

EDITORIAL VIEW

CORONA EXPERIENCE

Ivermectin for COVID-19; to use or not to use?

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Abstract

COVID-19 has engulfed the continents into a pandemic, filling the hospitals with this viral disease, heavily taxing the healthcare facilities and claiming thousands of lives in almost every country. In the absence of a known evidence-based remedy, many treatment options have been tried with variable results. Multiple vaccines have been developed by the drug industry, but none can be claimed to be 100% effective in prevention of the disease. There has been some evidence about the beneficial effects of ivermectin – an anthelmintic drug. This editorial discusses the various aspects of the use of ivermectin for the treatment of active COVID-19.

Key words: COVID-19; Pandemic; Mortality; Prevention; Ivermectin

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A Japanese pharmacologist, Dr. Satoshi Omura, and his colleagues discovered a new species of actinomycetes in soil collected from a golf course in 1974. Because, streptomycin and many other antibiotics had been found in actinomycetes, they had been searching for novel actinomycetes. When a culture of this bacterium was administered to the mice, the parasites in the mice were drastically reduced. Merck, a pharmaceutical company collaborating with Dr. Omura, succeeded in improving its activity by adding molecular hydrogen and named it ivermectin. This drug was initially marketed as an antiparasitic drug for animals and later for humans.

Ivermectin was effective in the treatment of onchocerciasis, which is an endemic disease in the tropics, is caused by nematode infection, and leads to blindness. It is also effective against lymphatic filariasis, a disease in which nematodes interfere with the lymphatic system. Ivermectin has been administered to > 300 million people worldwide, making it a drug that saves the world. Dr. Omura and his colleagues were awarded the Nobel Prize for their discovery of this new treatment against parasitic infections in 2015.

Ivermectin is thought to bind to glutamatergic chloride ion channels in the parasite's neurons and muscle cells; thereby increasing the permeability of the cell membrane to chloride ions, inhibiting neurotransmission, and paralyzing neurons and muscle cells. In addition, ivermectin has been reported to have antiviral effects by

inhibiting the nuclear transfer of viral proteins. It has been reported to inhibit the growth of the acquired immunodeficiency syndrome and dengue viruses and is also expected to be effective against the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

Drugs for treating COVID-19

SARS-CoV-2, which spread from Wuhan, China, in January 2020, rapidly gained the dimensions of a pandemic and effected all regions in the world. A worldwide vaccination campaign has been initiated, but the coverage remains low in many countries due to various reasons.

Studies have shown that antiviral drugs might be effective in the early to moderate episodes, but immunosuppressive drugs, such as dexamethasone, are now being used in the moderate to severe cases.¹ Thus, there are two approaches depending on the stage of the disease. Remdesivir is an antiviral drug developed for the Ebola virus and has been used in patients with moderate COVID-19.² However, its supply is currently limited. Moreover, it needs to be administered intravenously. Antibody cocktail therapy, which combines two artificially produced monoclonal antibodies for SARS-CoV-2, can block the entry of the virus into cells and inhibit multiplication when administered intravenously, thus preventing the progression to severe disease.³ But it is expensive and its supply is currently limited, so it's use

is reserved for patients who are in the initial stage but are at risk of progressing to severe disease.

Currently, orally administered drugs that decrease mortality by preventing disease progression from the initial stage to serious stages are required. Ivermectin is commonly used orally and has been used in patients with COVID-19 in many countries, although its usefulness against SARS-CoV-2 has not been evaluated.

Is ivermectin effective against COVID-19?

Ivermectin attracted attention when it was reported to be effective in inhibiting the growth of SARS-CoV-2 in *in vitro* studies.⁴ Since then, several clinical studies have been reported, but their usefulness is currently unclear. Many studies relied on small sample sizes or were not randomized or well-controlled.⁵ One study showed that ivermectin can reduce the death rate in patients with COVID-19 by > 90%.⁶ However, the study was withdrawn because of ethical concerns. Moreover, a randomised clinical trial published in the JAMA did not show the benefit of ivermectin in patients with mild COVID-19.⁷ In this trial, 476 adult patients with mild symptoms were enrolled. Patients were randomised to receive either ivermectin or a placebo for 5 days. The median time to resolution of symptoms was 10 days in the ivermectin group compared with 12 days in the placebo group, with no significant difference. To date, this is the only randomised study on ivermectin and COVID-19, published in a high-quality medical journal.

However, there has been a lot of indirect evidence. There are 134 COVID-19 cases per 100,000 people in African countries where ivermectin was administered prophylactically, compared with 951 cases per 100,000 people in countries without ivermectin prophylaxis. Indirect evidence should be interpreted with caution. In the early stages of the pandemic, countries with high BCG vaccination rates were reported to have lower infection rates. However, no such difference is currently observed. Therefore, more evidence is needed to support the aggressive use of ivermectin.

Current status of ivermectin in the treatment of COVID-19?

Although there is a lack of clear evidence, ivermectin has been used in many countries.⁸ Despite the limited experience, ivermectin has been reported to reduce the duration of COVID-19 symptom resolution and prevent infection in healthcare workers.^{5, 9} Alternatively, there are critics of the use of ivermectin. In the United States, poisoning caused by ivermectin for animals has been reported because of overdoses. The FDA issued a warning against the use of ivermectin to treat or prevent COVID-19.¹⁰

Both these opinions are understandable. When there is no effective treatment for a new infection, it is natural for the physicians to try any drug that has fewer side effects and might be effective. Ivermectin is recommended mainly by the physicians who treat the patients in the community.

On the other hand, experts in infectious diseases are critical of treatments without adequate evidence. In addition, there is the question of whether randomized studies with placebo can be conducted, when there are so many critically ill patients during the COVID-19 pandemic.¹¹

With the progress of vaccination, the incidence of COVID-19 infections worldwide is expected to reduce. However, the effectiveness of vaccines is not complete. There is no guarantee that vaccination will be effective against future viral mutations. Already many mutations have been reported with variable virulence, the Indian (delta) variant being the most lethal one.¹² Therefore, the development of therapeutic drugs against COVID-19 is utmost necessary. Currently, ivermectin is the only potentially effective and inexpensive treatment that can be administered orally. The usefulness of ivermectin is still under investigation in many countries, including Japan. Hopefully, the efficacy of ivermectin and other antiviral drugs will be proven in the near future, and I hope ivermectin can save the world again.

Understanding these debates will help clinicians to decide whether to use ivermectin in patients with COVID-19. We need to calmly evaluate the effectiveness of drugs and treat COVID-19.

Conflict of interest

None declared by the author.

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