Ivermectin in Covid-19: Review of the Current Evidence

Sandeep Nayar[1], Puneet Khanna[2], Pankaj Anand[3], N.K. Soni[4], Niraj Tyagi[5], Yashwant Dubey[6], Siddharth Patanwar[7], Aaditi Phadke[8], Parthasarathy Muralidharan[8], Amit Qamra[8]

Abstract

The COVID-19 pandemic has gripped the world in fear with more than 109 million cases and more than 2.4 million deaths as of 16th February 2021. After US, India has the second highest number of cases in the world. A pandemic of this scale has clearly become an unmet medical need warranting research on effective pharmaco-therapeutic agents. Given the time constraints, existing drugs have been repurposed to fill in the gap. Ivermectin is an FDA-approved broad spectrum anti-parasitic agent. It is enlisted in the core list of WHO Model List of Essential Medicine 2019. Ivermectin is economical, easily available and safe without any major side effects. Recent research has shown that Ivermectin possesses strong anti-viral properties. It can also be safely combined with other repurposed drugs for Covid-19. Here, we review mechanism of action and current scientific evidence of Ivermectin in treatment and prophylaxis of Covid-19. A number of ongoing clinical trials are evaluating the drug further in the treatment and prophylaxis of Covid-19. Based on the current clinical evidence in treatment and prophylaxis, Indian Experts' consensus and recommendations by multiple Indian state governments, Ivermectin may effectively and safely add to the current armamentarium of Indian clinicians involved in the care and management of Covid-19 patients.

Keywords: **Ivermectin, Covid-19. SARS-CoV-2**

Conflict of Interest: **Aditi Phadke, Parthasarathy Murlidharan and Amit Qamra are salaried employees of Macleods Pharmaceuticals Ltd., Mumbai, India. Other authors declare no conflict of interest.**

Source of funding: **None**

[1] Senior Director and Head, BLK centre for Chest & Respiratory diseases, BLK Super Speciality Hospital, New Delhi;
[2] Senior Consultant and Head, Department of Interventional Pulmonology, Respiratory & Sleep Medicine, Manipal Hospitals, New Delhi;
[3] Senior Consultant, Critical Care & Internal Medicine, Fortis Escorts Hospital, Jaipur;
[4] Senior Consultant & Head- Internal Medicine & Diabetology. Yatharth Super Speciality Hospital, Greater Noida;
[5] Consultant, Institute of Critical Care Medicine, Sir Ganga Ram Hospital, New Delhi;
[6] Senior Consulting Physician, Arpan Sugar Clinic, Bilaspur;
[7] Department of Pulmonary Medicine, AIIMS, Raipur;
[8] Department of Medical Affairs, Macleods Pharmaceuticals Ltd, Mumbai
Corresponding Author: Aaditi Phadke, Department of Medical Affairs, Macleods Pharmaceuticals Ltd, Mumbai. Email: aditip@macleodspharma.com

Introduction

The COVID-19 pandemic has gripped the world in fear with more than 109 million cases and more than 2.4 million deaths as of 16th February 2021. After US, India has the second highest number of cases in the world.[1] COVID-19 has worse prognosis if associated with disease conditions such as cardiovascular disease, COPD, Asthma, Diabetes, Hypertension, Chronic Kidney Disease and Cancer.[2] Our knowledge about the virus and the disease caused by it was minimal during the initial phases of the pandemic. With passage of time, the medical fraternity is more empowered with knowledge, experience and scientific evidence. Further, in the beginning of 2021, silver lining in India has been the emergency approval of two Covid-19 vaccines with over 8.7 million healthcare professionals and frontline workers been vaccinated till date.[3,4]

As of yet, there are no proven antiviral medication(s) available for COVID-19.[5] A pandemic of this scale and magnitude has clearly become an unmet medical need warranting research on effective pharmaco-therapeutic agents. Given the pandemic proportion and time constraints, existing drugs may be repurposed to fill in the gap.[6] Drug repurposing (process of identifying new uses for approved or investigational drugs) is an effective strategy for drug discovery as it involves lesser time and cost to find a therapeutic option in sharp contrast to the *de novo* drug discovery process which may take years. An interesting lesser known fact is that 75% of existing drugs can be repurposed for existing diseases.[6] Table 1 depicts the commonly used repurposed drugs in India for Covid-19 with their mechanism, route of administration, etc.

SARS-CoV-2 structure

SARS-CoV-2 is one of the largest known RNA viruses with genome size ranging between 27-32 kilobase pair (kbp). When SARS-CoV-2 virions are viewed under an electron microscope, they have large peplomers that give it the appearance of a crown, hence the name "corona" (meaning crown or halo). Its genome comprises positive-sense, single-stranded RNA (+ssRNA).[9] The main proteins in the SARS-CoV-2 virion are spike (S) proteins, envelop (E) proteins, membrane (M) proteins and nucleocapsid (N) proteins. These proteins are involved in the infectivity and pathogenesis of COVID-19.[9,10]

The Spike (S) protein recognises and attach-

Table 1: Commonly repurposed drugs for Covid-19 in Indian scenario: [7,8]

Repurposed drug	Mechanism of action	Route of administration/ Clinical usage	Adverse drug reactions
Hydroxychloroquine[7,8]	Blockade of viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Additional immunomodulatory effects through inhibition of cytokine production, autophagy, and lysosomal activity in host cells	Oral/ Mild-moderate Covid-19	Abdominal cramps, anorexia, diarrhoea, nausea, vomiting. Cardiovascular effects (including QTc prolongation), hematologic effects (including haemolysis with G6PD deficiency), hypoglycemia, retinal toxicity, neuropsychiatric and central nervous system effects, idiosyncratic adverse drug reactions.
Favipiravir[7]	RNA dependent RNA polymerase inhibitor	Oral/ Mild-moderate Covid-19	Hyperuricemia, diarrhoea, elevated transaminases, reduction in neutrophil count
Remdesivir[7,8]	RNA dependent RNA polymerase inhibitor	IV/ Severe Covid-19	Elevated transaminases (reversible), kidney injury
Tocilizumab[7,8]	IL-6 inhibition (reduction in cytokine storm)	IV/ Severe Covid-19	Increase in upper respiratory tract infections (including tuberculosis), nasopharyngitis, headache, hypertension, increased AST, infusion related reactions, hematologic effects, infections, hepatotoxicity, gastrointestinal perforations, hypersensitivity reactions

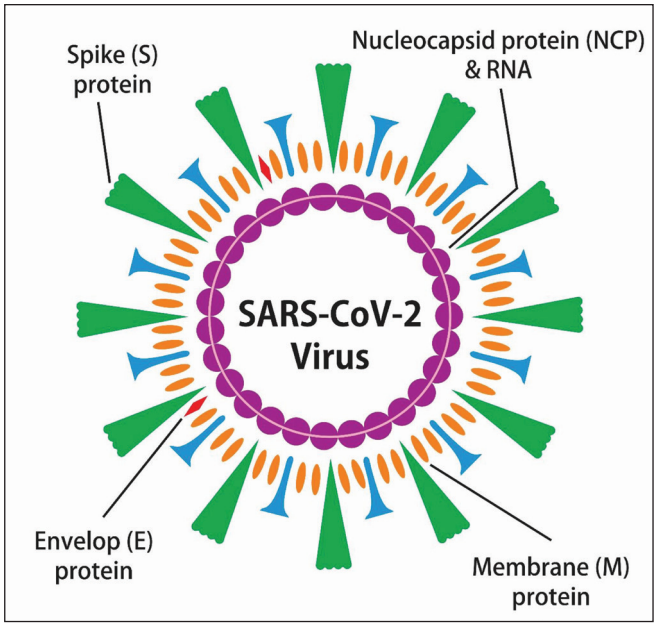

Figure 1: Simplified structure of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)

es to ACE2 receptors of the host cell. [11,12] Membrane (M) proteins are responsible for shaping the virion. Envelope (E) proteins have the function of virion assembly and release. The role of nucleocapsid proteins (NCPs) is packaging of the RNA genome in the virions and also function as interferon (IFN) inhibitor.[9] Figure 1 depicts the structure of SARS-CoV-2.

The replication of SARS-CoV-2 (RNA and proteins synthesis) occurs in cytoplasmic organelles of the host cell [9,13]. Research done on SARS-CoV (to which SARS-CoV-2 is closely related), depicts that the virus has mechanisms to interact with the host cell's nuclear import pathways. The viral Nucleocapsid protein (NCP) gets translocated into the host-cell nucleus through the nuclear-pore-complex (NPC). This seems to be a vital step in viral pathogenesis and viral defence against host immune response.[13] The intranuclear shuttling of the SARS-CoV-2 Nucleocapsid protein seems to occur by utilization of host cell proteins called importins α and $\beta1$.[13,14] Once these proteins are transported into the host-cell nucleus, they reduce the host cell antiviral response and can enhance the SARS-CoV-2 infection (Figure 2).[14]

This rapid nuclear sequestration of the viral nucleocapsid protein (NCP) occurs during the initial period of infection. At this time primary viral protein translation occurs in the host cell followed by a relatively silent stage during which the virus replicates in the cytoplasm. During the later stages, the stored NCP returns back to the cytoplasm of the host cell to participate in

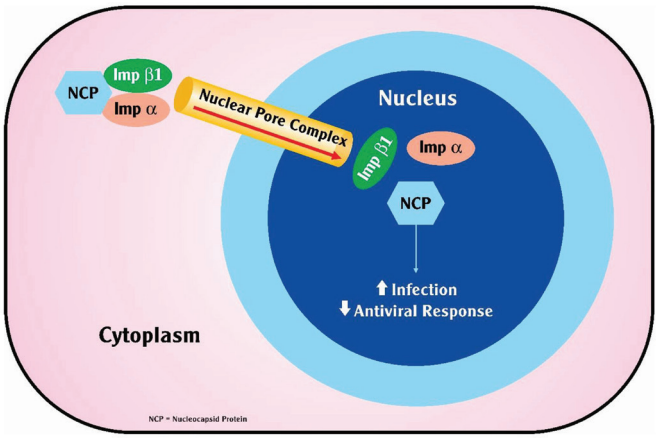

Figure 2: SARS-CoV-2 Nucleocapsid protein and nuclear import

assembly and release of the virion.[13] Hence, the NCP may function as a trojan horse by silently entering the nucleus exerting a negative influence on the host cell's antiviral response.

Ivermectin

Ivermectin is an FDA-approved broad spectrum anti-parasitic agent. It is enlisted in the core list of WHO Model List of Essential Medicine 2019. Ivermectin is currently approved by United States Food and Drug Administration and European Medicines Agency as an anti-parasitic agent. In India, Ivermectin is approved by Drugs Controller General (India) as an anthelmintic. Ivermectin is economical, easily available and safe without any major side effects. Recent research has shown that Ivermectin possesses strong anti-viral properties. It has the potential to convert Covid-19 patients to RTPCR negative quickly. Further, Ivermectin can be used across the severity of COVID-19. It can also be combined with other repurposed drugs for Covid-19. [13,14,15]

Here, we review mechanism of action and current scientific evidence of Ivermectin in treatment and prophylaxis of Covid-19 which will help the healthcare professionals in informed decision making in the management and care of Covid-19 patients.

We searched three bio-medical databases (Google Scholar, PubMed and medrxiv.org) for Ivermectin in Covid-19. We only considered studies specific to Ivermectin in Covid-19 which were pre-clinical (in-vitro) and clinical involving treatment and prophylaxis of Covid-19.

Mechanism of action in Covid-19

Ivermectin has been shown to selectively inhibit the host importin $\alpha/\beta1$ transporter protein resulting in reduced translocation of SARS-CoV-2 NCP from the host

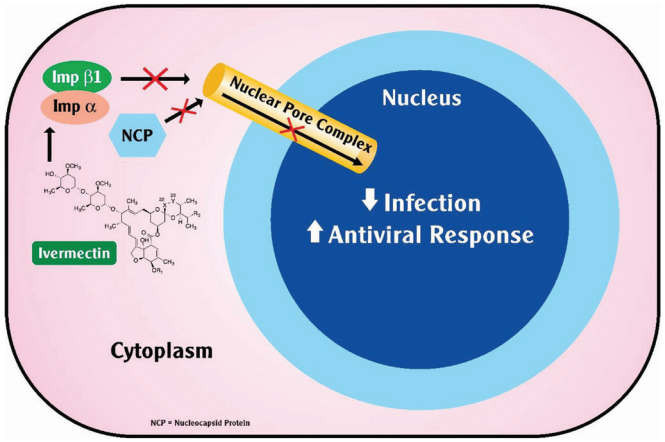

Figure 3: Mechanism of action of Ivermectin in Covid-19

cytoplasm to the host nucleus. This, altered NCP distribution disrupts viral propagation & survival and thus retains cellular viral response. [14,15] (Figure 3)

Experimental Study of Ivermectin in COVID-19

An experimental study was conducted in Australia by Leon Galy, et al to evaluate antiviral activity of Ivermectin against SARS – CoV – 2 viruses. This study showed that at 24 hours, there was 93% viral RNA reduction which was indicative of released virions and 99.8 % cell associated viral RNA reduction which was indicative of indicative of unreleased and unpackaged virions. By 48 hours there was about 5000-fold reduction in viral RNA with Ivermectin as compared to controls.[14]

Clinical Studies of Ivermectin in COVID-19

On the basis of results of above experimental/ preclinical study from Australia which showed 99.8% invitro reduction in SARS – Cov-2 viral RNA several clinical studies have been conducted and are ongoing to evaluate the efficacy and safety of Ivermectin in prophylaxis and management of COVID 19. Table 2 summarizes the treatment and prophylaxis studies.

ICON Study (USA)

A retrospective study was conducted in South Florida, USA by Rajter, *et al*. Patients were categorized into two treatment groups based on whether they received at least one dose of Ivermectin at any time during the hospitalization. Records of 280 patients with confirmed COVID-19 infection were evaluated. Out of 280 patients 173 patients were treated with Ivermectin and other 103 patient received usual care without Ivermectin. 27 patients were not reviewed. The primary outcome measure was all-cause in-hospital mortality, and secondary outcomes included subgroup mortality in patients with severe pulmonary involvement and extubating rates for patients requiring invasive ventilation. The results of this study showed significantly lower mortality in the Ivermectin group (15.0% versus 25.2%, OR 0.52, 95% CI 0.29-0.96, P=.03). In patients with severe pulmonary disease (n=75), it was found that mortality was significantly lower with Ivermectin (38.8% vs 80.7%, OR 0.15, CI 0.05-0.47, P=.001). On the parameter of successful extubating rates, there was no significant difference (36.1% vs 15.4%, OR 3.11 (0.88-11.00), p=.07).[16]

Iraq Study

A pilot study was conducted by Faiq I Gorial, et al, in Iraq. This study evaluated effectiveness of Ivermectin as an add on therapy in treatment of mild to moderate hospitalized COVID 19 patients. This study included 87 patients out of which 71 patients were in control group which received hydroxychloroquine (HCQ) and azithromycin (AZT) and 16 patients received one dose of Ivermectin (200 mcg/kg) along with HCQ and AZT. Primary outcome measure of this study was percentage of cured patients (defined as symptoms free to be discharged from the hospital and 2 consecutive negative RT-PCR tests from nasopharyngeal swabs at least 24 hours apart). The secondary outcomes were time to cure in both groups which was evaluated as time from admission of the patient in the hospital till his/ her discharge. The results of this study showed that all patients in the Ivermectin group were cured compared with the controls [16 (100%) versus 69 (97.2%)]. Two patients in the control arm died. Mean time of stay in hospital was significantly lesser in the Ivermectin group as compared to control (7.62 ± 2.75 versus 13.22 ±5.90 days, p=0.00005). No adverse events were observed.[17]

Studies from Bangladesh

A single centre, open-label, randomised controlled study was conducted by Chinmay Saha Poddar, *et al*, from Bangladesh. They studied the effectiveness of add on Ivermectin 200 mcg/kg therapy to usual care which included Doxycycline 100 mg BD, antipyretics and cough suppressants. 62 patients with mild to moderate COVID-19 diagnosed by RT-PCR test were included in the study. 32 patients were randomized to Ivermectin group (Intervention arm) and 30 received usual care (control arm). The results of this study showed no difference in intervention versus control arm in total recovery time (onset of symptoms to complete resolution of symptoms), mean recovery time and negative repeat RT-PCR. Thus, there was no beneficial effect on the disease course over usual care in mild to moderate COVID-19 cases in this study.[18]

Another study conducted by ATMM Chowdhury,

et al, randomized mild to moderate Covid-19 patients tested by RT-PCR into two groups. Ivermectin 200 mcg/kg single dose plus Doxycycline 100 mg BID for 10 days in group A, and Hydroxychloroquine 400mg on day one, then 200mg BID for 9 days plus Azithromycin 500 mg daily for 5 days in group B. 116 patients were included in the study out of which 60 were randomized in group A and 56 patients were randomized in group B. All patients in the Ivermectin-Doxycycline group (group A) reached a negative RT-PCR at a mean of 8.93 days, and all reached symptomatic recovery, at a mean of 5.93 days, with 55.1% patients being symptom-free by the 5th day. In the Hydroxychloroquine-Azithromycin group (group B), 96.36% reached a negative PCR at a mean of 6.99 days and were symptoms-free at 9.33 days. The authors concluded that Ivermectin-Doxycycline combination showed a trend toward superiority to the Hydroxychloroquine-Azithromycin combination therapy in patients with mild to moderate COVID-19, though the difference in time to becoming symptom-free and the difference in time to negative PCR was not statistically significant.[19]

In an observational study conducted by Rahman M, *et al*, which compared the viral clearance between Ivermectin and Doxycycline combination with Hydroxychloroquine and Azithromycin combination, 400 patients with mild to moderate Covid-19 were enrolled. 200 patients received Ivermectin/ Doxycycline and remaining 200 patients received Hydroxychloroquine/Azithromycin. The results of this study found that viral clearance as measured by RT-PCR was 66% (n=132) on day 5 and 83.5% (n=167) on day 6 in the Ivermectin/ Doxycycline group. 16.5% (n=33) patients remained RT-PCR positive after 6th day in the Ivermectin/ Doxycycline group. In the Hydroxychloroquine/Azithromycin group 77% (n=154) viral clearance was seen at the 11th day and 81.5% (n=163) viral clearance at 12th day. 18.5% (n=37) patients remained RT-PCR positive after 12th day in Hydroxychloroquine/Azithromycin group. The authors also reported significant p value (p=0.000427) considering 5th day viral clearance of Ivermectin ingestion and 11th day of hydroxychloroquine ingestion. However, considering 6th day and 12th day the P-value was 0.59 which was not significant.[20] Thus, the viral clearance was faster in the group that received Ivermectin.

In a case series of 100 mild, moderate and severe COVID-19 patients (Age range 8-84 years) reported by MT Alam, *et al*., combination of Ivermectin and Doxycycline along with supportive treatment was used. Ivermectin was given at the dose of 200 mcg/kg as single dose and 100 mg Doxycycline was given for 10 days. 73 patients were mild, 20 were moderate and 7 had severe Covid-19. All the patients showed symptomatic improvement by 72 hours. In mild-moderate patients 50% symptomatic improvement was seen between 3rd to 5th day after starting treatment. Symptoms of all 7 severe patients subsided by 50% by 7th day of treatment. Retesting was done between 4 to 18 days of starting medication as per availability of testing centers. 25 patients underwent RT-PCR testing between 4-8 days, 51 between 9-13 days and 24 between 14-18 days after starting medication. All 100 of the patients tested negative. No patient needed intensive care admission and no death was reported. Thus, the authors conclude that Ivermectin with Doxycycline was found to be very effective.[21]

Prophylaxis Study from India

A recent study from All India Institute of Medical Sciences, Bhubaneswar, India is reported by Priyamadhaba Behera, *et al*. This study evaluated association between Ivermectin prophylaxis and development of COVID-19 infection among healthcare workers (HCWs). This study concluded that two doses of Ivermectin as prophylaxis at a dose of 300 mcg/kg given 72 hours apart was associated with a 73% reduction of COVID-19 infection among HCWs for the following month. Authors suggested further research is required before its large-scale use.[22]

Indian Consensus on Use of Ivermectin

On 19th July 2020 a group of senior doctors with vast experience in treating Covid-19 with support of Academy of Advanced Medical Education got together. These doctors shared their experience of using Ivermectin in COVID-19. At the end of discussion following consensus was made:

"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."

The group also emphasized the urgent need for well-designed randomized control trials & also proposed judicious use of Ivermectin for Covid-19 treatment.[15]

Indian State Government(s) recommendations

Ivermectin is included in several Indian state government COVID-19 management protocols. In protocol released by Uttar Pradesh Government on 4th August 2020 following recommendation were given for use of Ivermectin: [23]

- Prophylaxis in Covid-19 patients' contact* – 12 mg on Day 0 and Day 7

Table 2: Summary of clinical studies of Ivermectin in Covid-19

Authors	Population	Key Findings
Treatment Studies		
Rajter JC, *et al.* [16]	280 patients with confirmed COVID -19 infection. Out of 280 patients 173 patients were treated with Ivermectin and other 103 patient received usual care without Ivermectin. 27 patients were not reviewed	• Significantly lower mortality in the Ivermectin group (15.0% versus 25.2%, OR 0.52, 95% CI 0.29-0.96, P=.03) • In patients with severe pulmonary disease (n=75), mortality was significantly lower with Ivermectin (38.8% vs 80.7%, OR 0.15, CI 0.05-0.47, P=.001) • On the parameter of successful extubation rates, there was no significant difference (36.1% vs 15.4%, OR 3.11 (0.88-11.00), p=.07)
Fariq I Gorial, *et al.* [17]	87 patients with mild to moderate hospitalized COVID 19 patients	• All patients in Ivermectin group were cured compared with the controls [16 (100 %) versus 69 (97.2 %)]. Two patients in the control arm died. • Mean time of stay in hospital was significantly lesser in Ivermectin group as compared to control (7.62 ± 2.75 versus 13.22 ±5.90 days, p=0.00005) • No adverse events were observed
Chinmay Saha Poddar, *et al.* [18]	62 patients with mild to moderate COVID-19 diagnosed by RT-PCR test	• No difference in intervention versus control arm in total recovery time (onset of symptoms to complete resolution of symptoms), mean recovery time and negative repeat RT-PCR.
ATMM Chowdhury, *et al.* [19]	116 patients with mild to moderate Covid-19 patients tested by RT-PCR	• All patients in the Ivermectin-Doxycycline group (group A) reached a negative RT-PCR at a mean of 8.93 days, and all reached symptomatic recovery, at a mean of 5.93 days, with 55.1% patients being symptom-free by the 5th day. In the • In the Hydroxychloroquine-Azithromycin group (group B), 96.36% reached a negative PCR at a mean of 6.99 days and were symptoms-free at 9.33 days. • Difference in time to becoming symptom-free and the difference in time to negative PCR was not statistically significant.
Rahman M, *et al.* [20]	400 patients with mild to moderate Covid-19	• Ivermectin/ Doxycycline group: Viral clearance as measured by RT-PCR was 66% (n=132) on day 5 and 83.5% (n=167) on day 6, 16.5% (n=33) patients remained RT-PCR positive after 6th day. • Hydroxychloroquine/Azithromycin group: 77% (n=154) viral clearance was seen at the 11th day and 81.5% (n=163) viral clearance at 12th day. 18.5% (n=37) patients remained RT-PCR positive after 12th day. • Significant p value (p=0.000427) considering 5th day viral clearance of Ivermectin ingestion and 11th day of hydroxychloroquine ingestion. However, considering 6th day and 12th day the P-value was 0.59 which was not significant.
MT Alam, *et al.* [21]	100 mild (n=73), moderate (n=20) and severe (n=7) COVID-19 patients	• All the patients showed symptomatic improvement by 72 hours • In mild-moderate patients 50% symptomatic improvement was seen between 3rd to 5th day after starting treatment • Symptoms of all 7 severe patients subsided by 50% by 7th day of treatment • Retesting was done between 4 to 18 days of starting medication as per availability of testing centers. All 100 patients tested negative • No patient needed intensive care admission and no death was reported • Authors concluded that Ivermectin with Doxycycline was found to be very effective.
Prophylaxis Study		
Priyamadhaba Behera, *et al.* [22]	186 matched pairs or 372 healthcare workers	• Two doses of Ivermectin as prophylaxis at a dose of 300 mcg/kg given 72 hours apart was associated with a 73% reduction of COVID-19 infection among HCWs for the following month.

- Healthcare workers* – 12 mg on Day 0, Day 7 and Day 30. Then every 30 days.
- For treatment of COVID 19 patients* – 12 mg once a day for 3 days

** 2 hours after dinner, Not recommended for pregnant/ lactating women and children below 2 years*

Conclusion

Ivermectin is widely available, economical drug with good safety and tolerability. A number of ongoing clinical trials are evaluating the drug further in treatment and prophylaxis of Covid-19. Considering the proportion of Covid-19 pandemic, pre-clinical evidence, current clinical evidence in treatment and prophylaxis, Indian Experts consensus and recommendations by multiple Indian state governments, we believe that Ivermectin may effectively and safely add to the current armamentarium of Indian clinicians involved in the care and management of Covid-19 patients.

References:

1. Worldometer [Internet]. Coronavirus. [cited 2021 Feb 16]. Available from https://www.worldometers.info/coronavirus/
2. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, Hosein Z, Padda I, Mangat J, Altaf M. Comorbidity and its Impact on Patients with COVID-19. *SN Compr Clin Med. 2020* Jun 25:1-8.
3. Ministry of Health and Family Welfare, Government of India [Internet]. Covid 19 Vaccination Status. [cited 2021 Feb 16]. Available from https://www.mohfw.gov.in/.
4. Financial Express [Internet]. Covid-19 vaccine rollout: India approves Covaxin, Covishield; what next?. 2021Jan 5. [cited 2021 Feb 16]. Available from https://www.financialexpress.com/lifestyle/health/covid-19-vaccine-rollout-india-approves-covaxin-covishield-what-next/2164444/
5. Long L, Wu L, Chen L, Zhou D, Wu H, Lu D, *et al*. (2021) Effect of early oxygen therapy and antiviral treatment on disease progression in patients with COVID-19: A retrospective study of medical charts in China. *PLoS Negl Trop Dis* 15(1): e0009051.
6. Singh TU, Parida S, Lingaraju MC, Kesavan M, Kumar D, Singh RK. Drug repurposing approach to fight COVID-19. *Pharmacol Rep. 2020* Dec;72(6):1479-1508.
7. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA. 2020* May 12;323(18):1824-1836.
8. Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. Clinical Management Protocol: COVID-19 [Internet]. Version 5. 2020 July 3 [cited 2020 Oct 20]. Available from https://www.mohfw.gov.in/pdf/UpdatedClinicalManagementProtocolforCOVID19dated03072020.pdf
9. Alanagreh L, Alzoughool F, Atoum M. The Human Coronavirus Disease COVID-19: Its Origin, Characteristics, and Insights into Potential Drugs and Its Mechanisms. *Pathogens. 2020* Apr 29;9(5):331.
10. Al-Kuraishy HM, Hussien NR, Al-Naimi MS, Al-Buhadily AK, Al-Gareeb AI, Lungnier C. Is ivermectin–Azithromycin combination the next step for COVID-19?. B*iomed Biotechnol Res J 2020*;4, Suppl S1:101-3
11. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell. 2020* Apr 16;181(2):281-292.e6.
12. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L, Wang X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature. 2020* May;581(7807):215-20.
13. Banerjee K, Nandy M, Dalai CK, Ahmed SN. The Battle against COVID 19 Pandemic: What we Need to Know Before we "Test Fire" Ivermectin. *Drug Res (Stuttg). 2020* Aug;70(8):337-40.
14. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res. 2020* Jun;178:104787.
15. Vora A, Arora VK, Behera D, Tripathy SK. White paper on Ivermectin as a potential therapy for COVID-19. *Indian J Tuberc. 2020* Jul;67(3):448-51.
16. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019: The Ivermectin in COVID Nineteen Study. *Chest. 2021* Jan;159(1):85-92.
17. Gorial FI, Mashhadani S, Sayaly HM, Dakhil BD, AlMashhadani MM, Aljabory AM, Abbas HM, Ghanim M, Rasheed JI. Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management (Pilot Trial) [Preprint]. medRxiv 2020.07.07.20145979. Available from https://www.medrxiv.org/content/10.1101/2020.07.07.20145979v1
18. Podder S, Chowdhury N, Sina M, Ul Haque W. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomized controlled study. *IMC J Med Sci 2020*; 14 (2): 002.
19. Chowdhury ATMM, Shahbaz M, Karim MR, Islam J, Guo D, He S. A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients [preprint]. medRxiv 2020.07.07.20145979. Available from https://www.medrxiv.org/content/10.1101/2020.07.07.20145979v1
20. Rahman MA, Iqbal S, Islam MA, Niaz MK, Hussain T, Siddiquee T. Comparison of Viral Clearance between Ivermectin with Doxycycline and Hydroxychloroquine with Azithromycin in COVID-19 Patients. *Journal of Bangladesh College of Physicians and Surgeons. 2020*;38:5-9.
21. Alam MT, Murshed R, Bhiuyan E, Saber S, Alam R, Robin R. A Case Series of 100 COVID-19 Positive Patients Treated with Combination of Ivermectin and Doxycycline. *Journal of Bangladesh College of Physicians and Surgeons. 2020*;38:10-15.
22. Behera P, Patro BK, Singh AK, Chandanshive PD, S R R, Pradhan SK, Pentapati SSK, Batmanabane G, Mohapatra PR, Padhy BM, Bal SK, Singh SR, Mohanty RR. Role of ivermectin in the prevention of SARS-CoV-2 infection among healthcare workers in India: A matched case-control study. *PLoS One. 2021* Feb 16;16(2):e0247163.
23. Directorate of Medical & Health Services, Uttar Pradesh [Internet]. COVID 19 documents. c2021 [cited 2021 Feb 19]. Available from: http://dgmhup.gov.in/DocumentsCovid19/1621.pdf