Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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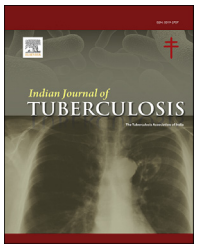

Letter to the Editor

White paper on Ivermectin as a potential therapy for COVID-19

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ABSTRACT

A group of senior doctors with vast clinical experience met on 19th July'20 under the aegis of Academy of Advanced Medical Education. The panel looked at Ivermectin, one of the old molecule and evaluated it's use in COVID 19 (Novel Coronavirus Disease 2019) management. After critical panel discussion, all the attending doctors came to a conclusion that Ivermectin can be a potential molecule for prophylaxis and treatment of people infected with Coronavirus, owing to its anti-viral properties coupled with effective cost, availability and good tolerability and safety.

1. Executive summary

SARS-CoV-2, a small 100 nm virus has emerged as an elusive foe, threatening mankind. Currently India is placed 3rd in terms of number of reported cases which warrants newer therapeutic treatment options that are widely available, affordable, effective and safe.

There are newer drugs on the horizon which have been recommended though with very limited experience & devoid of enough data about safety and efficacy.[1] These newer options are neither easily available nor affordable.

We have revisited some of the old molecules & have found Ivermectin, originally introduced as an anthelmintic to be an effective, safe and affordable therapeutic option in Indian settings for prevention and treatment of COVID-19.[2]

Recent research has shown that Ivermectin possesses strong anti-viral properties.[3] It has potential to convert RT-PCR negative quickly.[4] It can be used across the severity of COVID-19 especially in early viremic phase.[5] It can be combined with other molecules of interest, like Hydroxychloroquine, azithromycin, doxycycline.[6] Ivermectin is affordable, easily available, and safe without any major side effects.[5]

This white paper is an attempt to propose Ivermectin, a strong antiviral drug as a therapeutic option in the prevention and treatment of mild, moderate and severe cases of COVID-19.

A group of senior doctors with vast experience in the management of COVID-19 got together on 19th July'20 under the leadership of Prof Dr V. K. Arora, Prof. Dr D. Behera, Prof. Dr Suryakant Tripathy, Dr. MohanKumar Thekkinkattil, Dr. Agam Vora, Dr. Vasant Nagvekar, Lt Gen (Rtd) Dr. B.N.B.M Prasad, Dr. K.S. Satish, Dr. V.K.Singh, Dr. Mangesh Tiwaskar, Dr. Parthiv Mehta, Dr. P. Sarat Singh, Dr. Narayana Pradeep, Dr. Rahul Mayekar and Dr. Bhupesh Dewan, under the auspices of Academy of Advanced Medical Education. Many of the attending doctors shared their personal experience of using Ivermectin successfully with very good results in their patients. The group, at the end of the discussion, proposed the following consensus statement:

> **"Ivermectin in the dose of 12 mg BD alone or in combination with other therapy for 5 to 7 days may be considered as safe therapeutic option for mild moderate or severe cases of Covid-19 infection. It is cost effective especially when the other drugs are very costly & not easily available".**

However, the group strongly feels the urgent need for a well-designed randomized control trial & proposes judicious use of Ivermectin for Covid-19 treatment.

2. Epidemiology

COVID-19 pandemic has affected more than 14 million people worldwide and number is going up daily.[7] There is no definite therapy available and repurposing of the older molecules is being studied vigorously.[8] The earlier touted molecules like hydroxychloroquine have little efficacy and that too in early

stage of the disease cycle.[9,10] On the other-hand, with the limited clinical evidence available till date, Ivermectin has shown its promise in all phases of the disease and is being used both prophylactically and for treatment of all phases of disease from mild to severe.[5]

3. Phases of COVID-19 infection

It has been proposed that COVID-19 infection in the lungs encompasses three main phases: an initial phase involving viral replication and relatively mild symptoms (early infection phase); a second phase characterized by adaptive immunity stimulation and predominance of respiratory symptoms (pulmonary phase); and, in some cases, a third and last phase with progress to a hyper inflammatory condition (hyper inflammation phase). According to phase of infection, clinical features ranges from mild symptoms (fever, cough, myalgia or fatigue, sore throat, headache) to acute respiratory distress syndrome (hypoxemia, shortness of breath) to ARDS, shock, multi-organ failure respectively.[11]

4. Ivermectin is an old molecule with proven safety[5]

Ivermectin is a well-known anthelmintic agent from the late-1970s. In recent times, the antiviral function of ivermectin has been discovered. Already its effectiveness against certain flavivirus (dengue fever, Japanese encephalitis and tick-borne encephalitis virus) and chikungunya virus has been demonstrated in vitro. Since then the same activity has been assessed in numerous other viral infections. Off lately its potency has been recognized in eliminating coronavirus in vitro.[12] It reduces the SARS-CoV-2 viral load by a factor of 5000 in 48 hours.[4]

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, showing promising results both in terms of symptomatology as well as viral load reduction.[13]

5. Ivermectin mechanism of action

Sequestration of the **SARS-CoV-2** viral nucleocapsid protein (NCP) into the host nucleus through the nuclear-pore-complex is a vital step in viral pathogenesis and defense against host immune response.[5]

Ivermectin selectively inhibits host importin α/β transporter protein which decreases translocation (shuttling) of SARS CoV nucleocapsid protein (NCP) from the cytoplasm to the nucleus, altered NCP distribution disrupts viral propagation & survival.[4]

5.1. *Sequestration in the pulmonary tissue*

Ivermectin was found to selectively concentrate in the pulmonary tissue, around 3 times the plasma concentration and is sequestrated in the pulmonary tissue with a long residence time.[5]

5.2. *Adverse reactions*

Ivermectin has been demonstrated to be generally well tolerated. For the most part side effects have been mild and transient in nature.[14]

6. Special populations

6.1. *Pregnancy*

Pregnancy Category C. Ivermectin has been shown to be teratogenic in mice, rats, and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.[15]

6.2. *Nursing mothers*

Ivermectin is excreted in human milk in low concentrations. Treatment of mothers who intend to breastfeed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the neonates.[15]

6.3. *Pediatric use*

Safety and effectiveness in pediatric patients weighing less than 15 kg have not been established.[15]

6.4. *Geriatric use*

Clinical studies of ivermectin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.[15]

7. Ivermectin is easily available and highly affordable[5]

Ivermectin therapy costs less than Rs. 1000 for the complete course (at a dose of 12mg BID for 7 days). Ivermectin is easily available at retail stores throughout India.

8. International status

The **Australian team** that conducted the breakthrough lab study recently received funds from the Helmsley Charitable Trust to advance Ivermectin targeting COVID-19.[4]

8.1. *In Peru*

Ivermectin is now approved for at least mild cases of COVID-19.[16]

8.2. *In Bolivia*

Ivermectin is approved in the north-eastern Beni region.[16]

8.3. *Indian council of medical research*

(ICMR) is now reviewing the benefits of Ivermectin and doxycycline as a potential therapy for COVID-19.[17]

Recently, there have been several observational studies in Bangladesh showing encouraging results in a case series of Covid 19 patients given a combination of Ivermectin and Doxycycline.[6] The combination was tested by Dr. Tarek Alam at the Bangladesh Medical College.[17]

9. Ongoing clinical trials in various countries

1. **USA STUDY I:***Printed in Medscape (Jul 15, 2020, Author: David J Cennimo, MD, FAAP, FACP, AAHIVS; Chief Editor: Michael Stuart Bronze, MD.)* Ivermectin at four Florida hospitals showed significantly lower mortality rates in those who received ivermectin compared with usual care (15% vs 25.2%; P = 0.03). It was a retrospective cohort study (n = 280) in hospitalized patients with confirmed SARS-CoV-2 infection. Ivermectin, showed in vitro reduction of viral RNA in Vero-hSLAM cells 2 hours' post-infection with SARS-CoV-2 clinical isolate Australia/VIC01/2020. The mortality rate was also lower among 75 patients with severe pulmonary disease treated with ivermectin (38.8% vs 80.7%; P = 0.001), although the rate of successful extubation did not differ significantly.[18,19]
2. **USA STUDY II:**An observational registry-based study from 169 hospitals across Asia (AS), Europe (EU), Africa (AF), North (NA) and South America (SA), evaluated critically ill hospitalized patients diagnosed with COVID-19 with lung injury requiring mechanical ventilation, between January 1st 2020 and March 1st 2020. In this series of 1,970 patients, 1,609 survived hospitalizations to discharge and 361 died (18.3%). 52 patients (AS-7, EU-21, AF-3, NA-14, SA-7) who received Ivermectin (150 mcg/Kg) once after mechanical ventilation were instituted. The indications for use of the drug were related to clinician preference and based on prior data on the broad antimicrobial and specifically antiviral effects of this agent. Compared to 1,918conventionally treated patients a survival benefit for Ivermectin mortality rate was observed (18.6% vs 7.7%; HR 0.18, 95% CI, 0.07–0.48; log rank [Mantel–Cox] p < 0.001). The hospital length of stay was 15.7 ± 8.1 days' vs 10.9 ± 6.1 days, p < 0.001 and intensive care unit length of stay was 8.2 ± 6.2 days' vs 6.0 ± 3.9 days, p < 0.001 respectively.[20]
3. **DOMINICAN REPUBLIC STUDY**: Ivermectin was administered in 1,300 early stage COVID-19 patients. Treatment began with standard dose of 100–200 mcg/kg and have escalated that to 400 mcg/kg. Some of the patients also received azithromycin.99% of them were cured. Average duration of full infection went down from 21 days to 10 days. Ivermectin starts inhibiting the virus within a couple days in humans. Only side effects reported were mild heart burn and diarrhea.[21]
4. **BANGLADESH STUDY**: RCT involving mild to moderate degree of COVID-19 patients Study groups, A (n = 60): Ivermectin 200 mcg/kg single dose + Doxy 100mg BID for 10 days; and B (n = 56): HCQ 400 mg 1st day, then 200mg BID for 9 days + Azithromycin 500mg daily for 5 Days. Treatment outcomes were evaluated on 5th day in case of asymptomatic patients and 2nd non-symptomatic day onward from 1st day of the drug intake. Outcome: **Group A vs. Group-B**: Recovery rate was 100% vs 96.36%, mean symptomatic recovery duration was 5.93 days' vs 6.99 days, negative PCR was achieved on 8.93 days vs. 9.33 days, and by 5th day, 55.10% vs23.8% of patients gained symptomatic recovery. Adverse events Group A (31.67%) and B (46.43%). Ivermectin–Doxycycline combination therapy has a better success of symptomatic relief; shortened recovery duration, reduced adverse effects, and superior patient compliance compared to the Hydroxychloroquine–Azithromycin combination.[6]
5. **INDIA:** A study on 2000 patients is ongoing in Max Super Speciallity Hospital (DDF), East Block, Internal Medicine Department, 2- Press Enclave Road, New Delhi.[22]

10. Urgent need for randomized clinical trial

There is urgent need of well-designed randomized controlled trial to assess its efficacy for validating the use of Ivermectin against SARS-CoV-2.[23] Nearly 40 clinical trials are ongoing world over for measuring the outcome of COVID-19 treatment with Ivermectin.

Author's contributions

All authors provided critical feedback and contributed to the final manuscript.

Declaration of Competing Interest

The authors have none to declare.

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