Anti-inflammatory activity of ivermectin in late-stage COVID-19 may reflect activation of systemic glycine receptors

James J DiNicolantonio, Jorge Barroso-Aranda, Mark F McCarty

Ivermectin, a drug commonly used to treat a range of parasitic infections, has been shown to halve the mortality elicited by a fatal dose of lipopolysaccharide in mice, in an oral dose (4 mg/kg) that can be extrapolated to 2–4 times the standard clinical dose in humans (0.2 mg/kg). It has been suggested that this phenomenon is highly pertinent to the clinical utility of ivermectin in the cytokine storm phase of COVID-19, which has been documented in a number of clinical studies. A meta-analysis of 18 clinical studies to date examining the impact of ivermectin therapy in hospitalised COVID-19 patients has observed a roughly 68% reduction in mortality associated with its usage.

The basis of ivermectin’s potent anti-inflammatory activity remains unclear. However, it is notable that ivermectin can act as a partial agonist for glycine-gated strychnine-inhibitable chloride channels, which are expressed by a number of types of immune cells—including alveolar macrophages and neutrophils—as well as vascular endothelium. The anti-inflammatory effects of high-dose dietary glycine in rodents have been attributed to activation of such channels on immune and endothelial cells. The mechanism whereby glycine receptor activation achieves these effects remains unclear; hyperpolarisation of plasma membranes may be involved, as well as inhibition of endosomal nicotinamide adenine dinucleotide phosphat oxide activity.

In striking homology to the effects of ivermectin, high dietary glycine (5% of diet) has been shown to halve the mortality of a lethal dose of lipopolysaccharide (LPS) in rats. Glycine preadministration also blunts the lung injury induced by inhalation of aerosolised LPS in mice; this effect is associated with inhibition of NLR family pyrin domain containing 3 (NLRP3) inflammasome activation (thought to play a key role in COVID-19 lung inflammation and production of proinflammatory cytokines). Moreover, it is notable that, whereas 1 mM ivermectin suppresses the activating effect of LPS on Kupffer cells in vitro, removal of chloride from the medium completely eliminates ivermectin’s impact in this regard.

Nonetheless, it is not completely straightforward to predict that ivermectin administration will activate glycine-gated chloride receptors in vivo. At a concentration of 0.03 µM, ivermectin does not directly activate such receptors, but rather potentiates their response to sub-saturating concentrations of glycine. As ivermectin increases to 0.3 µM, these receptors are irreversibly activated by ivermectin, and glycine cannot further activate them. However, since ivermectin is only a partial agonist, the maximal channel activity achieved with ivermectin is about 20% less than that seen with a saturating concentration of glycine.

The affinity of ivermectin for the homomeric alpha1 glycine receptor has been determined to be about 160 µM, whereas human fasting plasma glycine concentrations are near 100 µM. These values appear consistent with the possibility that clinical concentrations of ivermectin could indeed boost the activity of systemic glycine receptors in humans. (Ivermectin is largely excluded from the brain by P-glycoprotein transporters, which accounts for its relative safety.)

It is therefore suggested that the clinical utility of ivermectin in the cytokine storm phase of COVID-19 reflects, at least in part, an anti-inflammatory effect mediated by increased activation of glycine receptors on leukocytes and possibly vascular endothelium. An evident corollary of this is that ingestion of high-dose glycine may provide...
somewhat analogous anti-inflammatory protection in COVID-19, as has previously been suggested.\(^{26,27}\) However, in light of accumulating evidence that ivermectin may have important utility for the primary prevention of COVID-19, it is likely that it also exerts an antiviral effect with respect to SARS-CoV-2, as suggested by in vitro studies.\(^3,28\) It is not clear whether glycine receptor agonism might have anything to do with this effect.

**Contributors** All authors contributed to the final manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** JJD is director of scientific affairs for advanced ingredients profit sectors. JJD has not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

**ORCID iD** James J DiNicolaianintio http://orcid.org/0000-0002-7888-1528

**REFERENCES**


