Drug Corner

Ivermectin in COVID 19 — Promises and Prospects

Shambo Samrat Samajdar[1], Santanu K Tripathi[2], Jyotirmoy Paul[3], Bibhuti Saha[4]

Age old anthelmintic drug ivermectin is showing some promises in the management of COVID 19 patients. In vitro study suggests anti SARS CoV2 viral role of ivermectin but there is some controversy regarding dose selection. Ivermectin has immunomodulatory role which may be responsible for its beneficial effects. Though it is not included in interim COVID 19 management guideline by GOI, but several states like West Bengal, Bihar, UP, Assam have included it in state COVID 19 management guideline. It is important to be vigilant and more focused to prospectively observe the outcome in COVID 19 patients.

[*J Indian Med Assoc* 2020; **118(10):** 86-9]

Key words **: COVID 19, Ivermectin.**

"The most fruitful basis for the discovery of a new drug is to start with an old drug."

— Sir James Whyte Black,
Winner of the 1988 Nobel Prize in Medicine[1]

Due to rapid increase in number of cases and geopolitical issues we cannot afford regular time duration for new drug development which is generally 12-18 years. Even after that we have to be cautious regarding the safety concerns for new drugs. This compressed timeline for drug development generally has directed us to revisit the Nobel Prize winner pharmacologist Professor James Whyte Black's advice on drug discovery, which is mentioned above. COVID 19 therapeutics starting from hydroxychloroquine, remdesivir, favipiravir, doxycycline to tocilizumab is used by applying the same principle of drug repurposing. Drug repurposing (also called drug reprofiling, repositioning or re tasking) is a developmental blueprint for selecting new indications for approved or investigational drugs other than original medical indication[2]. Ivermectin, indicated for strongyloidiasis of the intestinal tract and onchocerciasis; is used in COVID 19 patients following the principle of 'drug repurposing'.

As an anthelmintic drug, its mechanism of action is mainly the selective opening of glutamate-gated and Gamma aminobutyric acid (GABA)-gated chloride channels in invertebrates, which leads to increased inward movement of chloride ions. There would be subsequent motor paralysis in parasites[3]. Ivermectin has shown antiviral potential against human and animal viruses like parvoviruses in a freshwater crayfsh (Cheraxquadricarinatus) model[4], RNA viruses, like infuenza A virus[5], Venezuelan equine encephalitis virus[6], West Nile virus[7], porcine reproductive and respiratory syndrome virus[8], Newcastle disease virus[9], chikungunya virus[10], human immunodefciency virus (HIV-1)[11], Zika virus[12], yellow fever virus, dengue virus, Japanese encephalitis virus, and tick-borne encephalitis virus[13]. On this background there was a ray of hope initially whether ivermectin can show anti SARS-CoV2 viral effects. One in-vitro study done on Vero-hSLAM cells, which were treated with ivermectin after 2 hours of SARS-CoV-2 infection and result was promising as there was decrease in ~5000-fold reduction in viral RNA after 48 hours. The proposed mechanism is as there is attachment of ivermectin to the Impα/β1 heterodimer, which causes destabilization and prevention of Impα/β1 binding to SARS CoV2 viral proteins. This leads to prevention of viral proteins from entering the nucleus which causes thereby inhibition of antiviral responses. Fig 1 depicts the anti-viral mechanism of ivermectin[14]. In Vitro evidences with

Editor's Comment :

- **Ivermectin shows some promises in in-vitro studies that it inhibits SARS-COV 2 viral entry in host nucleus.**
- **It has immunomodulatory role which may produce benefits in preventing inflammation cascade of COVID 19.**
- **Dose of ivermectin use both prophylactic and therapeutic indication creates some controversy. We need to focus on prospective studies to have the final call.**

[1]MBBS MD DM (Clinical Pharmacology), Consultant Clinical Pharmacologist at Diabetes – Allergy Asthma Specialty Therapeutics Clinic, Kolkata
[2]MBBS MD DM (Clinical Pharmacology), Professor &Head of The Department of Clinical Pharmacology, School of Tropical Medicine, Kolkata
[3]MBBS MD (Medicine) FRCP WHO Fellow, Professor, Department of General Medicine, R G Kar Medical College & Hospital
[4]MBBS DTMH MD (Tropical Medicine)Professor, Department of Tropical Medicine & Dean of School of Tropical Medicine, Kolkata
Received on : 12/10/2020
Accepted on : 13/10/2020

ivermectin need to be evaluated with in vivo studies and well-designed clinical research. One study had shown that therapy with ivermectin at a dose of 150 µg/kg associated with a reduced mortality rate and lesser healthcare resource use[15]. There is a hypothesis that combination of hydroxychloroquine and ivermectin can produce a synergistic inhibitory efect on SARS-CoV-2. Mechanism wise hydroxychloroquine inhibits the entrance of SARS-CoV-2 into the host cells, whereas ivermectinprevents viral protein entrance into host nucleus and inhibits viral replication[16].

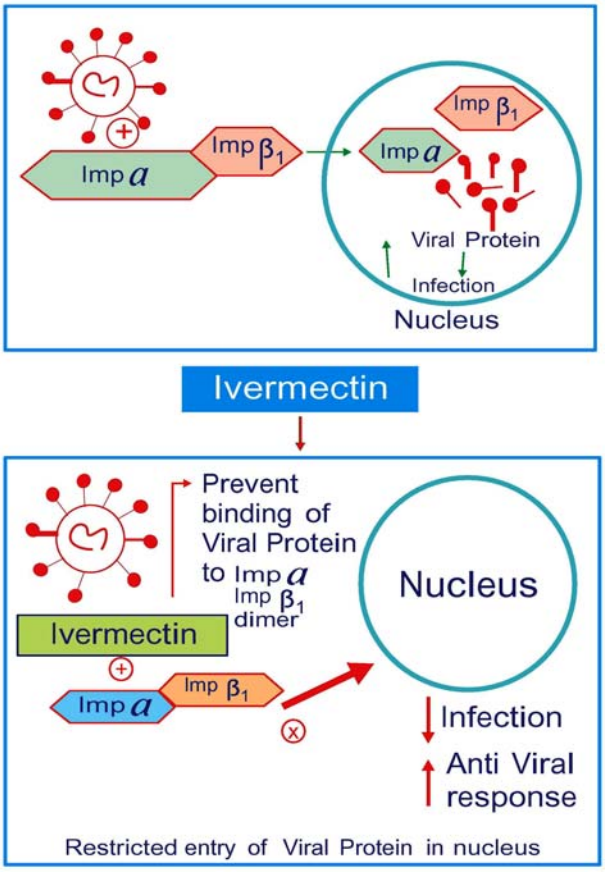

Figure 1 : Antiviral oction of Ivermectin

Dose selection of ivermectin and controversy :

Single dose of ivermectin (200 µg/kg) produces plasma level of 0.0327 uM [CI 0.0228, 0.0429] and if we convert it into lung concentration it would be 0.0873uM [CI 0.0609 - 0.115]. Predicted lung concentration is calculated based on reported lung:plasma ratio of 2.67 in cattle[17]. 120 mg single dose of ivermectin can produce 0.307 uM [CI - 0.204-0.449] plasma level and 0.820 uM [CI 0.545 - 1.20] lung concentration[18]. IC50 reported by Caly et al. for SARS CoV2 is 2 µM, which is much lower than predicted ivermectin concentration even with 120 mg weekly dose of ivermectin[14]. It is important to consider that as there is more day to day clinical experiences are in favor of ivermectin use, lung tissue concentration may be not correlating with concentrations at the site of action. There may a few doubts on the IC50 value, distribution into or retention in the lung tissue of humans which may be greater than in cattle, or that accumulation in lung tissue is much greater (>20-fold) than expected after repeat dosing[19]. Selective concentration around 3 times the plasma concentration and sequestration in the pulmonary tissue with a long residence time are features for ivermectin[20].

Though it is not included GOI guideline but a few states of India is recommending ivermectin in their protocol. Assam government recommends ivermectin 12 mg 1 tab twice daily for 5 daysalong with doxycycline 100 mg twice daily for 5 days. Bihar and UP government recommend ivermectin 12 mg once daily for 3 days. These states recommend using ivermectin 2 hours after meal. West Bengal government recommends ivermectin 12 mg once daily with fatty meal and doxyxcycline 100 mg 1 tab twice daily for 7 days in mild symptomatic COVID 19 patients. It is important to consider ivermectin after fatty meal as it increases systemic bioavailability, whereas label suggests taking it 2 hour after meal. When the indication is to have anthelmintic action then it is important to reduce systemic absorption but anti SARS CoV 2 action demands increase systemic absorption hence it should be taken just after taking fatty meal.

Immunomodulation by ivermectin :

Ivermectin has an immunomodulatory profile that alters the function of T-lymphocytes and changes the lymphocyte count[21]. This drug reduces the production of several cytokines, such as TNF-α, IL-1ss, IL6, IL-4, IL-13 and IL5[22,23]. By inhibiting a group of inflammatory cytokines which have an immense role in the development of the "cytokines storm", ivermectin reduces the complications of COVID-19. It also has effects on binding of viral spike protein to CD-147 receptors on blood cells and vascular endothelium which prevent haemagglutination and thrombogenesis. Beneficial effect of ivermectin is generally may be due to this immunomodulatory effects considering difficulty in reaching concentration for its anti SARS COV2 viral effect.

Future route of ivermectin delivery for its anti-viral effect :

Inhaled treatment with ivermectin can address the issue of less availability of ivermectin into pulmonary tissues. It is important to explore its feasibility. Inhaled therapy would allow for higher concentrations at the

site of action while limiting the systemic exposure. Further studies of the safety and tolerability in animal model and human are required to have success in this new route of ivermectin selection. This would also explore the anti -viral property of ivermectin. One in vivo study on inhaled ivermectin in Sprague Dawley rats is published. The study had shown that no-observed-adverse-effect level (NOAEL) after 28 days of inhaled ivermectin was identified to be 380 mg/m^3, which would be a potent anti-viral dose[24]. Need to explore its safety in higher animal and then in human before making final comment and intiating clinical trials.

Clinical Pharmacokinetics :

Food and a fatty meal increases absorption of ivermectin. As it is Lipophilic in nature, widely distributed, high Volume of distribution needs a large loading dose. It has high protein (albumin) binding affinity; does not cross BBB (blood brain barrier) unless in inflammation. The BBB is weakened with raised endothelial permeability in the hyper-inflammatory state of severe Covid-19. This may cause ivermectin leak into the CNS, potentially causing harm. So need to be vigilant regarding high dose of ivermectin and its CNS adverse effects. It is mainly metabolized in the liver and excreted exclusively in feces over an estimated 12 days.Elimination $t_{1/2}$ of ivermectin is 18 hours.Tmax is generally 6 hours and mean residence time in body is around 4 days[3].

Drug interactions :

Post-marketing surveillance studies show some evidences of increased INR (International Normalized Ratio) rarely reported when ivermectin was co-administered with warfarin. Ivermectin is primarily metabolized by CYP3A4 enzyme. Medicines that are potent CYP3A4 inhibitors like clarithromycin, diltiazem, erythromycin, itraconazole, ketoconazole, ritonavir, and verapamil can increase the systemic availability of itraconazole, may potentiate it's anti SARS CoV2 effect but need to be cautious regarding safety issues with ivermectin. CYP3A4 activity is induced via the pregnane X receptor (PXR), the constitutive androstane receptor (CAR), peroxisome proliferator-activated receptor (PPARα) and probably the *glucocorticoid receptor (GR)*. Use of concomitant phenobarbital, phenytoin and rifampicin, glucocorticoids induce CYP3A4, may theoretically reduce ivermectin concentration and residence duration in body but need to explore its clinical significance. Grapefruit is a potent inhibitor of intestinal CYP3A4 that has been proposed to increase the concentration of ivermectin in circulation.

Adverse effects :

Generally it is a well-tolerated drug. But as we are using higher than labelled dose need to be vigilant on the following adverse effects like asthenia/fatigue, abdominal pain, anorexia, constipation, diarrhea, nausea, vomiting, dizziness, somnolence, vertigo, tremor, pruritus, rash, and urticarial. One safety pharmacokinetics study suggests that ivermectin was generally well tolerated. There was no evidence of associated CNS toxicity for doses up to 10 times the highest FDA approved dose of 200 ìg/kg. [25]

Clinical Evidences :

1. USA STUDY I : Printed in Medscape (Jul 15, 2020) Study was done at four Florida hospitals. Ivermectin arm had showed significantly lower mortality rates compared with usual care (15% *versus* 25.2%; P < 0.03). It was a retrospective cohort study in 280 hospitalized patients with confirmed SARSCoV-2 infection. There were 75 patients with severe pulmonary disease. The mortality rate was also lower in ivermectin treated group compared to usual care (38.8% *versus* 80.7%; P< 0.001). There is no significant difference in rate of successful extubation[26,27].

2. 1,300 early stage COVID-19 patients were treated with ivermectin in Dominican Republic. Treatment was initiated with standard dose of 100 - 200 mcg/kg. Dose was increased upto400 mcg/kg. 99% of the patient population was cured. Average duration of full infection decreased from 21 days to 10 days. Only mild gastro intestinal adverse effects like heart burn and diarrhea were reported[28].

3. RCT involving mild to moderate degree of COVID-19 patients was conducted in Bangladesh. In one group around 60 patients were given ivermectin 200 mcg/kg single dose and Doxycycline 100mg twice daily for 10 days. Another group of 56 patients were administered HCQ 400 mg 1st day, then 200mg twice daily for 9 days along with azithromycin 500mg daily for 5 Days. Recovery rate was 100% *versus* 96.36%, mean symptomatic recovery duration was 5.93 days *versus* 6.99 days, negative PCR was achieved on 8.93 days *versus* 9.33 days in favour of ivermectin doxycycline group. 5th day gaining symptomatic recovery, 55.10% in ivermectin doxycycline arm compared to 23.8% of patients on HCQ azithromycin arm. Adverse events were lesser in ivermectin doxycycline arm compared to HCQ azithromycin arm 31.67% versus 46.43%[29].

Conclusion :

It spurred huge enthusiasm with off-label use of ivermectin for Covid-19 Prevention and treatment. Anecdotal evidences show some ray of hope with it. More than 450 publications have since been cited but

robust evidences yet to be reported from well powered RCTs. Nonetheless, it's off-label and compassionate use in Covid-19 requires careful risk-benefit considerations with due diligence and critical review. Should we wait until hard evidence from well powered RCTs, or can we start cautious and guarded 'experimental' use of an old, time-tested, well-tolerated drug for based on mechanistic reasoning and some empiric preliminary evidence as available till date?

There are lots of controversies and arguments counter-arguments with dose and regime of ivermectin usage in COVID 19.We just resolved to start a cautious and guarded 'experimental' use of an old, time-tested, well-tolerated drug for based on mechanistic reasoning and some empiric preliminary evidence as available till date.

References

1 Raju TN — The Nobel chronicles. 1988: James Whyte Black, (b 1924), Gertrude elion (1918-99), and George H Hitchings (1905-98) *Lancet* 2000; **355:** 1022. [PubMed] [Google Scholar]

2 Ashburn TT, Thor KB — Drug repositioning: identifying and developing new uses for existing drugs. *Nat Re Drug Disco* 2004; **3:** 673-83.

3 Rang HP, Dale MM, Ritter JM, Flower RJ, editors — Rang and Dale's Pharma cology. 6th ed. China: Churchill Livingstone; 2007. p. 715-6.

4 Nguyen KY, Sakuna K, Kinobe R, Owens L — Ivermectin blocks the nuclear location signal of parvoviruses in crayfsh, Cheraxquadricarinatus. *Aquaculture* 2014; 420-1:288–94. https://doi.org/10.1016/j.aquacultur e.2013.11.022

5 Götz V, Magar L, Dornfeld D, Giese S, Pohlmann A, Höper D, Kong BW, Jans DA, Beer M, Haller O, Schwemmle M — Infuenza A viruses escape from MxA restriction at the expense of efcient nuclear vRNP import. *Sci Rep* 2016; **18(6):** 23138. https://doi.org/10.1038/srep23138

6 Lundberg L, Pinkham C, Baer A, Amaya M, Narayanan A, Wagstaf KM, Jans DA, Kehn-Hall K — Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis virus replication. *Antiviral Res* 2013; **100(3):** 662-72. https:// doi.org/10.1016/j.antiviral.2013.10.004

7 Nguyen C, Burton T, Kuklinski W, Gray M, Foy BD — Ivermectin for the control of west nile virus transmission. New Horizons Transl Med. 2015;2(4):127. https://doi.org/10.1016/j.nhtm.2015.07.043

8 Lee YJ, Lee C — Ivermectin inhibits porcine reproductive and respiratory syndrome virus in cultured porcine alveolar macrophages. *Arch Virol* 2016; **161(2):** 257-68. https://doi.org/10.1007/s00705-015-2653-2

9 Azeem S, Ashraf M, Rasheed MA, Anjum AA, Hameed R — Evaluation of cytotoxicity and antiviral activity of ivermectin against Newcastle disease virus. *Pak J Pharm Sci* 2015; **28(2):** 597-602

10 Varghese FS, Kaukinen P, Gläsker S, Bespalov M, Hanski L, Wennerberg K, Kümmerer BM, Ahola T — Discovery of berberine, abamectin, and ivermec tin as antivirals against chikungunya and other alphaviruses. Antiviral Res. 2016;126:117–24. https://doi.org/10.1016/j.antiviral.2015.12.012.

11 Wagstaf KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA — Ivermec tin is a specifc inhibitor of importin á/â-mediated nuclear import able to inhibit the replication of HIV-1 and dengue virus. Biochem J. 2012;443(3):851–6. https://doi.org/10.1042/BJ20120150

12 Barrows NJ, Campos RK, Powell ST, Prasanth KR, Schott-Lerner G, SotoAcosta R, Galarza-Muñoz G, McGrath EL, Urrabaz-Garza R, Gao J, Wu P, Menon R, Saade G, Fernandez-Salas I, Rossi SL, Vasilakis N, Routh A, Bradrick SS, Garcia-Blanco MA — A screen of FDA-approved drugs for inhibi tors of zika virus infection. Cell Host Microbe. 2016;20(2):259–70. https://doi.org/10.1016/j.chom.2016.07.004

13 Mastrangelo E, Pezzullo M, De Burghgraeve T, Kaptein S, Pastorino B, Dallmeier K, de Lamballerie X, Neyts J, Hanson AM, Frick DN, Bolognesi M, Milani M — Ivermectin is a potent inhibitor of favivirus replication specif cally targeting NS3 helicase activity: new prospects for an old drug. *J AntimicrobChemother* 2012; 67(8): 1884-94. https://doi.org/10.1093/jac/dks147

14 Caly L, Druce JD, Catton MG, Jans DA, Wagstaf KM — The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 2020. https://doi.org/10.1016/j.antiviral.2020.104787

15 Patel A, Desai S — Ivermectin in COVID-19 Related critical illness. SSRN. 2020. https://doi.org/10.2139/ssrn.3570270

16 Patrì A, Fabbrocini G — Hydroxychloroquine and ivermectin: a synergistic combination for COVID-19 chemoprophylaxis and/or treatment? *J Am Acad Dermatol* 2020. https://doi.org/10.1016/j.jaad.2020.04.017

17 Lifschitz A, Virkel G, Sallovitz J, Sutra JF, Galtier P, Alvinerie M, Lanusse C — Comparative distribution of ivermectin and doramectin to parasite location tissues in cattle. *Vet Parasitol* 2000; **87(4):** 327-38. doi: 10.1016/s0304-4017(99)00175-2. PMID: 10669102.

18 Guzzo CA, Furtek CI, Porras AG, Chen C, Tipping R, Clineschmidt CM, Sciberras DG, Hsieh JY, Lasseter KC — Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J ClinPharmacol* 2002; *42(10):* 1122-33. doi: 10.1177/009127002401382731. PMID: 12362927.

19 Schmith VD, Zhou JJ, Lohmer LRL — The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19. ClinPharmacolTher. 2020 Oct;108(4):762-765. doi: 10.1002/cpt.1889. Epub 2020 Jun 7. PMID: 32378737; PMCID: PMC7267287.

20 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. https:// doi.org/10. 1055/a-1185-8913

21 MS Sajid, Z Iqbal, G Muhammad, MU Iqbal — Immunomodulatory effect of various anti-parasitics: a review, Parasitology. 132 (2006) 301–313, https://doi. org/10.1017/S0031182005009108

22 S Yan, X Ci, N Chen, C Chen, X Li, X Chu, J Li, X Deng — Anti-inflammatory effects of ivermectin in mouse model of allergic asthma. *Inflamm Res* 2011; **60:** 589-96, https://doi.org/10.1007/s00011-011-0307-8.

23 X Zhang, Y Song, X Ci, N An, Y Ju, H Li, X Wang, C Han, J Cui, X Deng — Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. *Inflamm Res* 2008; **57:** 524-9, https:// doi.org/10.1007/s00011-008-8007-8.

24 Ji L, *et al* — Study on the subacute inhalation toxicity of ivermectin TC in rats. *Chinese J Comparat Med* 2016; **26:** 70-4.

25 Cynthia A Guzzo, Christine I Furtek BS, Arturo G Porras — Safety, Tolerability, and Pharmacokinetics of Escalating High Doses of Ivermectin in Healthy Adult Subjects. *The journal of clinical pharmacology* 2002; **42(10):** 1122-13. https://doi.org/10.1177/009127002237994.