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Review Article

Why Ivermectin, Azithromycin, Meplazumab and Vitamin D Helps to Control the Severity of SARS-CoV-2. The Role of ACE-2 and CD147 During Coronavirus Infection

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Abstract

As the world faces pandemic of COVID-19, the search for effective treatments modalities against the disease and its complications has turned its gaze to drugs that are classically used in other infectious diseases.

Some drugs are being examined for the recent evidence on its effects on viral replication and inflammation. The aim of the study was to review the mechanism of action of Ivermectin, Azithromycin, Hydroxycholoquine, and vitamin D therapy being used in the literature. This review found that the drugs might mitigate disease progression without significant adverse effects and can be used prophylactically, during the disease and after recover when in long hauler state. Further cohort studies are needed in order to extrapolate these findings in COVID-19. The discovery of CD147 will open the channel to discover some new more potent target therapeutic drugs.

Keywords: Coronavirus, COVID-19, Ivermectin. ACE2, CD147, Lucine, Histidine, SARS-CoV-2

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Introduction

In the first wave of the novel CORONA infection, there was a panic situation because of new rapidly spreading pandemic which was gripping and killing the world rapidly. The SARS-CoV-2 was new virus and was causing pneumonia, severe acute respiratory distress syndrome, microvascular thrombosis, cytokine storms, myocarditis, with sepsis and eventually multi-organ failure through involving the underlying inflammation and activating its chemical mediators. It came to know that it is attaching with ACE-2 receptors through its S-1 and S-2 receptors. The situation was so disturbing that it secured the globe socially and monetarily. There was no comprehension of this infection, how to treat and how to deal with its pathogenesis.[1-2]

Till third wave of COVID-19, the world has now better knowledge and skill dealing with and handling with this disease. Their understanding about the immunity, body response, pathophysiology, hypoxia, hemoglobin variation, dysmetabolism of the iron and body coagulation hemostatisis, role of genetics, represent additional key-factors to think the criteria for a COVID19 patient for the clinical practice to determine the need for an early therapeutic regimen and to decrease mortality. The mutation in the virus, interaction with CEA, red blood cells, hemoglobin molecule s through CD147, CD26 has opened a new door about this disease.

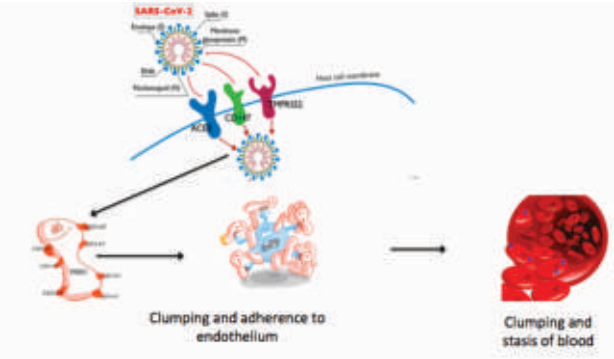

Figure 1: *Proposed Mechanism of Action, how Virus Causes Stasis of Blood, Clumping and Adherence of Blood Clot to Endothelium, Leading to Hypoxia.*

It has been contended that hemoglobinopathy might get from viral endocytosis, through a linkage between spike proteins and mobile receptors. Viral ORF8

protein and floor glycoprotein would tie to porphyrin, assaulting the heme on the 1-beta chain of hemoglobin; SARS-CoV-2 may cause hemolysis and may form a complex with the released heme, resulting dysfunctional hemoglobin with disruption in oxygen and CO_2 transport mechanism (Figure 1).[3-4]

These receptors are present more on blood group A and B as compared to O, there for malaria was seen more in these patients and same COVID-19. A significant association has been seen between the blood groups A, B & AB and their susceptibility with SARS-CoV-2 infection.[5] The COVID-19, patients with these blood were associated with more sever outcome due to their increased risk for mechanical ventilation. These patients were seen with prolonged ICU admission, poor prognosis and multiorgan damage (Figure 2).[6]

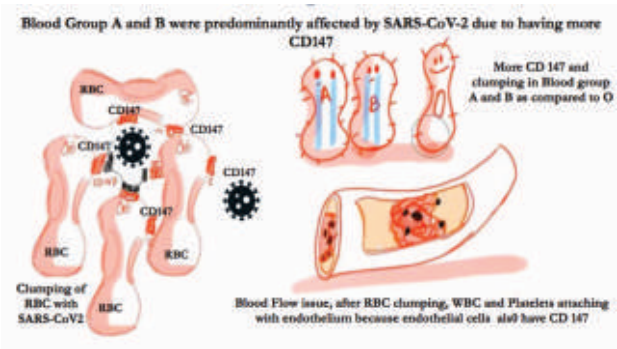

Figure 2: *The presence of CD147 Receptors on RBC, More of A and B as Compared to O. The Plasmodium and SARS-CoV-2 Attaches to these Receptors, While Targeted Drugs Block them and Inhibit the Rouleaux Formation. Modified but Adopted.*[6]

A similar picture are seen in severe malaria due to similar clumps and adhesions to endothelium centering on infected RBCs through CD147 for for blood groups A or B as compare to. O. It is caused by adhesive RBC membrane trisaccharides associated in patients with such blood groups. COVID-19 is likewise much more prevalent in patients with blood groups A or B as compared to patients of O blood group. When the coronavirus or malarial plasmodium attaches to these receptors causes clumping of the erythrocytes, slowing the blood flow, causing the hypoxia and destroying the endothelial cells (Figure 1-2).

Ivermectin is a macrocyclic lactone derived from the bacterium Streptomyces avermitilis. It is basically anti-worm, by paralyzing the nerve and muscle of the worm. It opens the glutamate gated chloride channels of the nerves and muscles, and make them more negative (hyperpolarized), so the worm muscles and nerves do not work due hyperpolarized state, so the worm dies eventually. This function is not seen on human muscles and nerves but may cause side effects through our Gama receptors and may damage the blood brain barrier rarely. The other function is viristatic, it reduces the viruses' effect and it does not kill the virus. The virus loads on human's alpha and beta proteins and enters its cargo inside the nucleus. After reaching inside the cells, the human alpha and beta proteins are broken down by releasing the viral proteins, which inhibits the synthesis of interferon, when the Interferon is not released, the nearby cells are not aware about the viral infection. So when we take the IVM, it stops the viral cargo to enter inside the cells and keep the synthesis of interferon up, which causes alertness of the nearby cells from the viral infection.

The fourth function of IVM is to binds the spike proteins and do not allow the SARS-CoV-2 to bind with ACE2 and CD147 receptors on RBC. Ivermectin docked in the region of leucine 91 of the Viral spike and histidine 378 of the human ACE2 receptor (Figure 3).

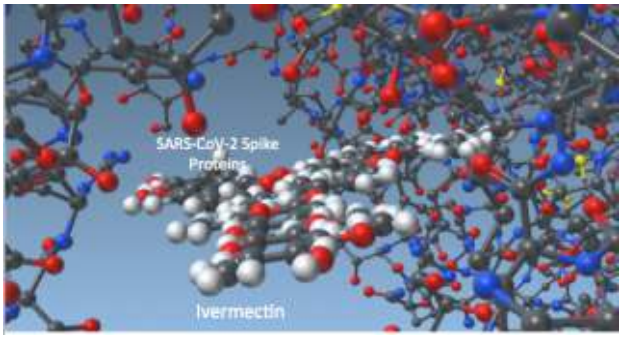

Figure 3: *Docking Effect of Ivermectin (Center, Silver, Black and while Dumbles) to Leucine 91 of the Viral Spike (Right and Let Red, Blue, Black Globular Structure) and Histidine 378 of the Human ACE2 Receptor.*[7]

It has so many other functions like it inhibits the binding of SARS-Cov-2 with ACE-2 receptors, It inhibits the entry of cargo of SARS-CoV-2 inside the human cells, It has anti-inflammatory function, and lastly it enhances the release of Interferon, which make aware to the other cells about the viral infection.

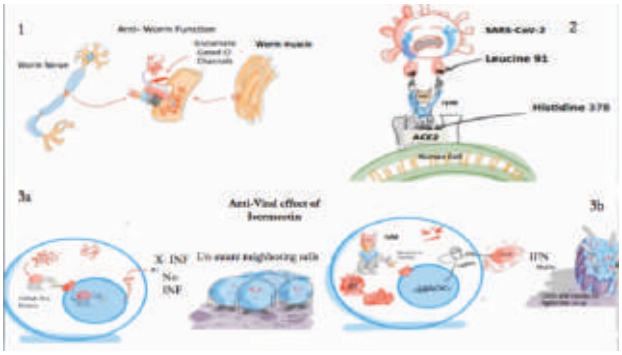

Figure 4: *The Mechanism of Action of Ivermectin, 1,*

Anti-worm Action, Causes Hyperpolarization of the Nerve and Muscle of the Worm but not Humans, 2, It Inhibits the Bindings of ACE-2 Receptors and not allows the SARS-CoV-2 to Attach it with these Receptors by Docking Effect. 3a&3b, the Anti Viral effect by Blocking the Cargo of SARS-CoV-2 to enter in Human Cell Nucleus and keep the Synthesis of Interferon up

The IVM inhibits the RDRP to stop viral RNA synthesis inside the cells. When the SARS-CoV2 enters in the cell through ACE-2, or CD147 through its proteases (TMPRSS2) cut the structural proteins and a positive sense SmRNA it released, which goes to ribosome as a recipe. The human ribosome kook them into polyproteins, which are released out by the proteases of the SARS-CoV2 into small proteins, it also synthesize the viral RNA dependent RNA polymerase (RdRP) which takes the genome of the SARS-CoV-2 to make new viruses, The remdesivir, lopinavir, ritonavir, and oseltamivir, zinc and Ivermectin, doxycyline blocks RdRP Pathway (Communicated by Ramaswamy H. Sarma) and inhibits the production of new virus in the body.[10-11] (Figure 5).

Ivermectin also inhibits LPS-induced NO and PGE(2) production and stops the inflammatory process due to this SARS-CoV-2. Consistent with these observations, the protein and mRNA expression levels of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) enzymes were inhibited by ivermectin in a concentration-dependent manner.[8] It also exerts anti-inflammatory effect by down regulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway.[9] (Figure 4)

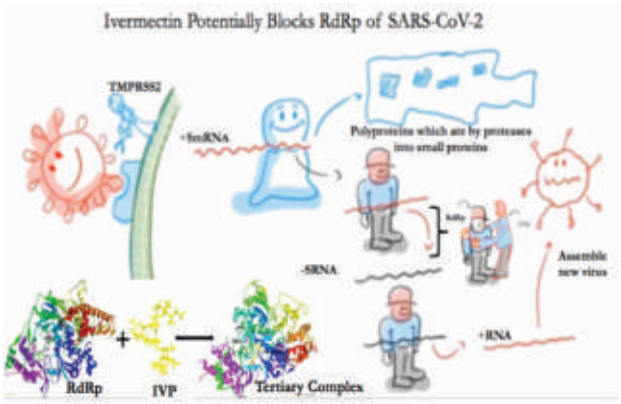

Figure 5: *The Picture showing how Ivermectin Inhibits the RDRP to Stop Viral RNA Synthesis inside the Cells. When the SARS-CoV2 Enters in the Cell through ACE-2, through its Proteases (TMPRSS2) Cut the Structural Proteins and Releasing a Positive Sense SmRNA, which goes to Ribosome as a Recipe. Some other Drugs like Remdesivir, Lopinavir, Ritonavir, and Oseltamivir, Zinc and Ivermectin, Doxycyline also Blocks Viral Production through Inhibiting RdRp Pathway.*

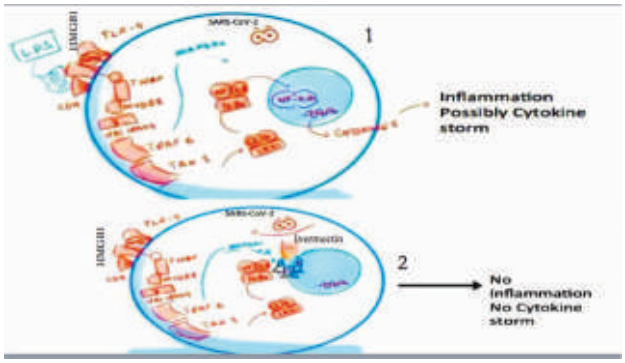

Figure 6: *The Picture is Showing, Anti-Inflammatory Effect of the Ivermectin.*

In situation 1, there is no Ivermectin and the SARS-CoV2 causes attachment with recptors, TLR4& CD14, enters the cells and activates the cell transduction machinery, through MAP3K3 (Mitogen-Activated Protein Kinase Kinase Kinase 3) enters the nucleus on one way and NF-K Beta and IKB2 pathway in cytokine storm, while in Situation 2, when given Ivermectin, no Inflammation and no CK storm, because it blocks the upper pathways.[10-13]

Dr. David E., Scheim hypothesizes that the COVID related hypercoagulability is due to the CD147 proteins on the RBCs attaching with SARS-COV-2 spike proteins. He proposes that Ivermectin binds with the spike proteins of the SARS-COV-2 hence, preventing the spike protein binding to the CD147 and RBC clumping.[14]

It is suggested that higher dosages of IVM could yield more noteworthy clinical advantages. In a few clinical investigations, IVM at dosages of up to 2,000 µg/kg, multiple times that utilized in the Florida study, were all around endured. The potential for significant portion reaction gains is assessed dependent on investigations showing that IVM shields SARS-CoV-2 spike protein and that this spike protein ties to the CD147 transmembrane receptor just as to ACE2. The plentiful circulation of CD147 on red platelets (RBCs) recommends a speculated "catch" and "cluster" system whereby virally-interceded ties of RBCs to different RBCs, platelets, white platelets and hairlike dividers.[13-14]

SARS-CoV-2 invades host cells via two receptors: angiotensin-converting enzyme 2 (ACE2) and CD147. Ezithromycin (Azomax) binds to CD147 of RBC possibly interferes with vital ligand/receptor interactions and also SARS-CoV-2 infection by inhibiting its bindings with RBCs and stops causing clumping, stasis and activating endothelial damage. Azithromycin induces anti-viral responses in epithelial cells by increasing levels of interferon and interferon-stimula-

ted proteins and decreasing viral replication and virus release. (Figure 7)[15-16]

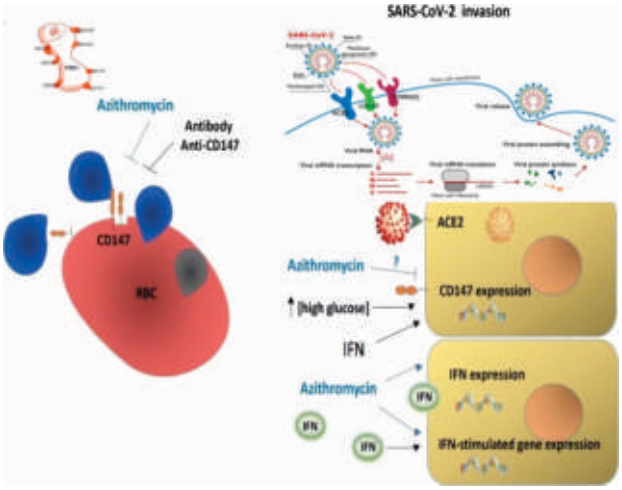

Figure 7: *Mechanism of Azithromycin, how it Prevents the COVID-19 by blocking the CD147 Receptors of RBCs and Enhancing the Release of Interferon and Interferon-Stimulated Proteins and Decreasing in Replication and Release of the Virus.*

Meplazumab is a monoclonal antibody and attaches to CD147. It stops the bindings of SARS-CoV-2 with these receptors. In a study hit has been seen that these monoclonal antibodies helps in clearing the viral load in 3 days as compared to non treated patients.[15]

It also causes anti inflammatory effect and reduce the IL6 release and cytokine storm like Ivermectin. It a study it has been seen that azithromycin (azomax) induces anti-viral responses primarily on human bronchial epithelial cells. It also enhances the production of interferon, (Seen in rhinovirus-induced interferons experiment) and consequently this interferon will stimulate mRNA and expression of protein resulting in decrease of the replication and release of the rhinovirus.[17]

It is a common practice the Vitamin D are being proposed during the COVID-19 treatment. It is suggested that this will regulate the proinflammatory process and, modulate innate and adaptive immunity. It is also suggested that Vitamin D may activate a few hepcidin-antagonist pathways by regulating the hepcidin-ferroportin Pathway. It is also proposed the if vitamin D deficiency is considered prothrombotic, so on the other hand active form calcitriol may have a net anti-coagulant effect. Interestingly, cholecalciferol has also shown an upregulatory epigenetic action on a few antioxidant systems (GSH complex and AA included), therefore it is considered the use of vitamin D would be beneficial in protecting the sever effects of COVID - 19 and will enhance the recovery by boos-ting the human immune system.[18]

Conflict of Interest

None

Funding Information

None

References

1. Weir EK, Thenappan T, Bhargava M, Chen Y. Does vitamin D deficiency increase the severity of COVID-19? Clin Med (Lond). 2020;20(4):e107-e108. doi: 10.7861/clinmed.2020-0301
2. Cooling L. Blood Groups in Infection and Host Susceptibility. Clin Microbiol Rev. 2015 Jul;28(3):801-70. doi: 10.1128/CMR.00109-14.
3. Wenzhong L, Hualan L. COVID-19 Disease: ORF8 and surface glycoprotein inhibit heme metabolism by binding to porphyrin. ChemRxiv. 2020; 10.26434/chemrxiv.11938173.v3
4. Wenzhong L, Hualan L. COVID-19: Attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv. 2020; 10.26434/chemrxiv.11938173.v8.
5. Rahim F, Amin S, Bahadur S, Noor M, Mahmood A, Gul H. ABO / Rh-D Blood types and susceptibility to Corona Virus Disease-19 in Peshawar, Pakistan. Pak J Med Sci. 2021;37(1):4-8. doi: https://doi.org/ 10.12669/ pjms.37.1.3655
6. More Evidence Points to Role of Blood Type in COVID-19. [Updated 2020, cited 2021] Available from: [https://www.medpagetoday.com/infectiousdisease/covid19/89117]
7. Lehrer S, Rheinstein PH. Ivermectin Docks to the SARS-CoV-2 Spike Receptor-binding Domain Attached to ACE2. In Vivo Sep 2020, 34 (5) 3023-6. doi: 10.21873/invivo.12134
8. Zhang X, Song Y, Xiong H, Ci X, Li H, Yu L, Zhang L, Deng X. Inhibitory effects of ivermectin on nitric oxide and prostaglandin E2 production in LPS-stimulated RAW 264.7 macrophages. Int Immunopharmacol. 2009;9(3):354-9. doi: 10.1016/j.intimp.2008.12.016.
9. Ci X, Li H, Yu Q, Zhang X, Yu L, Chen N, Song Y, Deng X. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. Fundam Clin Pharmacol. 2009 Aug; 23(4): 449-55. doi: 10.1111/j.1472-8206.2009.00684.x.
10. Bangladesh Medical College Hospital Physician See 'Astounding Results' with Drug Combination Targeting COVID-19. [updated 2020, cited 2021] Available from:[.https://www.trialsitenews.com/bangladesh-medical-college-hospital-physician-see-astounding-results-with-drug-combination-targeting-covid-19/]
11. Wang S, Liu C, Liu X, He Y, Shen D, Luo Q, Dong Y, Dong H, Pang Z. Effects of matrix metalloproteinase inhibitor doxycycline and CD147 antagonist peptide-9 on gallbladder carcinoma cell lines. Tumour Biol. 2017; 39(10): doi: 10.1177/1010428317718192.

12. Combining the medications improved conditions in patients with severe 2019-nCoV infections, say doctors in Thailand. [updated 2020, cited 2021] Available from: [https://www.the-scientist.com/news-opinion/flu-and-anti-hiv-drugs-show-efficacy-against coronavirus-67052]
13. Andersson U, Ottestad W, Tracey KJ. Extracellular HMGB1: a therapeutic target in severe pulmonary inflammation including COVID-19? Mol Med. 2020;26(1):42. doi: 10.1186/s10020-020-00172-4.
14. Scheim, David, Ivermectin for COVID-19 Treatment: Clinical Response at Quasi-Threshold Doses Via Hypothesized Alleviation of CD147-Mediated Vascular Occlusion. [updated 2020, cited 2021] Available from: [https://ssrn.com/abstract=3636557 or http:// dx. doi. org/10.2139/ssrn.3636557]
15. Ulrich H, Pillat MM. CD147 as a Target for COVID-19 Treatment: Suggested Effects of Azithromycin and Stem Cell Engagement. Stem Cell Rev Rep. 2020; 16(3):434-40. doi:10.1007/s12015-020-09976-7.
16. Wang K, Chen W, Zhou YS, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. BioRxiv preprint. 2020 doi: 10.1101/2020.03. 14.988345.
17. Gielen V, Johnston SL, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. Eur Respir J. 2010;36(3):646-54. doi: 10.1183/ 09031936.00095809.
18. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020;12(4):988. doi: 10.3390/ nu12040988.