REPOSITIONING IVERMECTIN: A BEACON IN COVID-19 PANDEMIC

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Abstract

COVID19 has emerged out as a most pandemic global threatening disease. Current research finding has brought into consideration about the repositioning of ivermectin, an anti-parasitic drug for the treatment of SARS-CoV-2 infected patients. This information augments the knowledge of present and past findings of ivermectin in antiviral research field.

Keywords: COVID19, SARS-CoV-2, ivermectin, antiviral.

INTRODUCTION

A high transmission coronavirus has emerged from China causing respiratory infections and pneumonia, has been named SARS-CoV-2. Mortality increases with age and underlying diseases (WHO, 2020). Although anti-viral drugs like ritonavir and lopinavir (anti-HIV agents), chloroquine and hydroxychloroquine (anti-malarial agents) are being currently used, some reports suggest that their efficacy is weak and they produce serious side effects as well (Cao et al., 2020; Keyaerts et al.,2004). A recent compelling study from Australia reports repurposing ivermectin could effectively decrease the SARS-CoV-2 (Australia/VIC01/2020) viral load in Vero-hSLAM cells within 24-48hrs of treatment in vitro (Caly et al.,2020) . In view of the unmet and urgent clinical need, this paper reviews the use of ivermectin in the field of antiviral therapeutics.

MECHANISM OF ACTION OF IVERMECTIN AS AN ANTIVIRAL DRUG

William Cecil Campbell had been awarded Nobel Prize in 2015 for the discovery of ivermectin which was initially used since 1987 to treat various parasitic diseases in animals and in humans. Ivermectin is a polycyclic lactone used in treating onchocerciasis, lymphatic filariasis and strongyloidiasis (Diawara et al., 2009). Promising anti-parasite activities have been identified via inhibiting nerve impulse conduction in peripheral neuromuscular synapses by acting as an agonist for the inhibitory neurotransmitter gammaaminobutyric acid (GABA) by binding GABA-gated and invertebrate-specific glutamate-gated anion channels. Mammals are protective to ivermectin since GABA receptors of the central nervous system are protected by the blood brain barrier system (Skopets et al.,1996).

Beyond its use as an effective anti-parasite, ivermectin also has been reported as an anti-viral and anti-cancer agent. Comparatively little is known about the anti-cancer mechanism elucidated by ivermectin, several in vitro studies have demonstrated mitochondrial dysfunction and generation of oxidative stress in cancer cell lines and it has been widely reviewed (Juarez et al., 2018). Pioneering work has been accomplished in anti-viral efficacy of ivermectin, primarily by acting as an inhibitor of integrase protein (IN) and the importin (IMP) α/β1 heterodimer accountable for IN nuclear import. Antiviral effect of ivermectin on HIV-1 has been determined by the arrest of HIV-1 replication and IN import(Wagstaff et al.,2012). Given its central role in the inhibition of IMP α/β1, ivermectin shows antiviral activity in Venezuelan Equine Encephalitis Virus (VEEV) and abrogating viral ribonucleoproteins in influenza A virus (Lundberg et al., 2013).

Consistent with these anti-viral activities, ivermectin also has been proven effective in inhibiting chikungunya (CHIKV) replication and also downregulated viral protein expression, mature virion formation and viral RNA synthesis(Varghese et al.,2016). Ivermectin has been tested to be effective against Zika virus in vitro but a recent in vivo study demonstrated failure to prevent the viral infection, and the study had a number of limitations, therefore, additional in vivo studies has to be investigated(Ketkar et al., 2019).

Ivermectin shows antiviral activity against all the four serological types of Dengue virus (DENV1-4). In addition, Ivermectin

has been determined to inhibit the recognition of serotypes of dengue virus 1 and 2 by inhibiting IMP α/β1 with an approximate half maximal concentration 2μM, which is the similar IC50 assessed for the killing of COVID-19 virus in Vero-hSLAM cells(Tay et al.,2013; Caly et al., 2020). A phase 3 clinical trial was conducted to assess the effectiveness of ivermectin against the dengue virus in Thailand and the drug turn out to be effective and safe in administering 200-400 μg/kg single doses for 2-3 days (NCT02045069). The wonder drug also shows antiviral activity on other flaviviruses like West Nile, Japanese encephalitis, tick-borne encephalitis and Yellow fever via targeting NS3 helicase activity (Mastrangelo et al., 2012).

Ivermectin for the treatment of COVID19

One of the most distinctive co-morbidity which increases mortality of Covid-19 patients is diabetes. Further supporting the notion, exposure of elevated glucose levels in the pulmonary epithelial cells might be another factor to the rapid replication of the virus. Ivermectin has been studied as a regulator of metabolism by acting as farnesoid X receptor (FXR) ligand decreasing serum glucose levels and in addition it also regulates serum levels of cholesterol, high-density lipoprotein and low-density lipoprotein (LDL)/very LDL in rodents(Jin et al., 2013). Although ivermectin contributes to promising insulin sensitization, care must be taken when administering with the regular anti-diabetic medication.

With such preliminary studies, it can be envisioned that the successful use of ivermectin in the treatment of Covid-19 could be magnificent, since it has been well tolerated for its antiviral activity in the clinical trials executed so far. Yet in vivo studies and clinical trials on Covid-19 are essential to draw the final interpretation. Despite the notable achievements of ivermectin, this intricate treatment strategy should also be studied for different age groups and different co-morbidities in addition with various stages of the disease.

Conclusion

To conclude, distinctive antiviral activities of ivermectin sheds light in the principal development of antiviral treatment against Covid-19. Strikingly, the safe and tolerability has been studied widely in humans gives us the ray of hope to end the current devastating pandemic.

References

1. Caly, L., Druce, J.D., Catton, M.G., Jans, D.A., Wagstaff, K.M., 2020. The FDA-approved Drug Ivermectin inhibits the replication of SARS-1 CoV-2 in vitro.Antiviral Research. doi:10.1016/j.antiviral.2020.104787.
2. Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan,. L, Song, B., Cai, Y., Wei,M., Li,X., Xia,J., et al.,2020. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. N. Engl. j. doi:10.1056/NEJMoa2001282.
3. Diawara, L., Traore, M.O., Badji, A., Bissan, Y., Doumbia, K., Goita, S.F., Konate, L., Mounkoro, K., Sarr, M.D., Seck, A.F., Toe, L., Touree, S., Remme, J.H., 2009. Feasibility of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: First evidence from studies in Mali and Senegal. PLoS Negl Trop Dis.3(7),e497. doi:10.1371/journal.pntd.0000497
4. Jin, L., Feng, X., Rong, H., Pan, Z., Inaba ,Y., Qiu, L., Zheng ,W., Lin, S., Wang ,R., Wang, Z., Wang, S., Liu, H., Li, S., Xie, W., Li, Y., 2013. The antiparasitic drug ivermectin is a novel FXR ligand that regulates metabolism. Nat Commun. 4,1937 . doi:10.1038/ncomms2924.
5. Juarez, M., Schcolnik-Cabrera, A., Duenas-Gonzalez,A.,2018. The multitargeted drug ivermectin: from an antiparasitic agent to a repositioned cancer drug.Am J Cancer Res. 8(2),317-331.
6. Ketkar, H., Yang, L.,Wormser, G.P., Wang, P., 2019. Lack of efficacy of ivermectin for prevention of a lethal Zika virus infection in a murine system. Diagnostic Microbiology and Infectious Disease . 95,38–40.doi:10.1016/j.diagmicrobio.2019.03.012
7. Keyaerts, E., Vijgen, L., Maes, P., Neyts, J., Ranst, M.V., 2004. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem. Biophys. Res. Commun.323, 264–268. doi:10.1016/j.bbrc.2004.08.085.
8. Lundberg, L.,Pinkham, C., Baer, A., Amaya, M., Narayanan, A., Wagstaff, K.M., Jans, D.A., Kehn-Hall, K., 2013. Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication. Antiviral Res.100(3), 662-672. doi:10.1016/j.antiviral.2013.10.004
9. Mastrangelo, E., Pezzullo, M., De burghgraeve, T., Kaptein ,S., Pastorino,B., Dallmeier, K., De Lamballerie,X., Neyts,J., Hanson,A.M., Frick,D.N., Bolognesi,M., Milani1,M., 2012 . Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. Journal of Antimicrobial Chemotherapy. 67(8), 1884–1894. doi:10.1093/jac/dks147
10. Skopets, B., Wilson, R.P., Griffith, J.W., Lang, C.M.,1996. Ivermectin toxicity in young mice.Lab Anim Sci .46(1), 111–2.
11. Tay, M.Y., Fraser, J.E., Chan, W.K., Moreland, N.J., Rathore, A.P., Wang, C., Vasudevan, S.G., Jans, D.A., 2013. Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Antiviral Res. 99(3), 301-306. doi:10.1016/j.antiviral.2013.06.002
12. Varghese, F.S., Kaukinen, P., Glasker, S., Bespalov, M., Hanski, L., Wennerberg, K., Kummerer, B.M.,Ahola,T., 2016. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Antiviral Research .126,117–124. doi:10.1016/j.antiviral.2015.12.012
13. Wagstaff , K., Sivakumaran, H., Heaton, S.M., Harrich, D., Jans, A.,2012. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem. J.443,851– 856. doi:10.1042/BJ20120150
14. WHO. Coronavirus disease 2019 (COVID-19) Situation Report – 38. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200227-sitrep-38-covid-19.pdf?sfvrsn=9f98940c_2. (Accessed 8 April 2020)