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Mini Review

Can hydroxychloroquine be protective against COVID-19-associated thrombotic events ?

Christian A. Devaux [a,b,*,1], Laurence Camoin-Jau [a,c,1], Jean-Louis Mege [a], Didier Raoult [a]

[a] *Aix-Marseille Univ, IRD, APHM, MEPHI, IHU-Méditerranée Infection, Marseille, France*
[b] *CNRS, Marseille, France*
[c] *Laboratoire D'Hématologie, Hôpital de La Timone, APHM, Boulevard Jean- Moulin, 13005, Marseille, France*

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Abstract Although SARS-CoV-2 is considered a lung-tropic virus, severe COVID-19 is not just a viral pulmonary infection, clinically it is a multi-organ pathology with major coagulation abnormalities and thromboembolism events. Recently, antiphospholipid (aPL) antibodies were found increased in a large number of COVID-19 patients. Elevated aPL have been well documented in antiphospholipid syndrome (APS), a systemic autoimmune disorder characterized by recurrent venous or arterial thrombosis and/or obstetrical morbidity. Among treatment regimen of APS, hydroxychloroquine (HCQ) is one of the molecules proposed in the primary prevention of thrombosis and obstetrical morbidity in those patients. Due to its antithrombotic properties documented in APS therapy, HCQ could be considered a good candidate for the prevention of thrombotic events in COVID-19 patients in association with anticoagulant and its repurposing deserves further evaluation.

* Corresponding author. IHU Méditerranée Infection, 19-21 Boulevard Jean Moulin, 13385, Marseille, France. Fax: +33 4 13 73 20 52.
E-mail address: christian.devaux@mediterranee-infection.com (C.A. Devaux).
[1] Contributed equally.

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Introduction

The 4-aminoquinoline drug hydroxychloroquine (HCQ) belong to the same molecular family than chloroquine (CQ), an amine acidotropic form of natural quinine that was synthesised in the early 1930s and emerged approximately 70 years ago as a substitute for quinine against malaria. HCQ was reported to be as active as CQ against *Plasmodium falciparum* and less toxic, allowing long periods of high dose therapy with very good tolerance.[1] Moreover, HCQ has been widely used for many years in the therapy of autoimmune diseases as it acts as immune modulator interfering with lysosomal activity and autophagy, modulating signaling pathways (such as inhibition of Toll-like receptor signaling in dendritic cells, phospholipase A2 activity and arachidonic acid production in platelets, nitric oxide production by endothelial cells, antiphospholipid-β2 glycoprotein complexes on monocytes surfaces, inhibiting cytokines production by T lymphocytes) and transcriptional activity.[2–4] The antithrombotic properties of HCQ was described as far as 1975.[5] In the context of autoimmune disease (SLE), HCQ inhibits stimulated platelets at the arachidonic acid pathway and thromboxane 2 generation in activated platelets (an activator of platelets aggregation), which is associated with decreased circulating levels of endothelin-1, and allows improvement of endothelial function.[3,6–8] Interestingly, using network-based approach to prediction and population-based validation of *in silico* drug repurposing it was found that the Healthcare registry data for 220 million people showed that HCQ intake (a series of 37,795 patients receiving HCQ) was associated with a lower risk for coronary artery disease.[9]

The main purpose of this review is to summarize the evidence supporting a potential beneficial role of HCQ in the prevention of thrombosis in patients with antiphospholipid syndrome and discuss the possible repurposing of this molecule as an additional member of the therapeutic arsenal in association with classical antithrombotic drugs used for the prevention of the obstructive thrombo-inflammatory syndrome associated with severe forms of COVID-19.

The pathophysiology of COVID-19

An outbreak caused by a novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first described in Wuhan in December 2019.[10–12] During the past nine months the SARS-CoV-2 has spread worldwide and was responsible for severe COVID-19 disease forms characterized by cytokine storm, acute respiratory distress syndrome (ARDS), and severe thrombotic events leading to multiple organ dysfunction syndrome (MODS), and high risk of fatal evolution.[11,13,14] To date (one year after the first outbreak in China), SARS-CoV-2 has been responsible for more than 1.57 million deaths among about 68.95 million of infected people (https://coronavirus.jhu.edu/map.html), and these numbers are still raising daily.

It is currently admitted that COVID-19 pathogenesis is mainly characterized by production of pro-inflammatory cytokines including IL-6, a key contributor in the development of cytokine storm associated with microvascular injury, obstructive thrombo-inflammatory syndrome which represent the primary causes of lethality,[15,16] with an estimated fatality rate of 2,27%. The lack of specific treatment for COVID-19 led all clinical teams to try to speed up the implementation of therapeutic strategies by carrying out drug repurposing. HCQ which was known to inhibit the replication of several coronavirus *in vitro*, was reported to inhibit SARS-CoV-2 *in vitro*.[17–20] This antiviral activity likely occurs through several mechanisms and cellular targets.[21,22] By February 2020, the first report from China on the clinical efficacy of chloroquine phosphate in treatment of COVID-19 associated pneumonia was submitted for publication.[23] Considering the possible benefit of this molecule as both antiviral agent and immunomodulator compound, it was tempting to evaluate its potential in the prevention and/or treatment of COVID-19.[24–28] This therapeutic approach has lead to an impassioned global debate on the promises and pitfalls of HCQ in COVID-19, in both clinical and scientific communities. By mid-July 2020, among 2654 registered clinical trials from 43 countries aimed at testing the capacity of compound at preventing severe COVID-19, 239 included HCQ treatment or prophylaxis while 82 addressed chloroquine efficiency (Clinicaltrials.gov). Still today, the debate remains fierce between those who consider HCQ to save lives, those who find no significant impact on COVID-19 progression and those who still claim that HCQ is toxic.[29–34] This does not make it possible to conclude whether HCQ is beneficial or not, it simply indicates that the case series and treatment protocols are different and that meta-analysis algorithms are either unsuitable or misused.

As knowledge about the disease grew it became evident that one of the major issues to be addressed in severe COVID-19 was that of thrombosis.[35,36] The use of anticoagulants was considered as a major therapy to reduce the harmful circle of inflammation-coagulation observed in patients with a severe form of COVID-19 [37,38]. Antithrombotic therapy improved COVID-19 patients outcomes.[39]

In vitro, HCQ was found to induce attenuation of human aortic endothelial cells activation upon exposure to proinflammatory cytokine TNFα by reducing of VCAM and IL-1β production.[9] The ectonucleoside triphosphate diphosphohydrolase I/CD39, present on endothelial cells and circulating blood cells such as leukocytes, neutrophils, T- and B-lymphocytes and macrophages is a known interface between vascular inflammation and thrombosis through regulation of ATP, ADP and AMP levels.[40] Mice lacking CD39 expression have marked fibrin deposit in pulmonary and cardiac tissues.[41] IL-6 and other cytokines are increased in COVID-19 patients,[38,42,43] and the profound inflammatory state of the patients can be characterized by high levels of C reactive protein (CRP) and fibrinogen. These observations led to the adoption of the anti-IL6 receptor monoclonal antibody tocilizumab for the treatment of pneumonia-associated to cytokine storm.[44,45] It is also known that blocking IL-6 increases the frequency of CD39+ Treg cells.[46]

In severe COVID-19, patients with thrombosis have significantly higher blood levels of markers of neutrophil extracellular traps (NETs), neutrophil activation (calprotectin, cell-free DNA) and D-dimers.[47] SARS-CoV-2 induces functional changes in platelet. Platelet hyperreactivity may contribute to thrombotic events through increased platelet–platelet and platelet–leukocytes interactions.[48]

Moreover, antiphospholipid (aPL) antibodies where recently found increased in a large number of COVID-19 patients.[49—54] Higher aPL antibodies were associated with neutrophil hyperactivity including the release of NETs.[55] Recently, it was reported that increased count of $CD15^{+}CD16^{+}$ neutrophils is a COVID-19 signature.[56]

Thrombotic disease in severe COVID-19 patients

Coagulation abnormalities are common in COVID-19 patients. Degree of elevation of fibrinogen and D-Dimers is correlated to the severity of the disease and elevated D-dimer upon admission and during course of disease is associated with increased mortality.[57—61] Clinical evidence indicated that COVID-19 is associated with an increase risk of thrombotic events leading to sustained activation of the clotting, generally venous thromboembolism (VTE) almost assuredly underdiagnosed, due to the difficulty of the performing blood vessels investigation when patients are under isolated care and the fact that the D-dimer level is already high.

However, 20—30% of acute pulmonary embolisms were reported in critically patients.[15,54,62—65] Large vessel occlusion stroke was also described.[66,67] While diagnosis of disseminated intravascular coagulopathy (DIC) has been mainly discussed in severe COVID-19, this diagnosis is limited to end stage of COVID-19. Yet, this disorder is not a typical DIC fibrinogen levels are often high and platelets are rarely reduced. It is more similar to complement mediated thrombotic microangiopathy (TMA) syndromes, that is involve disorders of complement. Mediators of TMA syndromes overlap with those released in cytokine storm.[68,69] Interestingly, the presence of platelet-fibrin microthrombi in small arterial vessels of lung tissues was reported in 87% (33/38) of patient who have died with COVID-19 and for whom pulmonary post-mortem examination was requested.[70] For the patients who have had symptomatic forms of the disease, delayed pulmonary fibrosis may be found in a relatively important proportion of COVID-19 patients once they have healed.[37] These observations allowed proposing a new pulmonary vasculopathy named pulmonary intravascular coagulopathy (PIC).[43,71] Moreover, microangiopathic vessel occlusions and endothelium damages was described in kidney.[72] Elevated plasma von Willebrand factor (VWF) concentrations in COVID-19 patients, a factor mainly biosynthesized by activated endothelial cells, was reported.[73—75] Deposits of complement components C5b-9, C4d in the microvasculature of lung and skin was also reported.[76] These observations would be in favor of complement activation which participates to microvascular injury.

Also, COVID-19 induced micro and microvasculature dysfunction. The cytokine storm observed plays a determining role in this immunoinflammatory thrombosis and in endothelial damages. All of these mechanisms, whose kinetics remains unclarified today, might explain the occurrence of various thromboembolic events and multiples organ dysfunction observed in critical COVID-19 patients.

In parallel to these observations, it is important to underline the fact that a high prevalence of antiphospholipid (aPL) antibodies has been observed in critical COVID-19 patients and is reminiscent of a clinical scenario of antiphospholipid syndrome (APS). Among aPL antibodies, Lupus anticoagulant (LA) are more associated to thrombotic events. In agreement with Helms' study,[54] it was demonstrated that 85% of critically COVID-19 patients presented Lupus anticoagulant.[77] Recently, our group described a prevalence of 62% and 25% of LA respectively in hospitalized and ambulatory patients (Camoin—Jau et al., Submitted). This high prevalence could be linked to cytokine storm and dysimmunity. To the best of our knowledge, the role of Lupus anticoagulant in the occurrence of thrombotic event is not yet demonstrated. High levels of aPL-β2GPI antibodies where also recently found in a large number of COVID-19 patients.[52,78] Regarding clinical events described during COVID-19 infection and biological abnormalities, Cavalli and colleagues,[79] suggested that a secondary form of APS is present in COVID-19 patients.

Lesson from the antiphospholipid syndrome (APS)

Mainly associated with systemic lupus erythematous (SLE) and other autoimmune diseases (such as rheumatoid arthritis, dermatomyositis, systemic scleoris, Sjörgren's syndrome), the antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by recurrent venous or arterial thrombosis with or without pregnancy morbidity in the presence of persistent antiphospholipid (aPL) autoantibodies including the lupus anticoagulant (LA) or, anticardiolipin (aCL) or anti-beta 2 glycoprotein (antiβ2-GPI) autoantibodies. In 53% of patients it exists alone as primary APS (PAPS).[80,81] The presence of antibodies directed against CL and/or β2-GPI has been observed in a percentage of healthy individuals without clinical symptoms of APS ranging from 4.5 to 5.5%.[82,83] There is still controversy about whether pharmacologic primary thromboprophylaxis is indicated in asymptomatic carriers of aPL antibodies.[84]

Many clinical trials have been focused on the benefit of aspirin on prevention of thrombotic events in APS patients. Actually, thromboprophylaxis with aspirin is proposed only for asymptomatic aPL carriers with high risk profile, especially in the presence of other thrombotic risk factors.[85,86] Low molecular weight heparin are proposed in all aPL carriers in high-risk situations, such as surgery, prolonged immobilization and the puerperium. Usually APS patient receive oral anticoagulant,[87—89] and/or low-dose aspirin.[90]

By opposite, HCQ (grade 1 B recommendation) and low-dose aspirin are proposed in SLE with LA or isolated persistent aCL.[86] Indeed, several studies suggest that beside its anti-inflammatory effects, HCQ could play a role in lowering antiphospholipid titers and potentially be antithrombotic through several mechanisms involving inhibition of platelet adhesion, intravascular aggregation of red blood cells, interactions between platelets and coagulation factors, and binding of antiphospholipid (aPL) antibodies phospholipid surface.[91—93] In antiphospholipid syndrome (APS) an important risk of thrombosis relapse should be considered.[94] HCQ benefit to protect against thromboembolism was described more than 30-years ago, with reported reduction of erythrocyte aggregation *in vitro* and

thrombus size.[95,96] *In vitro*, CQ at 1 mM inhibit both ADP-stimulated platelets aggregation and thrombin-stimulated platelets aggregation.[97] Jancinova and colleagues hypothesized that CQ, as a cationic amphiphilic molecule, might inhibit platelets aggregation either though interaction with membrane phospholipids, membrane receptor such as ADP receptor, induce the displacement of membrane-bound calcium, or pass membrane and directly act on platelets phospholipase A2, phospholipase C or calmodulin, or the production of aggregating-amplifying substances such as histamine, serotonine and adenine nucleotides. HCQ administration to patients was found to significantly reduce the thrombus size and duration.[98] Similar observation were reported using mouse models of APS in which administration of HCQ limited aPL binding on target cells decreased pro-inflammation, and reduced the size and duration of the thrombus.[98,99] Miranda and colleagues,[99] found that HCQ increased the p-eNOS/e-NOS ratio leading to an improvement in the production of NO. A protective effect of HCQ against thrombosis in asymptomatic aPL-positive APS individuals was reported.[100] In the LUMINA observational cohort of 442 SLE patients HCQ was found thromboprotective.[101] These encouraging preliminary reports lead to the organization of an international consortium (APS ACTION) with the aim to set up a randomized controlled trial of HCQ in the primary thrombosis prevention of persistently aPL-positive but thrombosis free patients without other systemic autoimmune diseases[102]; they had the objective to investigate a cohort of 1000 patients age 18—60 years, without pharmaceutical support, but 6-years only 20 patients had been included in the cohort and the trial was stopped.[103] However, there are evidences that HCQ could be beneficial to APS patients. Among asymptomatic aPL-positive patients with SLE, primary prophylaxis with HCQ appears to reduce the frequency of thrombotic events.[104] HCQ could reduce subclinical atherosclerosis and its use may provide survival benefit.[105] HCQ was found to protect patients against both venous and arterial thromboses.[106] HCQ is consider to have several antithrombotic effects.[107—110] Rand and colleagues,[108,109] demonstrated that HCQ reduces the binding of aPL autoantibodies/β2GPI complexes (responsible for the thrombotic effect) to phospholipid bilayers, and protect the anticoagulant annexinA5 (AnxA5) from disruption by aPL autoantibodies. Interestingly, HCQ blocks platelet aggregation and adhesion and improves cholesterol profiles.[111] Schmidt-Tanguy and colleagues,[112] reported that in patients with clinical history of venous thrombosis (one or two episodes) 6/20 patients treated with oral anticoagulants (fluindione) alone showed recurrent venous thromboses whereas no recurrent venous thromboses (0/20) in patients who received HCQ (400 mg daily) in addition to oral anticoagulants (fluindione). The long term administration of HCQ to PAPS patients reduced aPL antibodies.[92] HCQ also partially reverse the aPL-induced impaired trophoblast migration.[113] This is consistent with the observation that addition of HCQ to conventional treatment may be associated with a reduction of first-trimester miscarriages in pregnant patients.[114]

Trials are still ongoing. The HYPATIA multicenter trial will examine the use of HCQ versus placebo in aPL-positive women planning to conceive.[115] A more recent study, HIBISCUS, plans to examine the effect of HCQ on secondary thrombosis and APS-related morbidity in PAPS.[116] HCQ was also reported to decreases LDL cholesterol and serum glucose levels in PAPS patients likely contributing to reduce the risk of thrombosis.[117] Recently, a pilot open label randomized prospective study on the use of HCQ (200 mg daily for patients weighing below 60 Kg and 400 mg daily for those weighing above 60 Kg) for prevention of thrombosis in 50 patients with PAPS concluded to the efficiency of the treatment with a decreased incidence of thrombosis associated to a reduction in aPL titers.[118]

HCQ as a possible treatment of thrombotic events observed in COVID-19?

Right at the center of the debate on the use of HCQ as a prophylaxis and treatment of COVID-19 and lack of proper design of many trials, the idea that treatment of COVID-19 patients by HCQ might reduce the thrombotic events observed in severe forms of the disease has emerged.[119]

The vascular endothelium functions as an integral barrier, separating blood from the subendothelial tissue compartments. It maintains its integrity and blood fluidity by acting as an anticoagulant through suppression of platelets activation and induction of fibrinolysis. Anti-SARS-CoV-2 defense mechanism are likely to activate a tissue aggressive immune response including exaggerated IL-6 production that drives inflammatory reactions and the so called "cytokine storm" that increases tissue damage. Coagulopathy and vasculopathy walls following a pro-inflammatory process result in rapid activation of mechanism aimed at leading to local damage reparation, immune cells accumulation to prevent infection, platelets aggregation for primary and secondary hemostasis.

Thrombosis is common during critical illness especially in the oldest patients who had preexisting cardiovascular disease and it was reported in COVID-19 patients.[49,52,54] There is currently a debate whether or not the number of patients who experience arterial thrombotic events in COVID-19 is higher rate compared to critically ill patients without SARS-CoV-2 carriage.[120] Whatever the answer, COVID-19 appears to induce a hypercoagulable state with elevated fibrinogen and the fact remains that clinicians must prevent and/or treat thrombosis. In patients with previous thrombosis attributable to APS, anticoagulation has formed the cornerstone of treatment. Inflammation in the presence of aPL, is associated with an increased thrombotic risk, that requires rapid treatment with anticoagulant to reduce mortality. This is very similar to what is observed in COVID-19 (inflammation and thrombosis), which suggests that in this pathology also taking HCQ could have a beneficial effect against thrombotic events and preliminary investigation of such therapy is under evaluation[121] (see Fig. 1).

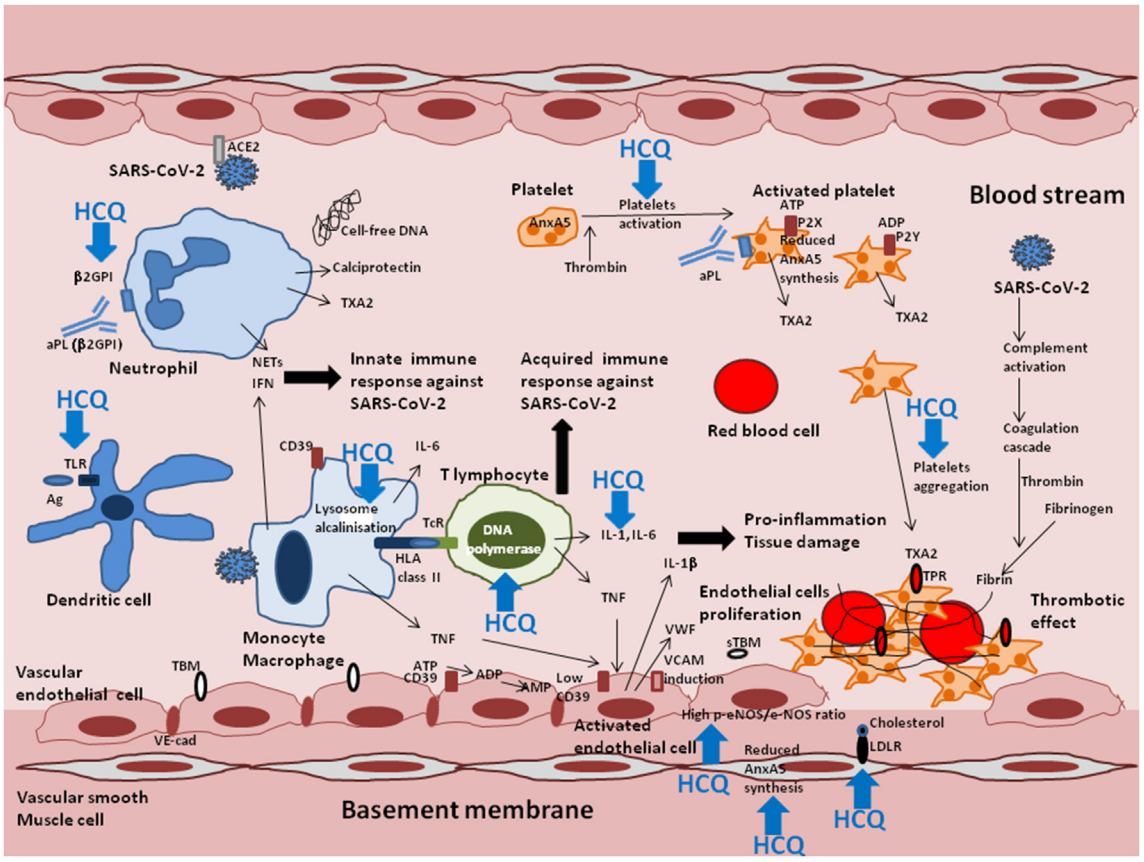

Figure 1. Possible mechanisms of action of hydroxychloroquine (HCQ) against COVID-19-associated thrombosis. The vascular endothelium functions as an integral barrier through myriad mechanisms including VE-cadherin, and maintains blood fluidity by acting as an anticoagulant through suppression of platelets activation and induction of fibrinolysis, mechanism including heparan sulfate proteoglycans and CD39. During SARS-CoV-2 infection, innate and acquired immune defense mechanisms are activated (including the cytokine storm IL-1, IL-2, IL-6, IL-8, IL-17, TNFα) that provokes tissue damage in the lung parenchyma and the immediately adjacent bronchial alveolar lymphoid tissue and disruption of blood vessel walls. The endothelial cells express the angiotensin I converting enzyme 2 (ACE2) molecule that act as cell-surface-receptor that facilitates SARS-CoV-2 entry into these cells. When activated by proinflammatory cytokines, or neutrophil extracellular traps, endothelial cells produce von Willebrand factor that retains platelets and leucocytes to the vessel wall and activates coagulation systems resulting in rapid activation of mechanism aimed at leading to local damage reparation, immune cells accumulation to prevent infection, platelets aggregation for primary and secondary hemostasis. The hyper-reaction set up in response to vascular damage, can influence a propensity toward local vascular micro-thrombosis. COVID-19 patients suffer from prominent alveolar oedema, intra-alveolar proteinosis, cell infiltration including lymphocytes apoptosis of virally-infected pneumocytes, fibrin deposition. HCQ treatment of COVID-19 patient is likely to reduce pro-inflammation and vascular micro-thrombosis due to its multiple actions (the expected mechanisms of action of HCQ to counteract pro-inflammation and thrombosis are indicated by a blue arrow and HCQ) in addition to reduce the patient viral load. aPL: antiphospholipids; IL-6: interleukin-6; TLR: toll like receptor; Ag: antigen; IFN: interferon; TNF: tumor necrosis factor; CD39/ENTPD1: Ectonucleoside triphosphate diphosphohydrolase-1 (also known as or P2 receptors: P2X receptors are ion channels that open upon binding of ATP; P2Y receptors mediate cellular response to purine and pyrimidine such as ATP, ADP, UTP; in physiological conditions CD39 catalyze the reduction of ATP and ADP pool to AMP and CD73 transform AMP to adenosine whereas nucleotides released during cell activation/injury bind to P2 receptors to activate thrombo-inflammatory programs); NETs: neutrophil extracellular traps; TXA2: Thromboxane A2 (induce platelets aggregation); AnxA5: annexinA5 (or annexin V or anchorin CII; anticoagulant, interact with phospholipids); TPR: thromboxane A2 prostanoid receptor: VE-cad: VE-cadherin; TBM: thrombomodulin prevents thrombosis; upon endothelial cell activation a soluble form of TBM (sTBM) is released in plasma further promoting procoagulant mechanisms. VWF: von Willebrand factor; Fibrin: fibrin is formed from blood plasma fibrinogen (produced in the liver) by the action of thrombin; red thrombus is composed of erythrocytes enmeshed in a fibrin network; LDLR: Low density lipoprotein receptor (bind LDL/cholesterol).

Conclusion

If the therapeutic use of HCQ in COVID-19 is still the subject of passionate debate in the infectious disease community, rheumatologists have successfully used it for a long time for the prevention of pro-inflammatory process and the thrombosis, two pathological processes frequently encountered in severe cases of COVID-19. When the HCQ/azithromycin was initiated in Marseille IHU Méditerranée infection for the treatment of people who were found positive for SARS-CoV-2, the main objective of this protocol was to take advantage of both the antiviral and immunosuppressive properties of HCQ.[122] Yet, we might hypothesize that the low mortality of COVID-19 patients treated in Marseille IHU with HCQ (fatality rate estimated 0.4% to be compared to 2.27% worldwide) could be also due to a protective effect of HCQ against thrombosis when used in association with a well-chosen anticoagulant. This will require further evaluation.

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Authorship

All authors contributed to the design of the study and conceived the manuscript. CD and LCJ wrote the paper. DR obtained the funding for this study. All authors reviewed and approved the final version of the manuscript.

Declaration of competing interest

CD declares a link of interest with the Sanofi pharmaceutical company which markets hydroxychloroquine. The other authors (LCJ, JLM, and DR) declare that they have no competing interests.

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