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# Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19

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Ivermectin, on the WHO's List of Essential Medications, has been in clinical use since 1981 as an orally and topically active agent for treating a range of parasitic infections in humans, including river blindness and lymphatic filariasis. It is also widely used in veterinary practice.

Anecdotally, the use of the standard clinical dose of ivermectin, 9 mg once, has been associated with some cases of rapid clinical resolution in severe hospitalised COVID-19; clinical studies evaluating its utility in this regard are underway. Ivermectin is reported to inhibit the proliferation of SARS-CoV-2 in vitro, but the $IC_{50}$ for this effect, $2\,\mu M$, has been noted to be 35-fold higher than the maximal concentration achieved after the administration of the approved clinical dose (9 mg) to humans, casting doubt on the utility of this agent as an antiviral drug in COVID-19 unless very markedly higher doses are used.[1 2] However, drugs blocking viral replication would be expected to be of lesser utility in the context of the late, cytokine storm-associated phase of COVID-19 and anecdotes of ivermectin's success in this disorder pertain to that phase. Hence, consideration should be given to the possibility that ivermectin is acting as an anti-inflammatory in these cases. This prompted us to search the research literature on ivermectin for anti-inflammatory actions.

In 2008, Zhang *et al* studied the impact of ivermectin in mice challenged with intraperitoneal lipopolysaccharide (LPS). They chose a dose of LPS that induced 100% mortality within 5 days. They then demonstrated that oral ivermectin, administering 2 hours prior to LPS, dose dependently reduced mortality in the LPS-treated mice, with a significant 50% reduction in mortality being achieved at a 4 mg/kg dose.[3] In vitro studies likewise confirmed the ability of this agent to block cytokine production by LPS-challenged macrophages.[3 4]

When we extrapolate this dose from 20 g mice to 70 kg humans, using the two-thirds power of relative body mass (ratio of body surface areas) as a correction factor, 4 mg/kg in mice corresponds to about 18 mg in humans—double the standard clinical dose. Allometric scaling by the three-fourths power (Kleiber's law) yields a dose of 36 mg.[5]

A study of related interest, published a year later, examined the impact of ivermectin—a group of 16-membered macrocyclic lactone derivatives of which ivermectin is a member—on LPS signalling in the RAW 264.7 murine macrophage-derived cell line. In concentrations ranging from 0.625 to 5 mg/L, ivermectin suppressed activation both of NF-kappaB and the stress-activated MAP kinases JNK and p38.[6]

Moreover, there are two reports that ivermectin, administered either systemically or topically, exerts anti-inflammatory effects in murine models of allergic inflammation (asthma and atopic dermatitis).[7 8] The systemic effect was achieved with a 2 mg/kg dose.

Although it is conceivable that these anti-inflammatory effects of ivermectin are restricted to LPS or toll-like receptor 4 (TLR4) signalling, it may well be the case that it works downstream in this signalling pathway in a way that would be pertinent to other proinflammatory signalling pathways. Moreover, there is reason to suspect that the damage-associated molecular pattern high mobility group box 1 (HMGB1), which is released by dying cells and acts as an agonist for the TLR4 receptor, is a mediator of the lung inflammation associated with COVID-19.[9] Hence, it is reasonable to suspect that, in doses at or modestly above the standard clinical dose, ivermectin may have important clinical potential for managing disorders associated with life-threatening respiratory distress and cytokine storm—such as advanced COVID-19. Ivermectin may have

been 'flying under the radar' in this regard during four decades of clinical use.

Two retrospective prepublication reports have appeared in which clinical outcomes were evaluated in hospitalised patients with COVID-19, some of whom received treatment with ivermectin. Rajter *et al* have reported that, in univariate analysis, mortality in 173 patients receiving one or more doses of ivermectin was significantly lower than in 107 patients not so treated (15% vs 25.2%, p=0.03); after multivariate adjustment for pertinent covariates, this mortality difference was confirmed (OR 0.27, p=0.03; HR 0.37, p=0.03).[10] Gorial *et al* examined the mean time of hospital stay in patients who either received or did not receive on admission a standard clinical dose of ivermectin (200 µg/kg) as an adjunct to treatment with hydroxychloroquine/azithromycin. The 16 patients who received ivermectin had hospital stays averaging 7.62 days, notably lower than the average hospital stays of 71 patients not receiving ivermectin (13.22 days; p=0.00005). Two patients died in the control group, none in the ivermectin group.[11] Note that these apparent therapeutic benefits were seen in hospitalised patients, in whom antiviral measures are suspected to be less effective than anti-inflammatory measures targeting cytokine storm.

As the impact of ivermectin on antiviral immunity has not been studied, it is unclear whether it would be prudent to withhold its use until later-stage COVID-19.

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