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## Ivermectin in COVID-19: What do we know?



Dear editor

Ivermectin is a drug of a wide range of bioactivity and has been in use for more than 30 years for treatment of parasitic infections in humans [1]. It is being considered as the possible target drug for SARS CoV-2 and is under extensive research in clinical trials [2]. Ivermectin is used in a dose of 0.15 mg/kg–0.2 mg/kg body weight for most of the parasitic infestations as oral tablet and is well tolerated. This is not the first time when the antiviral properties of ivermectin has been tested against human virus. Ivermectin has shown its potent in vitro antiviral effects against several RNA viruses, such as Zika virus, Influenza A virus, Newcastle disease virus, Chikungunya virus, Yellow fever virus, Dengue virus, Japanese encephalitis virus and DNA virus such as BK polyomavirus and Equine herpesvirus type 1 [3].

The anti-SARS-CoV-2 of ivermectin is likely through inhibition of viral IMP $\alpha$ / $\beta$ 1-mediated nuclear import, which reduces the replication of virus and thereby the viral load [4]. Caly et al. showed the in vitro benefit of ivermectin in Vero-hSLAM cells infected with SARS-CoV-2. The authors found that a single dose of ivermectin was able to effect ~5000-fold reduction in viral RNA at 48 h [4]. In a preprint article, authors used molecular docking and molecular dynamics simulation approach to explore the mechanism of action of ivermectin and doxycycline on inhibition of SARS-CoV-2 and revealed that combination of ivermectin and doxycycline might be executing the effect by inhibition of viral entry and enhance viral load clearance by targeting various viral functional proteins. The authors also concluded that both ivermectin and doxycycline have significantly bind with SARS-CoV-2 proteins but ivermectin had better binding properties than doxycycline [5]. However a contradictory pharmacokinetic report states that with the routine anti-parasitic dose of ivermectin, its inhibitory action on SARS-CoV-2 concentrations are practically not attainable in humans [6].

Recently, two in vivo studies of ivermectin alone or in combination with doxycycline has been published. In a Randomized Trial of 116 patients treated with Ivermectin-Doxycycline (n = 60) or Hydroxychloroquine-Azithromycin (n = 56) therapy the authors found Ivermectin-Doxycycline combination therapy had a better success of symptomatic relief; shortened recovery duration, reduced adverse effects, and superior patient compliance compared to the Hydroxychloroquine-Azithromycin combination. The authors concluded ivermectin as a better choice for the treatment of patients with mild to moderate COVID-19 disease [7]. In a retrospective study of 280 patients with SARS-CoV-2 infection treated with ivermectin (n = 173) or standard of care (n = 107) the authors found lower mortality in the ivermectin group (25.2% versus 15.0%, OR 0.52, 95% CI 0.29–0.96). The authors also reported lower mortality among patients with severe pulmonary disease

(n = 75) treated with ivermectin (38.8% vs 80.7%, OR 0.15, CI 0.05–0.47, P = .001), however no significant difference was found in successful extubation rates (36.1% vs 15.4%, OR 3.11 (0.88–11.00), p = .07) [8].

We searched the various trial registries to find out the ongoing trials of ivermectin in COVID 19. In the European Union Clinical Trials Register, we found 5 clinical trials of ivermectin in SARS-CoV-2 infection (2020-001994-66, 2020-001971-33, 2020-002091-12, 2020-001474-29, 2020-002283-32) [9]. According to government portal Clinical Trials Registry India (CTRI), ivermectin is part of at least five ongoing trials in the country [10]. At the latest, the US clinical trials registry has 38 clinical trials from different countries in different stages of completion [11]. Current clinical trials have used ivermectin in a dose ranging from 200 to 1200 mcg/kg body weight, for a duration of 3–7 days, which is showing promising results both in terms of symptomatology as well as viral load reduction [10].

Ivermectin is more cost effective as compared to hydroxychloroquine and azithromycin combination. The overall cost effectiveness, safety profile makes it more lucrative candidate for clinical trials. However, the safety of ivermectin at higher doses, in children less than 15 kg and pregnant women has insufficient evidence and hence is not recommended in these population groups [12]. With the fear of the disease among the population, herd mentality continues in India and social media is still dominated by how to take these drugs and inquiry about their doses continue among the crowd [13]. One such news of ICMR including ivermectin in treatment guidelines for COVID-19 circulated over the social media leading to a heavy over the counter sale of the drug in a short span. As a fact check the Indian Council of Medical Research (ICMR) is still reviewing the benefits of ivermectin and doxycycline as a potential therapy for COVID-19 and no such treatment guidelines is available on the website [14,15]. On April 10, 2020, FDA issued a statement concerning self-administration of ivermectin against COVID-19 referring to recently published in vitro study [4].

The clinical efficacy and utility of ivermectin in SARS CoV-2 infected patients are unpredictable at this stage, as we are dealing with a completely novel virus. However, repurposing existing drugs as possible COVID-19 treatment is astute usage of existing resources, and we await results of well-designed large scale randomized controlled clinical trials exploring treatment efficacy of ivermectin to treat SARS-CoV-2.

**Declaration of competing interest**

On the behalf of all the authors in paper, I corresponding author hereby accept that there are no conflicts of interest.

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