammatory form of cell death that often accompanies microbial infections, including those from SARS-CoV-2 (*31*), as part of the organism's innate immune response. Figure 1 shows a schematic of potential mechanisms.

Compared to most other repurposed drugs that are being evaluated for COVID-19 treatment, glycine is very affordable and widely available as a nutritional supplement. Many of the drugs under evaluation are biologics. Therefore, even if their clinical trials produce good results, it will take time to ramp up their production to meet the high demand generated by the rapidly rising patient population worldwide. Furthermore, the cost of such medicines may limit their use in less developed countries. In comparison, glycine, if proven to be beneficial in clinical trials, can be rapidly deployed to COVID-19 patients around the world.

Because of its excellent safety record, promising anti-inflammatory properties, and wide availability and affordability, I propose that clinical trials with glycine as a mitigator of cytokine storms should be conducted as soon as possible in COVID-19 patients. It may be administered either orally in patients with moderate symptoms or intravenously in patients with severe symptoms at doses of 0.5–1.0 g/kg/day. In early stages of the disease, glycine may suppress or blunt the onset of virus-induced cytokine storm. In late stages of the disease, its cytoprotective effect may protect lung tissues from severe damage and ARDS, the leading cause of the mortality. Under these circumstances, it may be used in conjunction with other treatments. These include dexamethasone, which was shown to reduce cell death in advanced-stage patients (*32*), radiotherapy, as reported recently (*14*), or anti-viral agents such as remdesivir (*33*). Glycine may potentially enhance the therapeutic effects of those treatments.

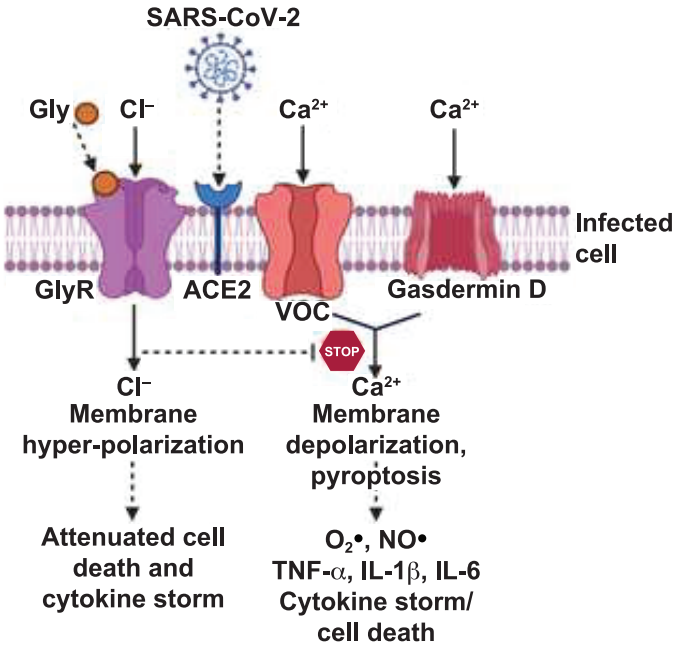

FIG. 1. A hypothetical mechanism of how glycine may reduce SARS-CoV-2-mediated tissue damage and cytokine storm. SARS-CoV-2 can infect target cells through the ACE2 protein. The infection may cause cell death through pyroptosis, which requires calcium influxes from voltage-operated calcium channel (VOC) or gasdermin D pores and ensuing cellular membrane depolarization, free radical generation and secretion of pro-inflammatory cytokines. Glycine, by binding its receptor GlyR, induces a chloride influx that causes cellular membrane hyperpolarization that protects the cells from pyroptosis and proinflammatory cytokine secretion.

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