Review and perspective

Ivermectin for COVID-19 treatment: clinical response at quasi-threshold doses via hypothesized alleviation of CD147-mediated vascular occlusion

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Abstract: The worldwide spread of the COVID-19 pandemic has prompted clinical testing of existing drugs with indicated activity against the SARS-CoV-2 virus. Among antimalarial drugs of such potential is ivermectin (IVM), a macrocyclic lactone of Nobel Prize-winning distinction. A retrospective study of 173 COVID-19 patients treated with IVM in four Florida hospitals at a dose of 200 μg/kg yielded a 40% reduction in mortality compared with 107 controls (15.0% vs. 25.2%, p=0.03). Mortality was cut by 52% with IVM for patients having severe pulmonary disease (38.8% vs. 80.7%, p=0.001). Stabilization and then improvement over 1-2 days frequently occurred for patients who had rapidly deteriorating oxygen status.

It is proposed that higher doses of IVM could yield sharply greater clinical benefits. In several clinical studies, IVM at doses of up to 2,000 μg/kg, ten times that used in the Florida study, were well tolerated. The potential for major dose-response gains is evaluated based upon studies indicating that IVM shields SARS-CoV-2 spike protein and that this spike protein binds to the CD147 transmembrane receptor as well as to ACE2. The abundant distribution of CD147 on red blood cells (RBCs) suggests a hypothesized "catch" and "clump" framework whereby virally-mediated bindings of RBCs to other RBCs, platelets, white blood cells and capillary walls impede blood flow, which in turn may underlie key morbidities of COVID-19.

The proposed catch and clump scenario for COVID-19 has a parallel in malaria, for which CD147 is central to the infectious process. The core morbidity of severe malaria is caused by similar clumps and adhesions to endothelium centering around infected RBCs. These underlie the much greater incidence of severe malaria for blood groups A or B vs. O, caused by adhesive RBC membrane trisaccharides associated with blood groups A and B. COVID-19 is likewise much more prevalent for blood groups A or B vs. O. More generally, hemagglutination, the formation of such RBC-pathogen clusters, is common for enveloped viruses. Under this hypothesized framework, a significantly higher rate of capillary flow in younger people could explain a corresponding decreased severity of COIVD-19. This proposed hypothesis and the associated potential for major IVM dose-response gains could be tested, for example, by monitoring blood flow in COVID-19 patients before and after IVM intake using nailfold capillaroscopy.

Keywords: SARS-CoV-2; COVID-19; ivermectin; CD147; basigin; BSG; EMMPRIN; red blood cell; RBC; erythrocyte; hemagglutination; spike glycoprotein; ACE2; hydroxychloroquine; chloroquine; azithromycin; doxycycline.

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Introduction

Ivermectin (IVM) is one of several drugs active against malaria, others including chloroquine (CQ), hydroxychloroquine (HCQ), azithromycin (AZ) and doxycycline,[1-7] which have also exhibited inhibitory activity *in vitro* against SARS-CoV-2,[3,7,8] SARS-CoV-1[9-13] and other viruses.[14-20] The first of these drugs deployed to treat COVID-19, in China,[21] South Korea,[22] and at Southeast France's main COVID-19 treatment hospital in Marseille,[23-25] were CQ and its hydroxyl derivative HCQ. Studies of CQ and HCQ related to these clinical applications have revealed connections between COVID-19 and malaria, as considered below, that in turn offer insights into potential biological mechanisms of IVM.

For COVID-19 treatments in Marseille, HCQ was used along with AZ,[23-25] the synergy of this combination against SARS-CoV-2 having been established *in vitro* at clinical lung tissue levels.[26] Treatments there of 3,320 positively tested mixed-stage COVID-19 cases yielded a mortality rate 16% of the WHO average,[27,28] consistent with clinical benefits seen in other studies using HCQ with early and mixed stage patients.[29-31] But HCQ and CQ are constrained in clinical use by an unusual, similar pharmacology.[32] Following oral intake, they are rapidly absorbed into tissue and sequestered in acidic intracellular lysosomes and endosomes.[1,32-39] These alkaline agents raise the pH of these organelles, impeding endocytosis of SARS-CoV-2 virus into a target cell.[11,12,14-16,40-45] With repeated intake of HCQ or CQ, tissue levels accumulate,[1,32,46,47] persisting with a weeks-long elimination half-life.[32,33,35-37,46-49] At the maximum safe daily dosage,[32,35,48,50] effective antiviral tissue levels require 5-10 days to accrue.[51] Commensurately, HCQ proved ineffective in studies with mostly advanced COVID-19 patients.[52-55]

QTc prolongation can sometimes occur with CQ or HCQ, but typically only with intensive intravenous dosing[33,56-58] or oral dosing over months.[59] In one series of 84 COVID-19 patients treated with HCQ plus AZ, 11% had significant QTc prolongation, but there were no TdP arrhythmias or cardiac deaths.[60] In the initial set of 3,000 Marseille patients assessed in a safety review, only one cardiac-related death occurred. A task force of the Council on Clinical Cardiology of the American Heart Association noted that "several hundred million courses of chloroquine have been used worldwide making it one of the most widely used drugs in history, without reports of arrhythmic death under World Health Organization surveillance."[61] It concluded that the risks of cardiac problems with AZ and with AZ plus CQ were likewise limited.[61]

Ivermectin (IVM): clinical outcomes, pharmacology and maximum tolerated doses

IVM is a multi-faceted drug that has been used worldwide to treat hundreds of millions of cases of river blindness and other parasitic diseases as well as scabies, malaria and other conditions.[62] Its discovery in 1973 was honored with the Nobel Prize for medicine in 2015.[63] Its clinical efficacy against COVID-19 was tested in a retrospective cohort study of consecutive hospitalized patients with confirmed SARS-CoV-2 who were treated at four Florida hospitals.[64,65] Patients (n=173) in the treatment group received at least one dose of IVM at 200 μg/kg, some with repeated doses at weekly intervals. The control group (n=107) received usual care. Most patients also received HCQ with or without AZ, a higher percentage receiving one or both in the control group. There were no significant differences in age, race, or comorbidities between the two groups other than a higher prevalence of hypertension in the IVM cohort.

Overall mortality was 15% in the IVM group, 40% less (p=0.03) than the 25.2% mortality in the control group. For 75 patients with severe pulmonary disease (receiving oxygen at FiO2 ≥ 50% or ventilation), those treated with IVM (n=46) had a mortality of 38.8%, 52% less (p=0.001) than the 80.7% mortality in corresponding controls (n=29). Stabilization and then improvement often proceeded in 1-2 days, even for

patients who had been deteriorating rapidly from room air to supplemental oxygen at up to a 50% mixture ($FiO2 \leq 0.5$).

The 1-2-day reversals of declining oxygen status in these Florida patients is consistent with rapid absorption and distribution into tissue of orally administered IVM. After oral intake, IVM levels in blood[62,66-74] and distribution in body tissues[75-77] reach peak levels typically within 4-8 hours after oral dosage. An average elimination half-life of roughly 18 hours has been observed after oral dosing of IVM in human subjects.[68,69,71,72,78] But antipathogenic effects have been observed several days after a single dose of IVM,[66,68,79,80] consistent with the half-life of its major metabolites being four-fold greater, about 3 days.[68,73]

The potential for enhanced clinical benefits for COVID-19 with higher or more frequent dosing of IVM will be considered below in the context of a hypothesized biological mechanism. Yet this potential is feasible given the proportionality of IVM plasma levels to oral dose up to 1.7 mg/kg,[69,81] and the linear or in some case more robust correlation of response to dose in some studies of antiviral agents.[82-84] And the safety of IVM at doses up to 2,000 μg per kg, ten times the dose of 200 μg/kg as used in the Florida clinical study, allows such latitude for dose escalation. This standard dose of 200 μg/kg is taken, for example, once to three times per year for river blindness[2,85] or twice, a week apart, for scabies.[86] Since 1987, 1.3 billion treatments for river blindness at 200 μg/kg have been provided worldwide.[2,85] But much higher doses of IVM have proven equally safe. In one clinical study at fixed doses, the highest at 120 mg (up to 2,000 μg/kg) taken once or at 180 mg (up to 3,000 μg/kg) taken in split doses over one week, IVM was generally well tolerated, with no difference in adverse events between placebo and these highest doses.[69]

Likewise IVM was well tolerated at a single dose of 800 μg/kg,[87] at 1,600 μg/kg over 12 weeks[88] and at 1,600 μg/kg over 13 days.[89] An oral dose of IVM of up to 1,400 μg/kg over one month is recommended by the US CDC as a treatment option for crusted scabies.[86] A meta-analysis of clinical experience with IVM found no significant differences in frequency or intensity of adverse events with doses up to 800 μg/kg vs. standard doses.[90] Also, long-term follow-up studies of IVM use in elderly populations at doses up to 400 μg/kg found no excess deaths.[91,92] The safety of IVM as noted in humans and other mammals derives from the shielding by the blood brain barrier of the central nervous system, the most potentially vulnerable tissue, from penetration by IVM.[69,70,93] However, since the blood brain barrier may be at risk for being compromised in some cases of COVID-19,[94] the most aggressive dose range of 1,000-2,000 μg/kg of IVM that would appear safe for normal subjects may not be appropriate for patients with this disease.

The CD147 receptor: key to RBC adhesion for the SARS-CoV-2 virus and the malaria parasite

The potential for more intensive dosing of IVM to improve response for COVID-19 rests on which morbidities of this disease that IVM might target and by what biological mechanisms. Consideration of these morbidities and mechanisms is confounded by a dual set of infectious targets, the respiratory and circulatory systems, that appears to characterize this disease. As with its predecessor, SARS-CoV-1,[95] SARS-CoV-2 typically gains an infectious foothold and base of replication in the respiratory system, with the lung a key target.[96,97] The ACE2 receptor, freely distributed in lung and airways tissue,[98-102] is the point of attachment and penetration of SARS-CoV-2 into the host cell, where replication occurs.[103,104] But other organ systems are also vulnerable to this virus,[97,105-108] and some COVID-19 patients suffer severe hypoxemia with normal respiratory system compliance, a combination rarely seen in typical cases of severe acute respiratory distress syndrome.[109-111] Circulatory system damage is also seen in many patients with

such features as intravascular clots and peripheral ischemia.[106,112-115] One clinical reviewer summarized that COVID-19 "is a systemic disease that primarily injures the vascular endothelium."[116]

A mechanism initially proposed for activity of IVM against SARS-CoV-2 is inhibition of nuclear transport by importin α/β proteins.[8,19,117] But the applicability of this effect at clinical tissue levels has been questioned,[74,118] as has whether the SARS-CoV-2 nucleocapsid protein localizes to the nucleus or nucleolus of an infected cell.[119,120] Another possible such mechanism for IVM emerged from a molecular modeling study that evaluated more than 100 selected agents for their potential to shield SARS-CoV-2 spike protein from host cell receptors.[121] Excluding one agent that bound only to one site region, the three most efficient viral shielding agents, in descending order, were IVM, heparin and azithromycin (AZ).

Consistent with these findings, heparin treatments of 1735 positively tested COVID-19 patients in 17 Spanish hospitals yielded an age- and gender-adjusted odds ratio for mortality of .55, a 45% lower death rate, vs. 340 controls not receiving heparin.[122] In another study, 27 hospitalized COVID-19 patients treated with high-dose heparin plus AZ, including eight on ventilation, had an 81% rate of hospital discharge with no deaths at follow-up evaluation.[112] Significant improvements in oxygen status were recorded 48-72 hours after treatment. The antithrombotic effect of heparin, however, confounds interpretation of these outcomes. Also consistent with the findings noted is that AZ, the third most efficient SARS-CoV-2 viral shielding agent identified, has shown *in vitro* and clinical indications of anti-SARS-CoV-2 activity.[3,23]

Certain enigmatic facets of COVID-19 shift the focus of examination from the SARS-CoV-2 virus and its spike protein to the host cell and its binding sites. Why do patients who progress to a serious condition often do so suddenly, with a rapid decline of oxygen status about a week after disease onset?[123] What caused the stabilization and improvement in a relatively short time period, 24-48 hours after taking IVM, in the Florida patients whose oxygen status had been rapidly declining? What accounts for the decreased incidence of COVID-19 for blood group O and in younger age groups?[124-126]

These enigmatic facets of COVID-19 compound the puzzle of key blood-related morbidities being associated with this respiratory-based disease, as noted above. Circulating through lung alveolar tissue about once per minute,[127] blood cells can indeed efficiently spread the virus.[99] Heightening curiosity as to these blood-related characteristics of this disease is the observation by an investigator from the Marseille research team that most of the antimalarial drugs tested *in vitro* were found active against the SARS-CoV-2 virus.[128] It turns out, in fact, that there is a specific connection between COVID-19 and malaria that centers around the CD147 transmembrane receptor,[129] which is densely distributed on blood cells,[99,130] especially on the RBC.[131] In contrast to the ACE2 receptor, which provides a locus for both binding and penetration of the SARS-CoV-2 into a host cell,[103,104] the CD147 receptor (also designated as basigin, BSG, or EMMPRIN) may enable the virus to wreak havoc in the vasculature through binding alone.

Key to the infectious process of malaria is the penetration of the host's RBCs by *plasmodium falciparum* in its merozoite form, facilitated by surface proteins on this tiny one-celled organism.[129,132,133] For all strains of *P. falciparum* tested, a particular ligand-receptor pair, the parasite ligand pfRh5 and the transmembrane receptor CD147 on the RBC, was found essential to the binding of parasite to host RBCs that preceded its subsequent penetration.[134,135] *In vitro*, CD147 antagonists blocked parasite invasion of RBCs,[134] and *in vivo*, a recombinant anti-CD147 antibody cleared established malarial infections with no overt toxicities.[135,136]

This same transmembrane receptor, CD147, has been identified, along with ACE2, as a key binding site for SARS-CoV-2 spike protein.[137] This binding of virus to CD147 was demonstrated by surface plasmon

resonance and ELISA assays and by the competitive inhibition of SARS-CoV-2 *in vitro* by an anti-CD147 antibody.[137] Cyclophilin A and B, molecules that bind with and activate CD147, can also serve as binding partners for CD147 in its attachment to SARS-CoV-2 spike protein.[99] Although the binding affinity of molecules of SARS-CoV-2 spike protein to CD147 is 12-fold weaker than to ACE2,[138] the surface density of CD147 on host cells (e.g., 1,695 per RBC[131] vs. orders of magnitude lower densities of ACE2 on all cell types[99,139,140]) would allow multiple bonds with significant combined affinity.[138]

To test the role of CD147 in the clinical course of COVID-19, a humanized monoclonal antibody against CD147, meplazumab, was used to treat 17 hospitalized COVID-19 patients.[100] These patients, 6 with severe disease and 7 in critical status, had an average time to viral clearance of 3 days vs. 13 days for 11 controls. Similar statistically significant improvements versus controls in case severity and time to hospital discharge were achieved in the treated group. Although the small number of cases and lack of randomized controls precludes firm conclusions as to clinical efficacy, these clinical findings align with multifaceted *in vitro* indications of CD147 as a clinically relevant binding site for the SARS-CoV-2 virus.

CD-147 mediated catch and clump vascular occlusion: a hypothesis

A framework for deciphering the duality of infectious targets of COVID-19, the respiratory and circulatory systems, is suggested by the distribution of ACE2 and CD147 on associated tissues. Both of these receptors are expressed in lung tissue and in the endothelial lining of the vasculature.[98-102] But only CD147, not ACE2, is present in RBCs and white blood cells.[99,130] The distribution of CD147 on reticulocytes (1-2% of all RBCs)[141] decreases as they mature,[142,143] yet this distribution on mature RBCs, 1,695 CD147 receptors per cell, remains abundant.[131] Since CD147 is an adhesion molecule,[101,131,144-146] given its dense distribution on blood cells and its binding to SARS-CoV-2 spike protein, the consequences of the formation of lattices of such bindings invite exploration. These bindings would likely not extend into cellular penetration, and may dynamically detach and reattach,[99] yet a cascade of extended such bindings could develop, obstructing blood flow and causing the vascular morbidities seen in COVID-19.

Figure 1 depicts such a hypothesized "catch" and "clump" model for CD147-mediated vascular occlusion in COVID-19. Viral particles are shown attached to CD147 receptors on RBCs, with others attached to CD147 or ACE2 receptors on the endothelial lining of capillaries; these are designated as "catches." For visibility, SARS-CoV-2 viral particles (actual size about 0.10-0.12 μm[147]) are shown at about six times actual scale relative to the diameter of the capillary cross section (which is typically 3-10 μm). The RBC, having a disk diameter of about 8 μm and thickness of about 2 μm,[148] fits tightly within the capillary wall, often distorting its shape[149] to flow through capillaries as small as 2-3 μm in diameter.[148] Thus, these attached viral particles, per their actual size, would not cause a gross obstruction to RBC passage but could rather act like tiny Velcro hooks in roughening the RBC and endothelial surfaces, causing a drag on flow.

Since both RBCs and platelets, which also have CD147 receptors,[150,151] are densely distributed in blood flowing through capillaries,[152,153] virally-linked clusters of both types of cells as depicted can also form. These clumps as well as catches would cause more drag on blood flow in smaller capillaries, with, however, such drag in pulmonary capillaries, average diameter 6 μm,[154] being counterbalanced by pulsed, high pressure flow driven by contractions of the left cardiac ventricle.[155] Single file flow of such cells in smaller capillaries would limit cluster formation mainly to abutting pairs or strings of cells. But larger clusters of red and white blood cells could form, for example, in arteries, which could then create bottlenecks as flow progressed into arterioles and then into capillaries.

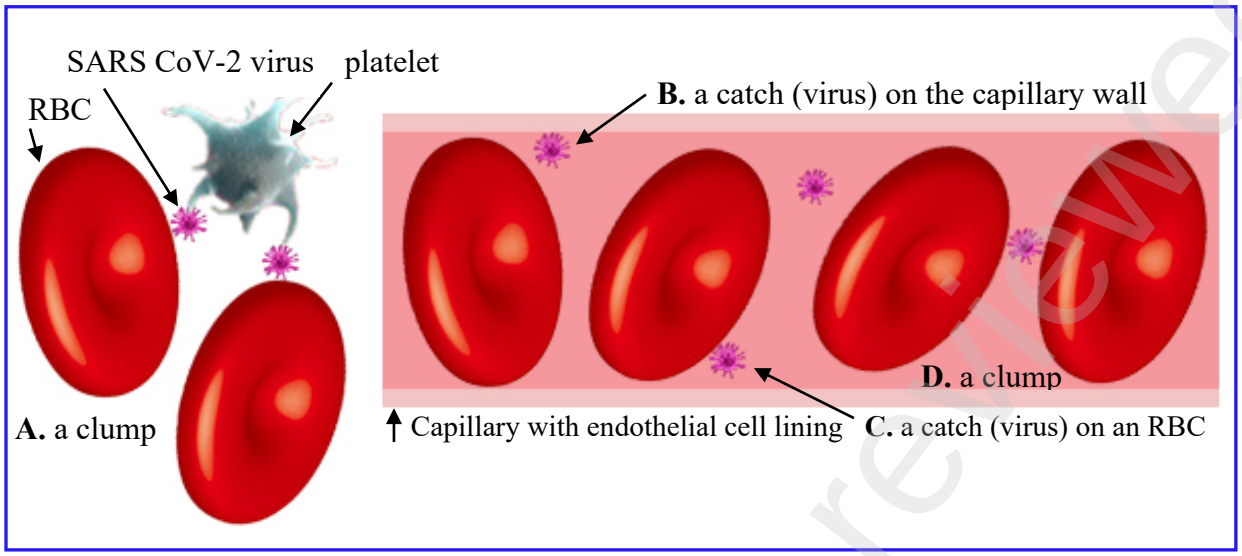

Figure 1. **Catch and clump impedance of blood flow**. This schematic depicts how a SARS-CoV-2 viral particle ("catch") attached to either an RBC or the capillary wall, or a "clump" of blood cells formed through mutual viral attachments, could impede blood flow. All attachments shown between viruses and blood cells are formed by the binding of viral spike proteins to a CD147 receptors on cells. Multiple such bindings between each virus-cell pair would strengthen this attachment. **A**) A clump of two RBCs and a platelet, the RBCs each joined to viral particles that are in turn joined to the platelet. Such a clump could form, e.g., in an arteriole, and cause a bottleneck when it flowed into a capillary. **B**) a virus joined to the endothelial cell lining of a capillary, denoted as a "catch." **C**) a virus joined to an RBC (another "catch"), which could snag on the capillary wall via a CD147 or ACE2 binding. **D**) a clump consisting of an RBC, a virus and another RBC. Note that viral particles are shown about six times larger than actual scale relative to the diameter of the capillary cross section (which in this schematic is the height).

RBCs can in fact form aggregates even without the presence of virus, joined by macromolecules in plasma, under conditions of low blood flow shear rates[156] such as in veins.[157] Such aggregation is reversible, the RBCs separating at higher shear rates.[156] In the presence of SARS-CoV-2 virus, blood flowing in capillaries even at moderate velocity might form catches and clumps having enough binding affinity to cause some drag on flow in the affected capillaries. Slower flow in turn would promote further such aggregation, causing a cascade of viral-mediated catching and clumping.

Insight into how this catch and clump scenario, as initially proposed in a prior working paper,[158] could unfold in COVID-19 can be drawn from analogous phenomena in severe cases of malaria. Here, the malaria-infected RBC (IR) rather than the virus particle is the nexus of vascular damage. IRs bind to endothelial cells lining blood vessels and also form rosettes with uninfected RBCs and platelets.[159-162] Figure 2 shows microscopic images of these forms of IR-induced cytoadhesion in severe malaria. Figure 3 depicts how these cytoadhesive attachments can cause microvascular occlusion. These can develop in the heart, lung and brain, with consequences including difficulty in breathing and multiorgan failure.[159,161] These cytoadhesive pathologies have been identified in multiple studies as the key cause of life-threatening complications of severe malaria.[160-164]

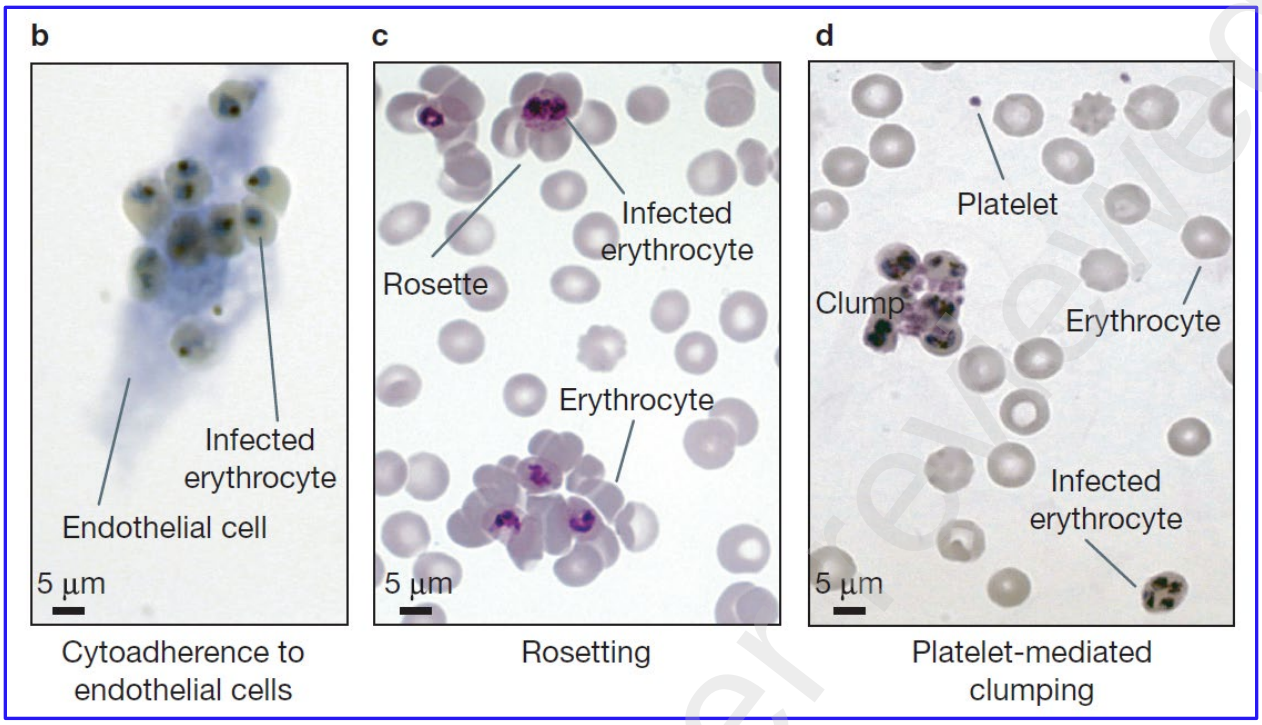

Figure 2. Adhesion of erythrocytes infected with *Plasmodium falciparum* to human cells. Reproduced (b-d) with permission from Cambridge University Press (Rowe et al., 2009).[159] (b) Cytoadherence of infected erythrocytes to *in-vitro*-cultured brain endothelial cells, visualized by light microscopy after Giemsa staining. (c) Rosettes detected in *in vitro P. falciparum* cultures, observed after preparation of Giemsa-stained thin smears and light microscopy. (d) Platelet-mediated clumps of infected erythrocytes formed after *in vitro* co-incubation of parasite cultures with platelets, observed by Giemsa-stained thin smears and light microscopy.

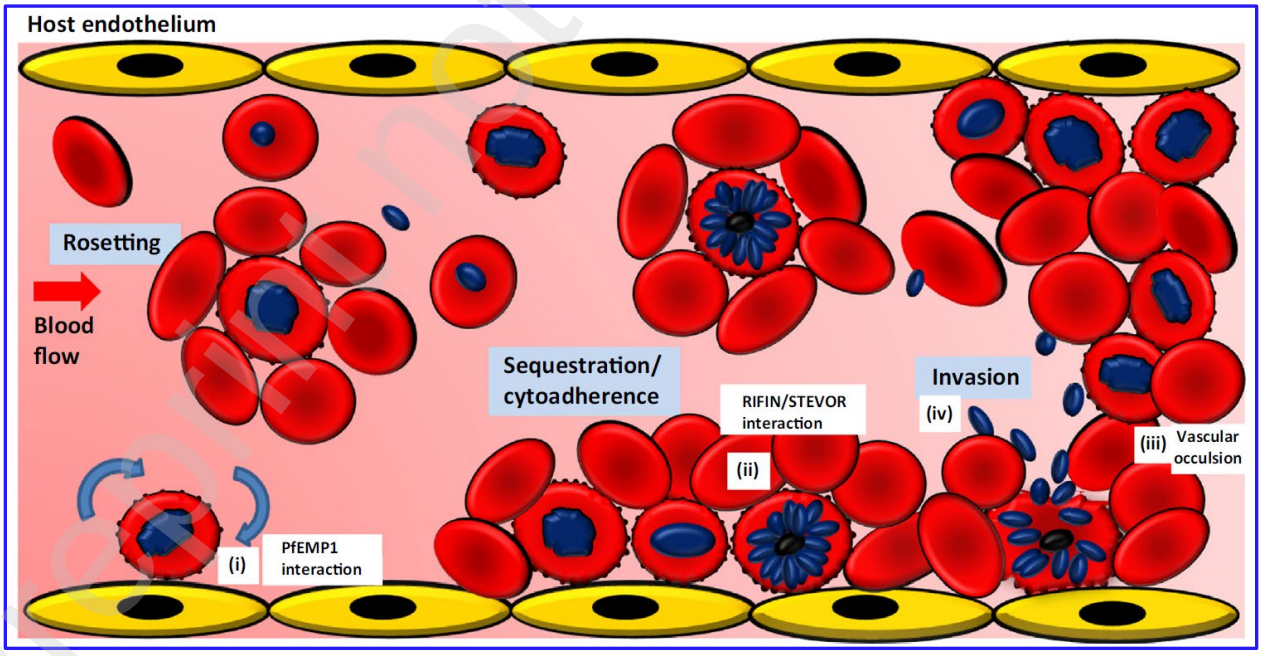

Figure 3. A schematic depicting rosetting, cytoadhesion and vascular occlusion caused by *Plasmodium f. parasites* (blue ovals). Reproduced with permission from Elsevier (Yam et al., 2017).[165] PfEMP1, STEVOR, and RIFIN are surface antigens specific to malaria.

More generally, these CD-147 based cytoadhesive phenomena in malaria and as proposed here for COVID-19 appear to be immune defense mechanisms that cause collateral damage. In a process known as immune adherence or hemagglutination as depicted in Figure 4, RBCs attach to enveloped viruses (as is SARS-CoV-2[121]) or other pathogens.[146,166-170] These complexes, which can extend to lattices of multiple RBCs and pathogens, can then attach to leukocytes, significantly expediting phagocytotic clearance.[146,167,168] Hemagglutination is common for several strains of enveloped viruses and is the basis of a widely used viral assay technique.[167,170-172]

For bacterial and fungal pathogens studied *in vitro*, hemagglutination was found to be promoted by CD147 and other adhesive molecules, as confirmed through inhibition by anti-CD147 antibodies.[146] Although hemagglutination is mediated by various hemagglutinin esterase (HE) glycoproteins on viral spike protein in earlier strains of coronavirus,[173-175] no such form of HE with cell-binding functionality is present for SARS-CoV-2.[175,176] Given the demonstrated binding of SARS-CoV-2 viral spike protein to CD147 and the density of CD147 receptors on RBCs, it appears that this binding pair would mediate hemagglutination in COVID-19. Further damaging immune adhesive effects could arise from endothelial activation, as caused, for example, by malaria-infected RBCs.[162,177,178] In cerebral endothelial cells from mice who had developed immunity to hepatitis virus, expression of CD147 increased by 250% after exposure to the virus.[101,179]

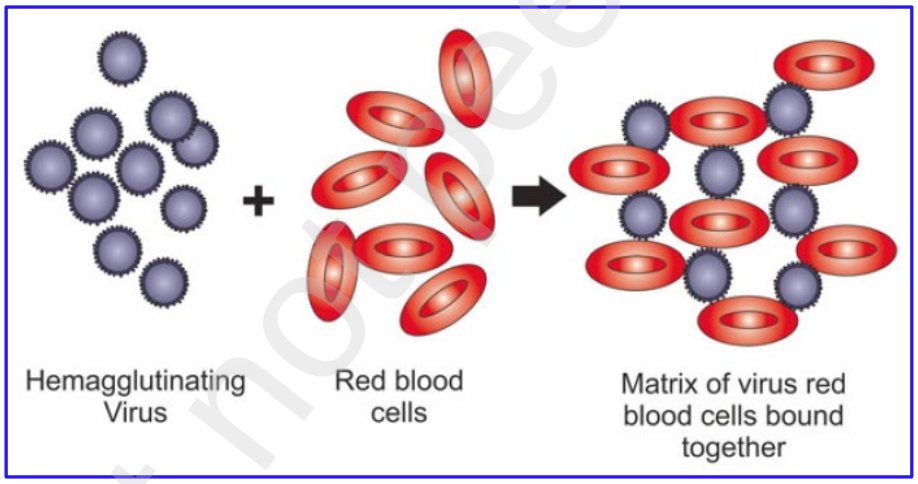

Figure 4. Illustration of the hemagglutination process. Reproduced with permission from Springer Nature (Killian, 2014).[172] Hemagglutination is common for several strains of enveloped viruses and is the basis of a widely used viral assay technique. For SARS-CoV-2, hemagglutination could be mediated by the binding of viral spike protein to CD147 rather than by a viral hemagglutinin esterase glycoprotein.

Risk factors and idiosyncrasies of COVID-19 as consequences of catch and clump vascular occlusion

1. Increased incidence of COVID-19 with increased age. Several clinical studies of blood flow in different tissues found much higher flow velocities in younger vs. older subjects. For capillary flow under toe and finger nails, flow rates in subjects of average age 26 were almost double those of average age 63.[180] In other studies of capillary flow in various tissues, older subjects had 23%[181] and 40%[182] diminished flow velocities vs. younger subjects and a 47% decrease in flux amplitude.[182] Differences in flow rates in arteries for older vs. younger subjects were significant but less pronounced: 26-27% lower.[183-185] The much higher blood flow

rates for younger age groups could be sufficient to counter binding forces of viral spike proteins to cellular CD147 receptors and prevent blood cell clumps and vascular adhesions from developing.

2. *Increased incidence for blood group A, decreased incidence for group O.* A genomic association study of 1,980 COVID-19 patients found that, with adjustments for age and sex, those with blood group O had a 35% lower risk of contracting COVID-19 than those of other blood groups.[124] Blood group A was associated with the highest risk of incidence, 45% higher than for other blood groups. Other studies reported similar reduced risks for blood group O.[125,126] For malaria, in a matched case-control study of 567 patients, its results consistent with other studies,[186,187] blood group O was associated with a 66% reduction in the odds of developing the severe form of the disease.[188] This reduced incidence of severe malaria correlated with reduced rates of rosette formation from the blood of group O malaria patients.[186,188] Both clinical[187] and *in vitro*[189,190] studies also showed a lesser reduction in risk of severe malaria for blood group A vs. B, again paralleling incidence rates for COVID-19. These group A and B risk factors for malarial rosette formation appear to be mediated by associated adhesive trisaccharides found on RBCs and white blood cells.[159,161] These could accelerate clumping in COVID-19 once a cascade of viral-cellular attachments developed.

3. *Rapid decline of oxygen status about one week after disease onset,[123] then improvement 24-48 hours after IVM.* Several days may elapse after onset of COVID-19 before viral concentration in blood reaches a level sufficient to cause hemagglutination to a significant degree. Once this process began, a cascade of clumping that slowed blood flow and in turn caused more clumping in the affected capillaries could result in the rapid decline of oxygen status. IVM would reach peak serum and tissue levels about 4-8 hours after intake, as noted above, and competitive inhibition by IVM with CD147 for dynamically detaching and reattaching bindings to viral spike protein could quickly begin to loosen those bindings and associated clumps.

4. *Blood clots, peripheral ischemia, "COVID toes" and other vascular related morbidities noted above*[106,112,113,191] would naturally arise from vascular occlusion. A similar pattern of vascular abnormalities including obstructed capillaries, microhemorrhages and a significant decrease in oxygen saturation occurs in severe malaria.[192-195] As noted above, in severe malaria, rosettes and endothelial bindings analogous to the proposed cytoadhesive attachments in COVID-19 have been identified as the key causes of life threatening complications,[160-164] including difficulty in breathing and multiorgan failure.[159,161] Vascular occlusion, particularly in the peripheral microvasculature, could explain why some COVID-19 patients function normally yet register dangerously low oxygen saturation levels,[109-111] as would typically be measured with a fingertip pulse oximeter.

Possibilities for significantly improving clinical response with higher and more frequent IVM dosing

The dose of IVM used in the Florida clinical study was 200 μg/kg, in some cases repeated weekly. But as reviewed above, IVM has been generally well tolerated in single doses of up to 2,000 μg/kg and in split doses totaling up to 3,000 μg/kg in a one-week period. An oral dose of up to 1,400 μg/kg over one month is recommended by the US CDC as a treatment option for crusted scabies.[86] It would thus be possible to use a higher dose regimen of IVM for COVID-19, for example, 500 μg/kg and then 250 μg/kg every three days following. Although a tenuous understanding of underlying biological mechanisms of IVM activity precludes identification of a specific dose-response relationship, certain considerations suggest that major clinical gains could be achieved at an increased IVM dose.

A standard dose of IVM is 200 μg/kg, taken, for example, once to three times per year for river blindness[2,85] or twice, a week apart, for scabies.[86] For lymphatic filariasis, a parasitic disease with a worldwide incidence

of 38.5 million in 2015,[196] microfilaria density at six months after treatment was respectively 22.2%, 9.3% and 2.9% of the pretreatment level at IVM doses of 100-150 μg/kg, 200 μg/kg and 400 μg/kg.[197] For this disease, the standard dose of 200 μg/kg thus performed significantly better than lower doses, while double that dose performed better still.

It is noteworthy that for such parasitic diseases in which IVM kills microfilaria (but typically not adult worms),[2,89,198] this cytotoxic process is irreversible. Thus efficacy is generally obtained by IVM when a cytotoxic concentration is maintained during a sufficient period of hours or days.[68] But in COVID-19 treatment, with antiviral agents such as IVM having cytostatic, not cytotoxic activity, virus would resume growth once plasma level of drug dropped below a critical threshold. Under the assumption that IVM competitively binds to viral spike protein, bindings of the latter to CD147 would detach over time for IVM at a threshold plasma level but reattach below that level. As noted, the elimination half-life of IVM in human subjects is about 18 hours,[68,69,71,72,78] with the half-life of its major metabolites being about 3 days.[68,73] Thus, for example, if IVM at 100 μg/kg yielded the minimum peak plasma level that would tend to detach such hemagglutination bindings, assuming that IVM metabolites are as effective as the parent molecule in such competitive binding, then a single IVM dose of 200 μg/kg would remain effective for only 3 days.

Further perspective is gleaned by comparing the molar concentration of IVM with that of CD147 receptors in blood. For IVM at a dose of 150 μg/kg, the average peak plasma level detected in three studies was 49.3 nM/L.[74] IVM binds strongly to albumin and other serum proteins, yielding a distribution of 93% in bound and 7% in unbound forms,[199-201] the latter active.[118] Multiplying that active fraction by 49.3 nM/L and Avogadro's number, 6.02×10^{23}, gives 2.08×10^{15} molecules per liter. The main metabolites of IVM reach about double its peak plasma level, with the times to peak concentration roughly the same.[68,73] Assuming equivalent competitive binding activity, the peak concentration of IVM taken at 150 μg/kg plus metabolites is then tripled, 6.24×10^{15} molecules/L. That extrapolates at a dose of 200 μg/kg (with IVM plasma level being proportional to oral dose up to 1.7 mg/kg[69,81]) to 8.32×10^{15} molecules/L. With an average RBC count of 4.8×10^{12}/L for adults (5.1×10^{12}/L for males, 4.5×10^{12}/L for females)[202] and 1,695 CD147 receptors per RBC,[131] there are thus about 8.14×10^{15} CD 147 receptors per liter, vs. 8.32×10^{15} molecules per liter for IVM.

The different spatial distribution of IVM and CD147 molecules in blood, respectively homogenous and clustered on RBC membranes, confounds the application of binding equilibrium calculations. But the one-to-one ratios of these molecular distributions suggests that at a dose of 200 μg/kg, IVM could begin to lose potency during the 3-day course of its elimination half-life and do so more sharply afterwards. It is likewise difficult to estimate the potential shielding effect of IVM for bindings of viral spike protein to ACE2 receptors, that binding strength being 12-fold greater than for CD147[138] but ACE2 distribution on all cell types being much sparser than for CD147.[99,139,140] It is conceivable, however, that IVM at a low dose might be able to disrupt bindings of viral spike protein to CD147 while at a high dose it could block ACE2 bindings as well.

Several studies suggest that clinical response to IVM for COVID-19 could also be enhanced with the adjunct use of azithromycin (AZ), an antibiotic with antimalarial activity.[4-6] AZ is a macrolide antibiotic with a 15-carbon core, similar in molecular structure to the 16-carbon macrocyclic lactone IVM.[70,203-205] In the molecular modeling study noted above, AZ was found to be the third most efficient agent, after IVM and heparin, in shielding SARS-CoV-2 spike protein.[121] A clinical study using high-dose heparin together with AZ at 500 mg on day 1 and 250 mg on days 2-10 to treat 27 hospitalized COVID-19 patients, including 8 on ventilation, yielded unusually good outcomes with no deaths.[112] AZ has exhibited *in vitro* synergy in

combination with IVM against the *Pediculus humanus* parasite[203] and has shown *in vitro* and clinical indications of anti-SARS-CoV-2 activity.[3,23] Doxycycline, another antibiotic with antimalarial activity, exhibited anti-SARS-CoV-2 activity *in vitro*,[7] and reduced CD147 levels in a carcinoma cell line[206] and in human gingival crevicular fluid.[129,207]

Opportunities for clinical testing

Three of the hypotheses proposed here are readily amenable to clinical testing:

1) Irregularities in the peripheral microvasculature would frequently accompany cases of COVID-19 having such symptoms as breathing difficulty or low oxygen saturation yet without clinically evident circulatory system abnormalities.
2) IVM would normalize these microvasculature irregularities in conjunction with clinical improvements over the course of 1-2 days.
3) Normalization of microvasculature irregularities in conjunction with clinical improvements would occur more rapidly and robustly with higher doses of IVM.

The peripheral microvasculature can be easily monitored for abnormalities such as derangement of capillary architecture and irregularities in rates of blood flow through nail fold capillaroscopy of either fingers or toes.[208-211] This is most conveniently performed using a handheld digital videocapillaroscope, equipment that is commonly used and readily available, ideally operated in conjunction with software to calculate blood flow velocity from video images. Were all three of these effects to be confirmed using this methodology, firmer conclusions as to the clinical efficacy and underlying biological mechanism of IVM could be drawn from a smaller set of patients than might otherwise be possible.

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Abbreviations

ACE2	angiotensin-converting enzyme 2
AZ	azithromycin
CD147	cluster of differentiation 147 (also known as basigin, BSG, or EMMPRIN)
CQ	chloroquine
HCQ	hydroxychloroquine
IVM	ivermectin
RBC	red blood cell

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