Review and perspective

Antimalarials for COVID-19 treatment: rapid reversal of oxygen status decline with the Nobel Prize-honored macrocyclic lactone ivermectin

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Abstract: The worldwide spread of the COVID-19 pandemic has prompted intense interest among researchers, physicians and patients in viable treatment options. Among the first antimalarial drugs repurposed for treatment of this pandemic was hydroxychloroquine (HCQ), as pioneered at Marseille's main COVID-19 treatment hospital. HCQ's unusual pharmacology has limited its effectiveness in advanced stages of the disease, but 3,300 mixed stage COVID-19 patients treated in Marseille with HCQ and azithromycin (AZ) had a mortality rate 16% of the world average. Optimal tissue levels of HCQ require several days to accrue, and some advanced stage COVID-19 patients may have cardiac complications that require screening for HCQ use. The Marseille research team found more generally that other antimalarial drugs were active *in vitro* against the SARS-CoV-2 virus.

One such antimalarial drug of Nobel Prize-winning distinction is ivermectin (IVM). As determined by a US research team from a database spanning 169 hospitals in three continents, 704 COVID-19 patients treated with a single, low dose of IVM (150 μg/kg) had a mortality rate that was one-sixth (1.4% vs. 8.5%) of that of untreated, case-matched controls. Treatments of 71 COVID-19 patients with IVM at 200 μg/kg plus HCQ, AZ and Zinc by a clinical team in Florida yielded a statistically significant reduction in mortality, with reversals in 1-2 days of rapidly deteriorating oxygen status. The pharmacology and toxicology of IVM is briefly reviewed, indicating the potential for an even sharper response at increased, safe doses. The central role of the CD147 transmembrane receptor in the binding of SARS-CoV-2 is considered. A catch and clump scenario for impedance of capillary flow through viral bindings to blood cells via CD147 is proposed as a possible explanation for the observed rapid clinical response to IVM and for other puzzling aspects of COVID-19.

Keywords: SARS-CoV-2; COVID-19; ivermectin; hydroxychloroquine; chloroquine; azithromycin; doxycycline; QTc prolongation; red blood cell; RBC; erythrocyte; spike glycoproteins; RNA helicase; ACE2; CD147; basigin; BSG; EMMPRIN

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Introduction

In studies dating back two decades, several antimalarial agents, notably chloroquine (CQ), hydroxychloroquine (HCQ), ivermectin (IVM), azithromycin (AZ) and doxycycline,[1-4] have exhibited inhibitory activity *in vitro* at physiological concentrations against SARS-CoV-2,[3-5] SARS-CoV-1[6-10] and other viruses.[11-17] The first of these drugs used to treat COVID-19 were CQ and its hydroxyl derivative HCQ. Among their well-established antiviral mechanisms is the alkalization of the normally acidic endosomes and lysosomes that would endocytose the SARS-CoV-2 virus into a target cell.[8,9,11-13,18-23]

A combination treatment of HCQ and AZ was pioneered earlier this year at Southeast France's main COVID-19 treatment hospital in Marseille.[24-26] Treatments there of 3,300 positively tested mixed-stage COVID-19 cases[27] yielded a mortality rate 16% of the WHO average.[28,29] These patient outcomes are in keeping with the synergy between HCQ and AZ against SARS-CoV-2 observed *in vitro* at clinical lung tissue levels.[17,30] In China and South Korea, where CQ[31] and HCQ[32] are, respectively, nationally recommended treatment options, scant new cases of COVID-19 have emerged since mid-April.[33,34]

A key limitation of any HCQ-based treatment derives from the unusual pharmacology of HCQ, similar to that of CQ.[35] Following oral administration, these agents are rapidly absorbed into tissue, diffusing freely through cell membranes and then sequestered in protonated molecular forms in acidic lysosomes and endosomes.[1,35-42] (Similarly, azithromycin accumulates 1,000-fold in acidic lysosomes.[43]) During several days of dosage of HCQ or CQ, tissue concentrations accrue,[1,35,44,45] after which they persist with a weeks-long elimination half-life.[35,36,38-40,44-47] Effective antiviral tissue concentrations of HCQ or CQ cannot be accumulated in less than 5-10 days[48] due to toxicity constraints on the maximum safe daily dosage.[35,38,46,49]

In the US, in the wake of widespread public interest in HCQ for COVID-19 treatment and ensuing shortages, supply was preferentially allocated to hospitals.[50] That was counterproductive, however, since advanced-stage patients are least likely to respond to this drug given the required 5-10 days to achieve effective antiviral tissue concentrations.[48] Also, such patients sometimes have cardiac complications, which can amplify otherwise minimal QTc prolongation risks for HCQ.[51] Commensurately, HCQ proved ineffective in prospective[52] or retrospective studies[53-56] with mostly advanced such patients; in treatments using underdoses or overdoses;[57] or in a study conducted with varied assortments of other drugs not including AZ.[58] But these results do not misalign with the sharp reduction in mortality for the 3,300 mixed stage Marseille patients[26,27] or with several other such studies having early and mixed stage patients.[59,60]

QTc prolongation can sometimes occur with CQ or HCQ, but typically only with intensive intravenous dosing[36,61-63] or cumulative oral dosing over months.[64] In one series of 84 COVID-19 patients treated with HCQ plus AZ, 11% had significant QTc prolongation, but no TdP arrhythmias or cardiac deaths resulted.[65] In the initial set of 3,000 Marseille patients assessed in a safety review, only one cardiac-related death occurred,[66] despite the cardiac complications that sometimes occur in cases of advanced COVID-19 infection.[67] HCQ may in fact be cardioprotective;[68,69] a three-fold reduction in cardiovascular events was obtained in 241 rheumatoid arthritis patients taking this drug compared with controls.[68]

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."[70] It concluded that the risks of cardiac problems with AZ and with AZ plus CQ were likewise limited.[70]

Nevertheless, both this task force and the Marseille research team[66] advise EKG screening for at-risk patients and avoidance of contraindicated other drugs.

Ivermectin (IVM): clinical response in COVID-19 patients

IVM is a multi-faceted drug, its discovery in 1973 honored with the Nobel Prize for medicine in 2015.[71] It is active against bacteria, viruses, malaria, scabies and an array of other diseases.[72] Its potential activity against COVID-19 was analyzed by a US research team in an observational propensity-matched case controlled study of 1,408 hospitalized such patients.[73] The underlying patient database drew from 169 hospitals in North America, Europe and Asia. Half (704) who took IVM had a striking one-sixth mortality rate vs. controls, 1.4% vs. 8.5%. Of those patients requiring mechanical ventilation, the death rate in the IVM-treated group was one-third vs. controls (7.3% vs. 21.3%). This same research team used similar analytical methods in a recent *Lancet* study of hospitalized HCQ-treated COVID-19 patients.[56]

Consistent with the six-fold reduction in mortality for these 704 IVM-treated patients were the outcomes for 71 COVID-19 patients treated by a team of pulmonologists in Florida with IVM at a dose of 200 μg/kg, repeated after 7 days when needed, plus HCQ, AZ and zinc.[74,75] They reported a statically significant reduction in mortality, including for patients requiring mechanical ventilation. Stabilization and then improvement frequently proceeded in 12-48 hours, 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 interest of this investigator in IVM was initially spurred by the case of a 65-year-old female whose symptoms of COVID-19 were cleared at a dose of 538 μg/kg and then again ten days later at a dose of 460 μg/kg.[76] She also took CQ and doxycycline switched mid-course to AZ. The second dose of IVM was taken after breathing function had rapidly deteriorated to labored breathing at rest, which then resolved 12 hours after IVM.

Pharmacology and maximum tolerated clinical doses of IVM

The rapid response against COVID-19 indicated in these cases is consistent with IVM being absorbed into blood[72,77-83] and distributed in body tissues[84-86] to peak levels typically within 4-8 hours after oral dosage. An average elimination half-life of IVM of roughly 18 hours has been observed after oral dosing in human subjects.[79,80,82,83,87] But the half-life of the major metabolites of IVM is four-fold greater.[79] These times likely underestimate the persistence of IVM in tissue, however, since significant biological effects have been manifested in humans[79,84,88] and rabbits,[89,90] respectively, from many days to one month after a single dose.

As noted above, the 704 case-controlled COVID-19 patients and the 71 COVID-19 patients in Florida each derived significant benefit from IVM at doses of 150 μg/kg and 200 μg/kg, respectively. Yet IVM has been safely tolerated at ten times these doses, up 2 mg/kg (details below). Since plasma levels of IVM have been found proportional to oral intake at up to 1.7 mg/kg,[80,91] increased doses could provide commensurately greater potency against COVID-19. Indeed, in several studies of antiviral agents, response varied roughly linearly or sometimes more robustly with dose.[92-94]

A standard dose of IVM is 200 μg/kg, taken, for example, twice, a week apart, for scabies[95] or once to three times per year for river blindness.[2,96] Since 1987, 1.3 billion of the latter such treatments have been provided worldwide.[2,96] But much greater 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.[80] Likewise IVM was well tolerated at a single dose of 800 μg/kg,[97] at 1.6 mg/kg over 12 weeks[98] and at 1.6 mg/kg over 13 days.[99] An oral dose of IVM of up to 1.4 mg/kg over one month is recommended by the US CDC as a treatment option for crusted scabies.[95]

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.[100] Also, long-term follow-up studies of IVM use in elderly populations at doses up to 400 μg/kg found no excess deaths.[101,102] A likelihood of safety for a combined treatment of IVM plus HCQ was provided in a study of high dose IVM plus CQ in rhesus monkeys, with no adverse events observed.[82] 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.[80,81,103] However, since the blood brain barrier may be at risk for being compromised in some cases of COVID-19,[104] the most aggressive dose range of 1-2 mg/kg of IVM that would appear safe for normal subjects may not be appropriate for patients with this disease.

The CD147 receptor: the nexus of penetration and morbidity for malaria and COVID-19

One proposed antiviral mechanism of IVM against SARS-CoV-2 is inhibition of nuclear transport of the virus by importin α/β proteins.[5,16,105] But the applicability of this effect at clinically achievable tissue concentrations has been questioned,[106,107] as has whether the SARS-CoV-2 nucleocapsid protein localizes to the nucleus or nucleolus of an infected cell.[108,109] Another such hypothesized biological mechanism is competitive binding by IVM of viral spike glycoproteins required for cellular penetration.[110,111] A third that has been proposed is the targeting of NS3, an RNA helicase required for viral RNA replication.[15,103,109,112] Yet perplexing characteristics of many COVID-19 cases raise broader questions as to which biological mechanisms of IVM and other antimalarial drugs might be clinically operative against this disease.

As with its predecessor, SARS-CoV-1,[113] SARS-CoV-2 is typically transmitted through the respiratory system, with the lung a key target,[67,114] but other organ systems also vulnerable.[67,115-118] 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.[119,120] A pattern of circulatory system damage is also seen in COVID-19 patients with such features as intravascular clots and peripheral ischemia.[116,121,122] One clinical reviewer summarized that COVID-19 "is a systemic disease that primarily injures the vascular endothelium."[123] One possible cause of both such hypoxemia and vascular injury could be the invasive binding of hemoglobin in the red blood cell (RBC) by the SARS-CoV-2 virus, as proposed in an intriguing hypothesis derived through molecular modeling.[124] Another possible explanation proposed below posits only the binding, not penetration, of virus to RBCs and the endothelial lining of blood vessels, causing a catch and clump impedance of blood flow.

These blood-related COVID-19 morbidities mesh with an intriguing commonality between COVID-19 and malaria centering around the RBC and the CD147 transmembrane receptor. The spur to exploring this connection was 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.[125] 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.[126,127] 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 parasite's binding to host RBCs that preceded its subsequent

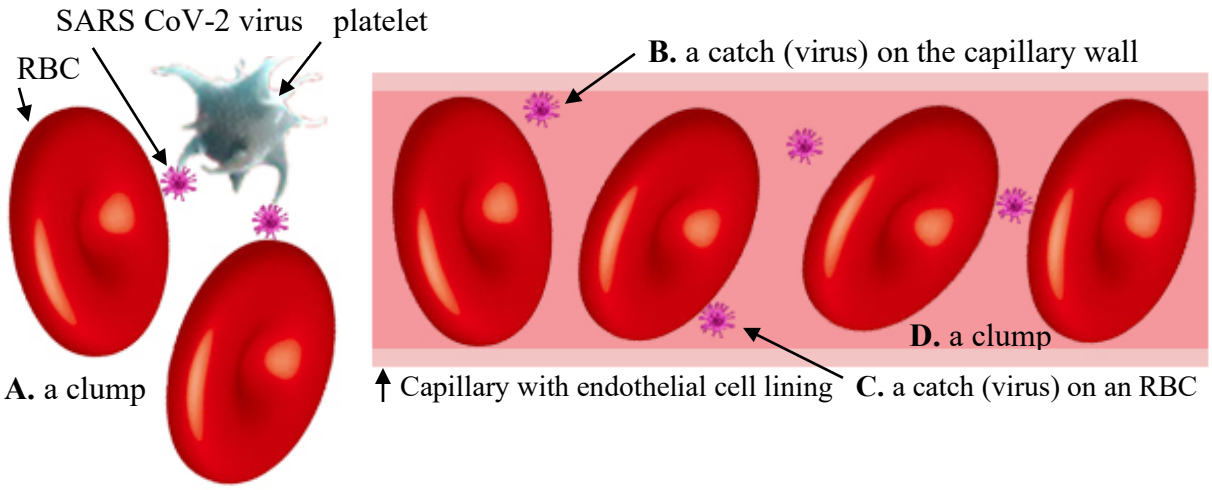

Figure 1. **Catch and clump impedance of blood flow**. This schematic depicts how a SARS-CoV-2 viral particle ("catch") attached to either an RBC or the capillary wall, or a "clump" of blood cells formed through mutual viral attachments, could impede blood flow. All attachments shown between viruses and blood cells are formed by the binding of viral spike proteins to a cellular CD147 receptors. 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).

penetration.[128,129] *In vitro*, CD147 antagonists blocked parasite invasion of RBCs,[128] and *in vivo*, a recombinant anti-CD147 antibody cleared established malarial infections with no overt toxicities.[129,130]

This same transmembrane receptor, CD147, has recently been identified, along with ACE2,[131] as a key binding site for SARS-CoV-2 spike protein.[132] This binding 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.[132] 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.[133] Although the binding affinity of molecules of SARS-CoV-2 spike protein to CD147 is weaker than to ACE2, the surface densities of these molecules on virus and of CD147 on cells (e.g., ~1,700 on each RBC[134]) would allow multiple bonds with significant combined affinity.[135]

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.[136] 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 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 on 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.

Catch and clump impedance of blood flow: a hypothesis

As noted above, the respiratory system is the point of penetration and central base of infection for COVID-19, yet the vasculature is emerging as central to the morbidity of this disease. Circulating through lung alveolar tissue about once per minute,[137] blood cells can efficiently spread the virus.[133] But beyond these known fundamentals, three central questions emerge. What is the biological mechanism behind blood and vasculature-based morbidities of COVID-19? 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?[138] And what caused the stabilization and improvement over the course of 12-48 hours for the Florida patients who had rapidly deteriorating oxygen status, as also occurred in the case report?

A starting point to approach these questions is the distribution of ACE2 and CD147 in key tissues of interest. Both of these receptors are expressed in alveolar and other lung tissue and in the endothelial lining of the vasculature.[131,133,136,139,140] But only CD147, not ACE2, is present in RBCs and white blood cells.[133,141] The distribution of CD147 receptors is especially well established for RBCs,[142,143] with an average of about 1,700 per RBC found in one study.[134] The possibility of an inflammatory cascade spurred by SARS-CoV-2 binding of white blood cells is suggested by multiple indications of a central role of CD147 and its partner cyclophilins in inflammatory processes behind several conditions, including ventilator-induced lung injury and atherosclerosis.[136,139,140,144-146] In a mouse model of acute lung inflammation, anti-CD147 antibodies significantly reduced neutrophil infiltration of lung tissue and associated tissue pathology.[139,144]

But CD147, which is abundantly distributed on RBCS and can act as an adhesion molecule there,[139,147-149] could also enable binding of viral particles to RBCs, platelets and endothelial cells lining the capillaries. Although contact between virus particles and blood cells may only be surface bindings that dynamically detach and reattach,[133] the catches and clumps as depicted in Figure 1 could still impede blood flow.

Viral particles attached to CD147 receptors on RBCs in this figure, as well as those attached to CD147 or ACE2 receptors on the endothelial lining of capillaries are represented as "catches." For visibility, SARS-CoV-2 viral particles (actual size about 0.10-0.12 μm[150]) 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,[151] fits tightly within the capillary wall, often distorting its shape to fit,[152] sometimes flowing through capillaries as small as 2-3 μm in diameter.[151] Thus, these attached viral particles, per their actual size, would not cause a gross obstruction to RBC passage but would 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,[145,153] are densely distributed in blood flowing through capillaries,[154,155] virally-linked clusters of both types of cells as depicted can also form. These clumps as well as catches would cause the most drag on blood flow in smaller capillaries including those in the lung, the average diameter of which is 6 μm.[156] Although single file flow of such cells in capillaries would limit cluster formation mainly to abutting pairs or strings of cells, larger clusters of red and white blood cells, all of which have CD147 receptors,[133,134,141-143] could form in larger blood vessels. These would then create bottlenecks as they progressed from arteries and arterioles into capillaries.

RBCs can in fact form aggregates even under normal conditions, without virus, joined by macromolecules in plasma, under conditions of low blood flow shear rates,[157] such as in veins.[158] But such aggregation is reversible, the RBCs separating at higher shear rates.[157] This process can proceed in a positive feedback loop, with RBC aggregation slowing blood flow, and new RBC clumps then more likely to form under such

conditions.[157] 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. Slower flow in turn would promote further such aggregation, causing a cascade of viral-mediated catching and clumping.

Although viral-cell bindings would be dynamically detaching and reattaching, a flow rate below a certain threshold would allow this cascading drag on blood flow by viral-mediated catches and clumps to proceed. Such a cascade of blood flow impedance, which would limit oxygen transfer by RBCs both from lungs and into tissue, could explain the sudden decline of oxygen status often experienced by those COVID-19 patients who deteriorate to serious status. It could explain blood clots and "COVID toes"[159] sometimes experience by patients. The dissolution of such bonds, on the other hand, by an agent that competitively bound to either viral spike protein or the CD147 receptor, would diminish the binding affinity of viral spike protein to the CD147 receptor and loosen these catches and clumps.

This catch and clump hypothesis for diminished oxygen status in COVID-19 patients could explain one more puzzling aspects of this disease: the resilience of younger people and increasing age-related vulnerability of others. Several studies of blood flow in different tissues found much greater 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.[160] In other studies of capillary flow in various tissues, older subjects had 23%[161] and 40%[162] diminished flow velocity vs. younger subjects and a 47% decrease in flux amplitude.[162] Difference in flow rates in arteries for older vs. younger subjects were significant but less pronounced: 26% lower,[163] 27% lower,[164] and 27% lower.[165] The much greater blood flow rates in younger age groups could be sufficient to overcome viral spike protein-CD147 binding forces and prevent a cascade of impeded capillary flow from developing.

While no positive determination has yet been made, there are suggestive indications that the antimalarial drugs of prime interest for COVID-19 treatment may be CD147 inhibitors. Doxycycline reduced CD147 levels in a carcinoma cell line[166] and in human gingival crevicular fluid.[167] AZ and other macrolide agents inhibit the binding and penetration of RBCs by the malarial parasite,[168] and AZ also decreases the expression of metalloproteinase molecules closely related to CD147.[168-170] IVM is a macrocyclic lactone with a 16-carbon core, similar in molecular structure to the 15-carbon macrolide antibiotic AZ[171-174] CD147 appears to promote joint irritation and damage[175-177] and atherosclerotic plaque growth[178] in rheumatoid arthritis (RA), the latter a major factor in significant excess mortality for RA patients due to cardiovascular disease.[178] HCQ is an effective and widely used drug for RA, and its use yielded a three-fold reduction in cardiovascular events in 241 RA patients compared with untreated controls.[68]

Also, a molecular modeling study found that ivermectin had the greatest multi-domain shielding potency for SARS-CoV-2 spike protein of more than 100 agents tested, with heparin second in shielding potency.[111] Clinical benefit was indicated using heparin for COVID-19 patients in assorted studies,[121,179,180] with most pronounced response obtained in conjunction with azithromycin.[121] A conversion of milligrams per week to moles per week of higher-end clinical doses of heparin (40,000 units per day) and ivermectin (400 μg/kg once per week) yields a factor of 12 greater for the weekly dose of ivermectin vs. heparin.[181,182]

Considerations for dosing of IVM, HCQ and AZ

As a reference point for dosing of IVM, HCQ and AZ toward optimal safety and efficacy, the regimen that has been used for COVID-19 treatment in Marseille is HCQ administered at 200 mg three times daily for

ten days, along with AZ at 500 mg on day 1 and at 250 mg per day on days 2-5.[26] In the study noted above of IVM plus CQ in rhesus monkeys, the human equivalent of the IVM dose used was 513 μg/kg given daily for seven consecutive days.[82,183] (CQ was at a human equivalent dose of 4.27 mg/kg once daily for seven days.) Studies cited above on the elimination half-life of IVM and its metabolites and other indicators of persistence in tissue as well as preliminary experience in COVID-19 treatment suggest that the clinical effects of IVM would persist for 7 days or longer.

There is insufficient clinical experience at this point with the combination of IVM, HCQ and AZ to indicate whether, for example, an optimal combination dose might be IVM at 500 μg/kg every 7 days along with the Marseille regimen doses of HCQ and AZ; IVM at 500 μg/kg every 7 days along with a tempered form of the Marseille regimen; or a more conservative IVM dose along with the full-strength Marseille regimen. Because of the molecular similarity between IVM and AZ and the *in vitro* synergy of AZ with HCQ against the SARS-CoV-2 virus,[3] it appears that IVM may be likewise synergistic with HCQ and that a combination of IVM with HCQ and AZ may be more effective than IVM alone. Routine screening for patients at risk for cardiac arrhythmias has been advised HCQ usage.[66,70] Some clinicians have added zinc sulfate to combination regimens including CCQ, and a retrospective study comparing outcomes for COVID-19 patients treated with HCQ, AZ and zinc vs. those treated with HCQ and AZ alone found a 50% reduction in mortality or transfer to hospice with treatment including zinc.[184]

Conclusion

A one-sixth mortality rate vs. untreated counterparts was reported in a case-controlled study of 704 COVID-19 patients treated with IVM at an average total dose of 150 μg/kg. Preliminary clinical experience suggests that a combined regimen of IVM with HCQ and AZ could yield dramatic, rapid responses for COVID-19 patients. Since IVM is safe at much larger doses than the 150-200 μg/kg used to date, it is likely that dose increases above that level could yield even greater efficacy against COVID-19.

An examination of the indicated role of the CD147 receptor provides clues as to potential biological mechanisms of these antimalarial agents against the SARS-CoV-2 virus. A proposed catch and clump scenario for impedance of capillary flow through viral bindings to blood cells via CD147 could explain several puzzling aspects of COVID-19, including markedly reduced severity in younger patients and rapid clinical response to IVM. Additional study of biological mechanisms related to CD147 bindings may be able to advance the pioneering work of the Marseille research team for the treatment of COVID-19.

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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
RA	rheumatoid arthritis
RBC	red blood cell

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