

Drug Corner

Ivermectin as a Chemo-prophylactic Agent against COVID-19: A Consensus Statement

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Under the aegis of Academy of Advanced Medical Education, a panel comprising of Infectious Disease Specialists and pulmonologists with years of experience met on August 30, 2020; September 22, 2020 and October 13, 2020. Based on the currently available evidence, the panel reached at a consensus that a dosage regimen of ivermectin with dose ranging from 200-400mcg/kg bw, can be used prophylactically (12 mg for below 60 kg, 18 mg for 60-90 kg, and 24 mg for >90 kg of body weight) against COVID 19. First three doses of 12 to 24mg, ivermectin should be given 72 hours apart and then once monthly. Four groups of individuals are recommended for prophylactic treatment; healthcare workers (Corona Warriors), asymptomatic close contacts of confirmed COVID-19 cases, individuals residing in containment zones and high risk groups: like diabetes, obesity, cardiac disorders, immunocompromised patients including HIV positive cases and individuals above 60 years of age.

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Currently, with more than 7 million confirmed coronavirus disease 2019 (COVID-19) cases, India ranks 2nd in the world.¹ This has resulted in an immense burden on both national economy and healthcare set-

up. To tackle this issue, ideal approach would be prevention of COVID-19, thereby decreasing the total number of cases.²

With the launch of COVID-19 vaccine being a distant

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dream, repurposing of already approved drugs present a realistic approach. Introduced in 1980s, as an anthelmintic agent, ivermectin has a known safety profile with low incidence of adverse events, when administered orally.³ Simultaneously, its antiparasitic, antiviral, immunomodulatory, and anti-cancer activity were discovered and it has been termed as a wonder drug.^{4,5}

Recently, researchers from Australia provided the first evidence of action of ivermectin against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).⁶ Subsequently, ivermectin is being used globally as a prophylactic and therapeutic agent against COVID-19 and is undergoing various randomized controlled trials.⁷⁻¹⁴

Academy of Advanced Medical Education held panel discussions on August 30, 2020 and September 22, 2020 under the guidance of Prof. Dr V K Arora in presence of following Infectious Disease Specialists

Prof Dr Agam Vora, Prof Dr AG Ghoshal, Prof Dr Surya Kant, Prof Dr Ravi Wankhedkar, Prof Dr Prasanta Mohapatra, Prof Dr Pradhyut Waghray, Dr Harsh Rastogi, Prof Dr Alladi Mohan, Prof Dr Pradeep Bhowmik, Dr Mangesh Tiwaskar, Dr Jayesh Lele, Dr Amit Gupta, Dr Parthiv Mehta, Prof Dr Ketan Mehta, Dr Arvind Ghongane, Dr Bhavin Shah, Dr Shuchin Bajaj and Dr Bhupesh Dewan.

Rationale for using Ivermectin as a Chemo-prophylactic agent :

(1) Following an *in-vitro* experiment by Caly *et al*, multiple mechanisms of action have been proposed that suggest anti-SARS-CoV-2 activity of ivermectin.

(a) It has been proposed that ivermectin does not target any specific viral protein, but rather acts by inhibiting the binding of importin- α (IMP α) to importin- β 1 (IMP β 1). Moreover, it acts by targeting the IMP α / β 1 heterodimer, resulting in its dissociation.¹⁵ This dissociation hampers binding of Imp α / β 1 to the viral protein, thereby preventing it from entering the nucleus. This leads to reduced inhibition of the antiviral responses, resulting in a normal, more efficient antiviral action.⁶

(b) The initial transfer of IMP α / β 1 heterodimer to cell nucleus results in initiation of the viral life cycle. This suggests that prior inhibition of importin receptor leads to decreased rate and intensity of viral growth. This may also decrease the chances of infection of non-infected host cells. Similarly, when administered in the early phase of infection, ivermectin halts the nuclear transportation of IMP α / β 1 heterodimer resulting in decreased severity and duration of disease, as well as attenuated spread of infection.¹⁶

(c) Another study has highlighted that ivermectin has a significantly better binding affinity for SARS-CoV-2 proteins than doxycycline and shows a perfect binding site to the interacting regions of Spike-RBD and angiotensin converting enzyme 2 (ACE2). This indicates that ivermectin might be acting by interfering in the interaction of spike with ACE2 and inhibiting the viral entry in to the host cells.¹⁷

(d) Ivermectin has been described to act as an ionophore. It generates pores in biological membrane of SARS-CoV-2, disturbs its hydro-electrolyte balance, and exerts antiviral action.¹⁸

(e) Recently, 'catch and clump' hypothesis has been proposed. The SARS-CoV-2 catches CD147 receptor on red blood cells (RBCs) and endothelial cell. Following this binding, RBCs forms clumps with other RBCs, leucocytes, platelets, and endothelial cells resulting thrombotic complications. It has been assumed that ivermectin acts by competitively binding the spike proteins of SARS-CoV-2 and prevents the formation of clumps, thereby exerting anti-thrombotic action.¹⁹

(f) Ivermectin is proposed to act on four important drug targets, spike protein, RNA-dependent RNA polymerase, 3-chymotrypsin- and papain-like proteases of SARS-CoV2.²⁰

(2) In an *in-vitro* experiment, Caly *et al*. demonstrated that a single application of ivermectin (5 μ M) could eliminate 99.98 % viral RNA within 48 hours in SARS-CoV-2 infected Vero/hSLAM cells. Moreover, it is worth highlighting that no cytotoxicity was observed at this high concentration.⁶

(3) Over the past 30 years, ivermectin has demonstrated a favourable safety profile in humans.²¹ A study involving healthy adult individuals evaluated the safety and tolerability of escalating doses of ivermectin and reported that safety and tolerability of ivermectin was comparable to placebo, even at dose that were 10 times the maximum approved dose.²²

(4) Finally, ivermectin is included in the 21st WHO Model List of Essential Medicine 2019 and also finds place in the National List of Essential Medicines of various member nations.²³ This had resulted in easy availability of ivermectin at reasonably affordable price in major areas of the world.

Ideal Candidates for Chemo-prophylactic Therapy:

- The healthcare workers (corona warriors including doctors, para medics, nurses and support staff like persons associated with morgue, crematorium, ambulance, security at health care etc)
- Asymptomatic close contacts of confirmed

COVID-19 cases including family members, household workers, immediate neighbors, care takers, office and business staff etc.

- Individuals residing in containment zones : Red Zone as declared by appropriate authorities or area with overcrowded residences with multiple COVID confirmed cases or buildings and colonies having confirmed cases on home quarantine.

- High risk group : People with comorbidities like uncontrolled Hypertension, uncontrolled diabetes, obesity, cardiac disorder, immune compromised diseases including HIV, elderly people with frailing immunity are ideal candidates for chemo-prophylactic therapy.

Ivermectin acts by suppressing the replication of SARS-CoV-2 within 24-48 hrs, it decreases the risk of contracting the COVID-19.⁶ Ivermectin can be beneficial and provides considerable protection in these candidates and this has been confirmed by the findings of recently completed clinical trial.²⁴

Pharmacokinetics – Rationale for dosing & frequency for prophylaxis :

Ivermectin is highly lipophilic, and rapidly absorbed ($T_{max} = 4$ hours). It binds strongly to plasma proteins (93 %), and has a predilection for sequestration in tissues (Volume of distribution~3.5 L per Kg).²⁵ Following single doses of 30 to 120 mg, AUC and C_{max} were generally dose proportional, with T_{max} ~4 hours and $t_{1/2}$ ~18 hours (range 12-36 hours). The geometric mean AUC of 30 mg ivermectin was 2.6 times higher when administered with food. Geometric mean AUC ratios (day 7/day 1) were 1.24 and 1.40 for the 30 and 60 mg doses, respectively, indicating that the accumulation of ivermectin given every fourth day is minimal.²⁶ Based upon the half-life range of 12-36 hours, once a week dosage schedule can be justified for prophylaxis, but due to paucity of safety data on frequent weekly dosing, the academy advocated the use of once monthly dosage schedule. This regimen may be modified to more frequent dosing, once we get more experience on the molecule and its long term safety.

Clinical Safety :

Ivermectin has been well tolerated when administered as a single dose of 800 μg per kg,²⁷ and multiple dose of 1,600 μg per kg over 12 weeks,²⁸ and 1,600 μg per kg over 13 days.²⁹ In a recent meta-analysis, Navarro *et al* compared the safety of standard (up to 400 μg per kg) and high dose (up to 800 μg per kg) ivermectin and reported no significant differences between them in terms of frequency or intensity of adverse events.³⁰ Moreover, long-terms follow-up

studies have reported that ivermectin in a dose of 400 μg per kg does not result in increased incidence of death amongst elderly.^{31,32}

However, ivermectin is contraindicated in pregnant women and its safety and efficacy is not established in children weighing less than 15 kg.³³

Hydroxychloroquine (HCQ) was initially recommended as a chemo-prophylactic agent in COVID-19. However, it should be avoided in cases with ischemic heart disease, as it has been found to be associated with cardiotoxicity and results in prolongation of QTc interval and cardiac arrhythmias.^{34,35} Moreover, in severe and critical COVID-19 cases with diabetes, use of HCQ is associated with the risk of hypoglycaemia.^{36,37} In these two subset of cases, HCQ is contraindicated. Comparatively, ivermectin has no such contraindications and can be given in high doses without any safety concerns.

Prophylactic Clinical Trials :

Currently, only one clinical trial (NCT04422561) evaluating the efficacy of ivermectin, as a prophylactic agent, in asymptomatic close family contacts (N = 340) of COVID-19 cases is complete (unpublished data). It is a randomized, open label, phase 2/3 study, in which individuals in Ivermectin group (N = 203) received 2 doses [dose of 15 mg per day (40-60 kg), 18 mg per day (60-80kg), and 24 mg per day (>80kg)] of tablet ivermectin 72 hours apart, while individuals in Control group (N = 101) were observed without prophylaxis. At the end of the study, the protection rate was 92.6% and 41.6% in the Ivermectin and Control group, respectively. This finding suggests that two doses of tablet ivermectin provided considerable protection in asymptomatic close family contacts.²⁴

As of Sep 2020, there are 5 ongoing clinical trials (NCT04446104, NCT04447235, NCT04527211, CTRI/2020/05/025333, and CTRI/2020/06/026232) evaluating the efficacy and safety of ivermectin as a chemo-prophylactic agent against COVID-19.⁷⁻¹¹ Variable doses of ivermectin are being evaluated in these trials and ranges from single dose of 200 μg per Kg (CTRI/2020/06/026232) to weekly dose of 200 μg per Kg for 7 weeks (NCT04527211).

Indian Prophylactic Guidelines :

On August 6, 2020, the Government of Uttar Pradesh Government had released a guideline regarding prophylactic use of ivermectin against COVID-19. As per the guideline, the close contacts of COVID-19 cases are recommended ivermectin tablets in a dose of 200 μg per Kg body weight on Day 1 and Day 7, 2 hours following the dinner. While, in healthcare

workers, ivermectin tablet is recommended in a dose of 200 µg per Kg body weight on Day 1, Day7, Day30, and then monthly, 2 hours following the dinner.³⁸

Recently, on September 29, 2020, the Government of West Bengal introduced ivermectin as a chemoprophylactic agent against COVID-19. As per the guideline, once daily dose of 12 mg ivermectin is recommended on Day 1, Day 7, and then monthly.³⁹

Global Prophylactic Guidelines :

In Brazil, for healthcare workers, the authorities have recommended ivermectin tablet 6 mg per 30 kg body weight for two days, and then every 15 days. While, in case of individuals at risk of COVID-19, other than healthcare workers, single dose of ivermectin (6 mg per 30 kg body weight) followed by every 15 days is recommended.⁴⁰

In Peru, healthcare workers and other individuals at risk are recommended a single dose of 6 mg/mL ivermectin suspension in a dose of 1 drop (200 µg) per Kg body weight, with maximum dose of 50 drops.⁴¹

Consensus Statement :

In light of the exigent circumstances, absence of a clearly safe and effective therapeutic agent/vaccine and the emerging evidence, especially a recently completed randomized control trial (RCT) in Egypt, the panel reached at a consensus that

- Ivermectin is economical, easily available, safe & is well tolerated drug and does not have any significant drug to drug interaction & it may be considered as a chemo prophylactic drug against COVID 19
- A dosage regimen of ivermectin with dose ranging from 200-400mcg/kg bw, can be used prophylactically (12 mg for below 60 kg, 18 mg for 60-90 kg, and 24 mg for >90 kg of body weight). First three doses of 12 to 24mg, ivermectin should be given 72 hours apart and then once monthly.

Four Group of Individuals are Recommended for Prophylactic Treatment :

1. Healthcare workers (Corona Warriors)- may receive prophylaxis till COVID 19 continues to be a public health problem.

2. Asymptomatic close contacts of confirmed COVID-19 cases- 3 doses 72 hours apart followed by one additional dose if the index case continues to shed the virus for a longer period of time.

3. Individuals residing in containment zones : for at least one month after the area is declared green zone or at least one month after the last case is cured in that area / building or colony

4. High risk groups: like diabetes obesity, cardiac

disorders, immunocompromised patients including HIV positive cases and individuals above 60 years of age – Till COVID 19 continues to be a public health problem

Panel emphasizes that due to paucity of evidence, this recommendation is preliminary and shall be revised based on the availability of new safety and efficacy data. The panel firmly believes the urgent requirement of a well-designed RCT involving healthcare workers, asymptomatic close contacts of confirmed COVID-19 cases, individuals residing in containment zones and high risk groups. The panel also feels that ivermectin may be combined with other drugs like Zinc, Vitamin C and Vitamin D3 to enhance the overall prophylactic benefit.

Disclosure and Acknowledgement :

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