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Global overview on treatment COVID-19 in humans with ivermectin

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Abstract

Given the urgency of the ongoing COVID-19 pandemic, its complications and deaths, the discovery of new mutated strains and the potential for re-emergence of novel coronaviruses, the reuse of drugs such as ivermectin may deserve attention. This review article aims to discuss the potential mechanisms of action of ivermectin against SARS-CoV-2, and COVID-19 by summarizing the available literature since the onset of the disease. Ivermectin inhibits the replication of SARS-CoV-2 in vitro at concentrations not readily achievable with currently approved doses. There is limited evidence to support its clinical use in COVID-19 patients In this comprehensive systematic review, multiple studies have reported that ivermectin exhibits antiviral properties against a wide range of RNA viruses, including Zika, dengue, yellow fever, West Nile, Hendra, Newcastle, Venezuelan equine encephalitis, chikungunya, Semliki Forest, Sindbis, Avian influenza A, Porcine Reproductive and Respiratory Syndrome, Human immunodeficiency virus type 1, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Furthermore, some studies have indicated that ivermectin also shows antiviral effects against DNA viruses, such as Equine herpes type 1, BK polyomavirus, pseudorabies, porcine circovirus 2, and bovine herpesvirus 1. Ivermectin's antiviral actions are attributed to its involvement in various biological mechanisms, suggesting its potential as a candidate for treating a wide array of viruses, including COVID-19, and other positive-sense single-stranded RNA viruses. This systematic review encompasses evidence dating back to 1970, underscoring ivermectin's capacity to combat a diverse array of viral infections. The findings of this study suggest that ivermectin might serve as a valuable antiviral agent for viruses, especially those with positive-sense single-stranded RNA genomes. Notably, experimental studies have shown significant effectiveness when ivermectin is administered during the early stages of infection, which implies its potential in early treatment or prevention. However, it's important to note that confirming these assertions requires human studies and clinical trials.

Keywords: SARS CoV2, COVID-19, Ivermectin, Treatment

Introduction

Ivermectin is an antiparasitic and anthelmintic drug that, after its discovery in 1975, Ivermectin is one of the most important drugs in veterinary and human medicine for controlling and eliminating parasitic infections, and was the joint focus of the 2015 Nobel Prize in Physiology or Medicine, nearly 35 years after its remarkable discovery (Laing, Gillan, & Devaney, 2017). was first used for the treatment and prevention of heartworm and Ascaris. Approved for use in humans in 1987, (Molyneux & Ward, 2015) today the drug is used to treat infestations including head lice, scabies, onchocerciasis, strongyloidiasis, trichomoniasis, ascariasis, and filariasis. It works through several mechanisms to eliminate and kill target parasites and can be taken orally as well as applied to the skin for external infection (Beard Jr, 2001).

Coronavirus disease 2019 (COVID-19) was detected in China in late December 2019. On January 30, 2020, the World Health Organization declared a public health emergency of international concern. As of May 15, 2020, there have been 4,621,410 cases of COVID-19 and 308,542 related deaths worldwide (Sohrabi et al., 2020). Several clinical trials around the world have explored the efficacy of existing drugs against COVID-19, including several antiviral and immune-modifying drugs, Australian researchers from Monash University have demonstrated the efficacy of ivermectin. Viral replication is stopped within 24 to 48 hours in the laboratory. It is a broad spectrum antiviral drug against severe acute respiratory syndrome coronavirus (Caly et al., 2020).

The results indicate moderate certainty that treatment with ivermectin in COVID-19 provides a significant survival benefit. Low certainty evidence suggests a significant effect of prevention. Overall, evidence also suggests that early use of ivermectin may reduce morbidity and mortality from COVID-19, and this is based on (1) reductions in COVID-19 infection when ivermectin was used as a preventative, and (2) better effect estimates for mild to moderate illness. compared to severe illness to death from any cause, and (3) to evidence showing reduced deterioration. Ivermectin is likely to be a global, equitable, acceptable and feasible intervention against COVID-19, and health professionals should strongly consider its use, both in treatment and prevention (Bryant et al., 2021).

Early in the COVID-19 pandemic, laboratory research suggested that ivermectin may have a role in preventing or treating COVID-19. Online disinformation and advocacy campaigns have boosted the drug's image among the public. While scientists and clinicians have remained largely skeptical, some countries have adopted ivermectin as part of their efforts to control epidemics. Some people, desperate to use over the counter ivermectin, took veterinary preparations, resulting in a short supply of ivermectin to treat animals. The US Food and Drug Administration (FDA) responded to this situation by tweeting "You are not a horse" to draw attention to the issue (Annie et al., 2022).

In a scenario marked by a rapid surge in COVID-19 cases and escalating global fatalities, the conventional drugs such as hydroxychloroquine, doxycycline, and azithromycin have proven ineffective as therapeutic options. However, a potential breakthrough emerged from an Australian research group's finding, indicating that ivermectin can suppress the replication of SARS-CoV-2 in in vitro infection experiments. Additionally, Caly et al. from the Royal Melbourne Hospital in 2020 confirmed that ivermectin, an FDA-approved antiprotozoal drug, can inhibit the growth of the SARS-CoV-2 virus in cultured cells in vitro (Wagstaff et al., 2012).

Ivermectin (Fig. 1) has been in widespread use since 1987 for controlling river blindness and lymphatic filariasis, and for treating human scabies. Due to its well-established safety profile and affordability, it was adopted for the treatment and prevention of COVID-19 in Central and South American countries. Within a month of the pandemic declaration, countries like Iraq, Egypt, Iran, and India initiated clinical trials, registering them with the US clinical trial registry and the WHO clinical trial registration platform. The world's first clinical trial results for ivermectin in COVID-19 were published in an observational study conducted at four hospitals in South Florida, USA. The study revealed a significantly lower mortality rate of 15.0% among 173 patients in the ivermectin group, compared to 25.2% among 107 patients in the control group (Yagisawa et al., 2021).

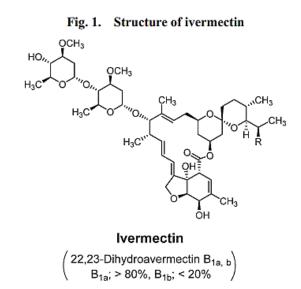


Fig. 1. Chemical structure of Ivermectin(Patil, Verma, & Masand, 2021)

The primary objectives of this study were to determine if ivermectin, given in different doses, is safe in treating patients with early-onset COVID-19 infection, asymptomatic or with few symptoms. The objective of this systematic review and analysis was to combine available results from published or unpublished randomized trials of ivermectin in SARS-CoV-2and COVID-19 infection.

WHO advises that ivermectin only be used to treat COVID-19 within clinical trials

The World Health Organization (WHO) has suggested that ivermectin, a drug used to treat parasitic infections, should only be used in clinical trials for COVID-19 patients. They made this recommendation because there isn't enough solid evidence to prove that it's beneficial in treating COVID-19. This recommendation aligns with the advice from the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), both of which have warned against using ivermectin for COVID-19 outside of clinical trials (Organization, 2021).

A review of studies on ivermectin as a preventive measure for COVID-19 found that the data is too uncertain to say whether it's effective or not. The EMA also looked into ivermectin's use in preventing and treating COVID-19 and concluded that the available evidence doesn't support its use outside of well-designed clinical trials (Bartoszko et al., 2021).

Ivermectin is approved for use in the EU for specific parasitic worm and skin conditions, but not for COVID-19 treatment.

Some laboratory studies have shown that ivermectin can hinder the replication of the COVID-19 virus, but only at much higher doses than those typically prescribed. Clinical studies have produced mixed results, with some suggesting a potential benefit and others finding no clear advantage. Given the limited and inconclusive evidence, it's not recommended to use ivermectin for COVID-19 without further research in controlled clinical trials (Domingo-Echaburu et al., 2021).

Even though there's uncertainty about its effectiveness, some people have used ivermectin for COVID-19, including as a preventive measure. However, its environmental impact, particularly when used in veterinary medicine, is well-known, but the potential environmental harm from its human use has not received much attention.

European Medicines Agency (EMA) advises against use of ivermectin for the prevention or treatment of COVID-19 outside randomized clinical trials

The European Medicines Agency (EMA) reviewed the latest evidence on the use of ivermectin for COVID-19 and concluded that the available data do not support its use for COVID-19 outside well-designed clinical trials (EMA, 2021). While ivermectin is approved for treating certain parasitic worm infestations and skin conditions in the EU, it has not been authorized for COVID-19 treatment, and no applications for such use have been received by the EMA.

The EMA's review considered various sources, including laboratory studies, observational studies, clinical trials, and meta-analyses. It found that ivermectin could potentially inhibit the replication of the SARS-CoV-2 virus at higher concentrations than typically prescribed, but clinical study results varied. Most of the studies reviewed by the EMA were small and had limitations, leading to the conclusion that the current evidence does not support the use of ivermectin for COVID-19 outside of clinical trials.

While ivermectin is generally well-tolerated at approved doses for other conditions, there may be increased side effects at the higher doses needed to effectively combat the virus in the lungs. As a result, potential toxicity cannot be ruled out. Therefore, the EMA advises against using ivermectin for COVID-19 outside of controlled clinical trials and calls for further well-designed randomized studies to determine its effectiveness and safety for COVID-19 prevention and treatment (EMA, 2021).

Despite the uncertainty regarding its clinical benefits, ivermectin has been used for COVID-19, even for prevention. The EMA's advice is in line with this situation, and it also highlights the known environmental concerns of ivermectin in veterinary medicine, while underlining the need for more attention to its potential environmental effects when used by humans (Domingo-Echaburu et al., 2021).

The U.S. Food and Drug Administration (FDA) approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*

In response to the global COVID-19 pandemic, most efforts have been focused on monitoring and containment, although several clinical trials are currently in progress to explore potential treatments. A noteworthy finding is that Ivermectin, an FDA-approved anti-parasitic medication previously known for its broad-spectrum antiviral activity in laboratory settings, has been identified as an inhibitor of the virus responsible for COVID-19, SARS-CoV-2. In experiments conducted on Vero-hSLAM cells, the addition of Ivermectin just 2 hours after the infection with SARS-CoV-2 resulted in a remarkable ~5000-fold reduction in viral RNA levels after 48 hours. These promising results indicate that Ivermectin merits further investigation for its potential benefits in human COVID-19 cases (Caly et al., 2020).

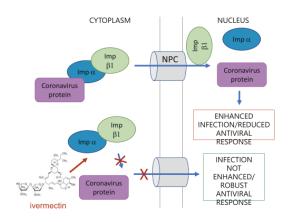


Fig. 2. Schematic of ivermectin's proposed antiviral action on coronavirus. IMP $\alpha/\beta1$ binds to the coronavirus cargo protein in the cytoplasm (top) and translocate it through the nuclear pore complex (NPC) into the nucleus where the complex falls apart and the viral cargo can reduce the host cell's antiviral response, leading to enhanced infection. Ivermectin binds to and destabilizes the Imp $\alpha/\beta1$ heterodimer thereby preventing Imp $\alpha/\beta1$ from binding to the viral protein (bottom) and preventing it from entering the nucleus. This likely results in reduced inhibition of the antiviral response, leading to a normal, more efficient antiviral response (Caly et al., 2020).

The effect of Ivermectin in patients with SARS-CoV-2 / COVID-19

The first clinical study examining the use of ivermectin for COVID-19 was conducted by Rajter et al. in South Florida, USA. This retrospective analysis found that administering ivermectin was associated with a significant reduction in inhospital mortality among COVID-19 patients, particularly those with severe lung involvement (Rajter et al., 2021).

Subsequently, these findings, which emerged in early April 2020, spurred numerous clinical studies at medical institutions worldwide, all seeking to validate the therapeutic and preventive potential of ivermectin for COVID-19. These studies received approvals from institutional or regional ethical review boards.

An experiment involving Syrian golden hamsters infected with SARS-CoV-2 revealed that subcutaneous ivermectin reduced the IL-6/IL-10 ratio in lung tissues and prevented pathological deterioration. Interestingly, the effects of ivermectin appeared to be gender-specific, with a more pronounced impact in females than in males. However, regardless of gender, ivermectin did not affect viral titers in lung or nasal tissues, suggesting that its mechanism of action is not directly related to antiviral activity (de Melo et al., 2020).

In Peru, the results of both the in vitro studies by Caly et al. and the clinical findings of Rajter et al. were highly regarded. Consequently, treatment guidelines were established on May 8th, recommending the use of hydroxychloroquine and ivermectin for mildly ill COVID-19 patients, and a combination of hydroxychloroquine, azithromycin, and ivermectin for moderately and severely ill patients. In an effort to combat COVID-19, the Ministry of Defense, Army, Navy, Air Force, and Police of Peru jointly carried out a large-scale operation named "Mega-Operation Tayta (MOT)," which included the mass distribution of ivermectin. This initiative led to a significant reduction in nationwide deaths, although the numbers started to rise after the program was discontinued due to a change in government in November. In neighboring Bolivia, ivermectin was distributed free of charge to 350,000 people from May 12th. Paraguay imposed restrictions on the sale of ivermectin, and in Colombia, advocacy groups sought policy decisions to prevent the abuse of ivermectin. In Brazil, local governments distributed ivermectin, although it was not implemented at a national level (Chamie-Quintero et al., 2021).

A meta-analysis website, [@CovidAnalysis], displayed a world map in Fig. 3 on its summary page as of February 5, 2021, depicting countries where ivermectin was being used as a COVID-19 countermeasure. The map provided information on each country's stance on ivermectin. The latest version of this map, updated on February 27th, included Japan in the category of "SOME REGIONS" in light green. Japan's inclusion was based on an announcement by the Ministry of Health, Labor, and Welfare on June 16, 2020, indicating that ivermectin, already approved for scabies treatment in Japan, could be used off-label in the clinical management of COVID-19 patients. However, it was emphasized that the use of ivermectin should be considered carefully by clinicians and patients, as it had not yet received official approval for COVID-19 treatment in Japan (Yamamoto et al., 2021).

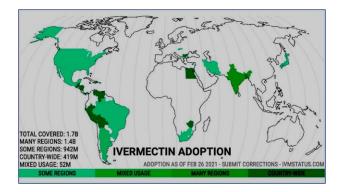


Fig. 3 Countries where ivermectin is adopted for COVID-19 [quoted from Covid Analysis Version 37, Feb 27, 2021 (Yamamoto et al., 2021)

In Fig. 3 the indicated cases (shades of green) where ivermectin is used across the country, where it is used extensively, where it is used in a limited manner, and where it is used in a mixed manner. Table 1 also summarizes these differences and terms of use for each country. Ivermectin is used to treat or prevent COVID-19 in 24 countries around the world. It has already been approved for use nationally in 14 countries and there is a backlog of results from clinical studies conducted for each of these countries. The number of countries is also increasing since the beginning of 2021 (Yamamoto et al., 2021).

Table 1. Global ivermectin adoption for COVID-19 (as of
the 26th of February 2021) https://ivmmeta.com,(Yamamoto et al., 2021)

Country	State	Condition	Data on	
Argentina	mixed usage		Jan 26,2021	
Bangladesh	country-wide adoption			
Belize	country-wide adoption	used for serious cases	Dec 18, 2020	
Bolivia	country-wide adoption			
Brazil	used in some regions		Jan 26, 2021	
Bulgaria	country-wide adoption			
Czech	country-wide adoption	use in hospitalized patients	Mar 3, 2021	
Dominican Rep.	country-wide adoption		Sep 30, 2020	
Egypt	country-wide adoption		Nov 30, 2020	
Guatemala	country-wide adoption		Jan 23, 2021	
Honduras	country-wide adoption		Apr 23, 2020	
India	used in many regions	used in many states		
Iran	used in some regions	Manufacturing own ivermectin		
Japan	used in some regions	*1 & *2 see footnote	Feb 13, 2021	
Lebanon	country-wide adoption		Jan 27, 2021	
Mexico	used in some regions		Dec 29, 2020	
Nicaragua	country-wide adoption		Jan 15, 2021	
North Macedonia	mixed usage		Jan 15, 2021	
Panama	country-wide adoption			
Peru	country-wide adoption		May 8, 2020	
Slovakia	mixed usage	only late treatment	Jan 27, 2021	
South Africa	used in some regions	must apply approval to use	Jan 27, 2021	
USA	used in some regions		Oct 31, 2020	
Venezuela	country-wide adoption			
Zimbabwe	country-wide adoption		Jan 28, 2021	

Used in 25 countries: 15 country-wide, 1 many regions, 6 some regions, 3 mixed usage

*1: Nikkei News (Feb 9, 2021)

*2: Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers Version 2.1 https://www.mhlw.go.jp/content/000646531.pdf on June 16, 2020 on page 26: Off-label use of drugs available in Japan:

other drugs (no clinical trials in Japan) ; ivermectin (anthelmintic; indication: scabies)

An interesting expansion of the clinical application of ivermectin in the prevention and treatment of COVID-19 can also be seen in long-term care facilities for the elderly. In such facilities, residents and staff may often be required to take ivermectin in response to an outbreak of scabies, and in France, the prevalence of COVID-19 in facilities using ivermectin for these purposes is much lower compared to those in facilities where ivermectin is not available (Bernigaud et al., 2021).

Clinical trials of ivermectin

A total of 91 studies from 27 different countries have been registered for COVID-19 research. India leads the way with 15 studies, including 10 in phase 2 or phase 3 clinical trials and 5 observational studies. Out of these, 12 studies focus on treatments, while the remaining 3 aim to prevent disease in healthcare workers and family members who have been in contact with COVID-19 patients. Egypt follows closely with 12 studies, Iran with 10, Brazil with 7, and Argentina with 5. It's worth noting that India ranks second in the world for the total number of COVID-19 infections, while Brazil holds the second position in terms of COVID-19 cases (Yagisawa et al., 2021).

Table 2. Global clinical trials of ivermectin for COVID-19[As of the 31st of January 2021] (Yagisawa et al., 2021)

Country		Phase of clinical trial			_	Purpose of studies			
	Registered Studies *1	1	2	3	4	Observational studies	Treatment	Prophylaxis	Completed studies
Argentina	5		2	1		2	4	1	4
Australia	1			1			1		0
Bangladesh	4		2	1		1	4		2
Brazil	7		3	3		1	6	1	0
Bulgaria	1		1				1		0
Columbia	4		2	2			3	1	0
Egypt	12		1	8		3	9	3	2
France	1	1					1		0
India	15		3	7		5	12	3	1
Iran	10		1	9			10		6
Iraq	2	1	1				2		2
Israel	1					1	1		0
Italy	2		2				2		0
Japan	1		1				1		0
Lebanon	1					1	1		0
Mexico	4		1	2		1	4		1
Nigeria	1			1			1		1
Pakistan	3		1	1		1	3		1
Peru	2		2				2		0
Saudi Arabia	1					1	1		0
Singapore	1			1				1	1
Spain	4		2	2			3	1	0
Thailand	1				1		1		0
Turkey	1			1			1		1
UK	1			1			1		1
USA	4		2	1	1		4		0
Zambia	1			1			1		1
27 Countries	91	2	27	43	2	17	80	11	21

Conclusion

Although the results of clinical trials in various countries of the world are accumulating and still show that ivermectin is effective in the treatment and early prevention of COVID-19, the basic in vitro results that could reasonably explain its effectiveness have not yet been obtained. As there is a wide range of biological activities in multiple stages that can act to exert a more comprehensive effect. Although it should be further clarified and documented by future studies, the conclusion of the research is that clinical efficacy can be determined by investigating antiviral activity, inhibition of the virus-host cell relationship, and actions related to the regulation of host interactions. It is also necessary to establish that other effects occur, and it appears that such investigations can be appropriate research topics for basic researchers, pharmacological researchers, and clinical researchers for collaboration and clarification. It has been confirmed by the collaboration of researchers around the world and its clinical use is being achieved on a global scale, and it could be of great benefit to humanity.

Conflict of Interest

The author hereby declares no conflict of interest.

Consent for publication

The author declares that the work has consent for publication.

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