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

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30 **Abstract**

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

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56 **Introduction**

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

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

82

83 **The pathophysiology of COVID-19**

84 An outbreak caused by a novel human coronavirus, severe acute respiratory syndrome
85 coronavirus 2 (SARS-CoV-2) was first described in Wuhan in December 2019 ¹⁰⁻¹². During
86 the past nine months the SARS-CoV-2 has spread worldwide and was responsible for severe
87 COVID-19 disease forms characterized by cytokine storm, acute respiratory distress

88 syndrome (ARDS), and severe thrombotic events leading to multiple organ dysfunction
89 syndrome (MODS), and high risk of fatal evolution ^{11,13-14}. To date (one year after the first
90 outbreak in China), SARS-CoV-2 has been responsible for more than 1.57 million deaths
91 among about 68.95 million of infected people (<https://coronavirus.jhu.edu/map.html>), and
92 these numbers are still raising daily.

93 It is currently admitted that COVID-19 pathogenesis is mainly characterized by production of
94 pro-inflammatory cytokines including IL-6, a key contributor in the development of cytokine
95 storm associated with microvascular injury, obstructive thrombo-inflammatory syndrome
96 which represent the primary causes of lethality ^{15,16}, with an estimated fatality rate of 2,27%.
97 The lack of specific treatment for COVID-19 led all clinical teams to try to speed up the
98 implementation of therapeutic strategies by carrying out drug repurposing. HCQ which was
99 known to inhibit the replication of several coronavirus *in vitro*, was reported to inhibit SARS-
100 CoV-2 *in vitro* ¹⁷⁻²⁰. This antiviral activity likely occurs through several mechanisms and
101 cellular targets ²¹⁻²². By February 2020, the first report from China on the clinical efficacy of
102 chloroquine phosphate in treatment of COVID-19 associated pneumonia was submitted for
103 publication ²³. Considering the possible benefit of this molecule as both antiviral agent and
104 immunomodulator compound, it was tempting to evaluate its potential in the prevention
105 and/or treatment of COVID-19 ²⁴⁻²⁸. This therapeutic approach has lead to an impassioned
106 global debate on the promises and pitfalls of HCQ in COVID-19, in both clinical and
107 scientific communities. By mid-July 2020, among 2,654 registered clinical trials from 43
108 countries aimed at testing the capacity of compound at preventing severe COVID-19, 239
109 included HCQ treatment or prophylaxis while 82 addressed chloroquine efficiency
110 (Clinicaltrials.gov). Still today, the debate remains fierce between those who consider HCQ to
111 save lives, those who find no significant impact on COVID-19 progression and those who still
112 claim that HCQ is toxic ²⁹⁻³⁴. This does not make it possible to conclude whether HCQ is
113 beneficial or not, it simply indicates that the case series and treatment protocols are different
114 and that meta-analysis algorithms are either unsuitable or misused.

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

120 *In vitro*, HCQ was found to induce attenuation of human aortic endothelial cells activation
121 upon exposure to proinflammatory cytokine TNF α by reducing of VCAM and IL-1 β
122 production ⁹. The ectonucleoside triphosphate diphosphohydrolase I/CD39, present on
123 endothelial cells and circulating blood cells such as leukocytes, neutrophils, T- and B-
124 lymphocytes and macrophages is a known interface between vascular inflammation and
125 thrombosis through regulation of ATP, ADP and AMP levels ⁴⁰. Mice lacking CD39
126 expression have marked fibrin deposit in pulmonary and cardiac tissues ⁴¹. IL-6 and other
127 cytokines are increased in COVID-19 patients ^{38, 42-43}, and the profound inflammatory state of
128 the patients can be characterized by high levels of C reactive protein (CRP) and fibrinogen.
129 These observations led to the adoption of the anti-IL6 receptor monoclonal antibody
130 tocilizumab for the treatment of pneumonia-associated to cytokine storm ^{44, 45}. It is also
131 known that blocking IL-6 increases the frequency of CD39+ Treg cells ⁴⁶.
132 In severe COVID-19, patients with thrombosis have significantly higher blood levels of
133 markers of neutrophil extracellular traps (NETs), neutrophil activation (calprotectin, cell-free
134 DNA) and D-dimers ⁴⁷. SARS-CoV-2 induces functional changes in platelet. Platelet
135 hyperreactivity may contribute to thrombotic events through increased platelet-platelet and
136 platelet-leukocytes interactions ⁴⁸. Moreover, antiphospholipid (aPL) antibodies were
137 recently found increased in a large number of COVID-19 patients ⁴⁹⁻⁵⁴. Higher aPL antibodies
138 were associated with neutrophil hyperactivity including the release of NETs ⁵⁵. Recently, it
139 was reported that increased count of CD15⁺CD16⁺ neutrophils is a COVID-19 signature ⁵⁶.

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141 **Thrombotic disease in severe COVID-19 patients**

142 Coagulation abnormalities are common in COVID-19 patients. Degree of elevation of
143 fibrinogen and D-Dimers is correlated to the severity of the disease and elevated D-dimer
144 upon admission and during course of disease is associated with increased mortality ⁵⁷⁻⁶¹.
145 Clinical evidence indicated that COVID-19 is associated with an increase risk of thrombotic
146 events leading to sustained activation of the clotting, generally venous thromboembolism
147 (VTE) almost assuredly underdiagnosed, due to the difficulty of the performing blood vessels
148 investigation when patients are under isolated care and the fact that the D-dimer level is
149 already high.
150 However, 20-30 % of acute pulmonary embolisms were reported in critically patients ^{15, 54, 62-}
151 ⁶⁵. Large vessel occlusion stroke was also described ^{66, 67}. While diagnosis of disseminated
152 intravascular coagulopathy (DIC) has been mainly discussed in severe COVID-19, this

153 diagnosis is limited to end stage of COVID-19. Yet, this disorder is not a typical DIC
154 fibrinogen levels are often high and platelets are rarely reduced. It is more similar to
155 complement mediated thrombotic microangiopathy (TMA) syndromes, that is involve
156 disorders of complement. Mediators of TMA syndromes overlap with those released in
157 cytokine storm ^{68, 69}. Interestingly, the presence of platelet-fibrin microthrombi in small
158 arterial vessels of lung tissues was reported in 87% (33/38) of patient who have died with
159 COVID-19 and for whom pulmonary post-mortem examination was requested ⁷⁰. For the
160 patients who have had symptomatic forms of the disease, delayed pulmonary fibrosis may be
161 found in a relatively important proportion of COVID-19 patients once they have healed ³⁷.
162 These observations allowed proposing a new pulmonary vasculopathy named pulmonary
163 intravascular coagulopathy (PIC) ^{43, 71}. Moreover, microangiopathic vessel occlusions and
164 endothelium damages was described in kidney ⁷². Elevated plasma von Willebrand factor
165 (VWF) concentrations in COVID-19 patients, a factor mainly biosynthesized by activated
166 endothelial cells, was reported ⁷³⁻⁷⁵. Deposits of complement components C5b-9, C4d in the
167 microvasculature of lung and skin was also reported ⁷⁶. These observations would be in favor
168 of complement activation which participates to microvascular injury.

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

174 In parallel to these observations, it is important to underline the fact that a high prevalence of
175 antiphospholipid (aPL) antibodies has been observed in critical COVID-19 patients and is
176 reminiscent of a clinical scenario of antiphospholipid syndrome (APS). Among aPL
177 antibodies, Lupus anticoagulant (LA) are more associated to thrombotic events. In agreement
178 with Helms' study ⁵⁴, it was demonstrated that 85 % of critically COVID-19 patients
179 presented Lupus anticoagulant ⁷⁷. Recently, our group described a prevalence of 62% and
180 25% of LA respectively in hospitalized and ambulatory patients (Camoin-Jau et al.,
181 Submitted). This high prevalence could be linked to cytokine storm and dysimmunity. To the
182 best of our knowledge, the role of Lupus anticoagulant in the occurrence of thrombotic event
183 is not yet demonstrated. High levels of aPL- β 2GPI antibodies where also recently found in a
184 large number of COVID-19 patients ^{52, 78}. Regarding clinical events described during COVID-

185 19 infection and biological abnormalities, Cavalli and colleagues ⁷⁹, suggested that a
186 secondary form of APS is present in COVID-19 patients.

187

188 **Lesson from the Antiphospholipid syndrome (APS)**

189 Mainly associated with systemic lupus erythematosus (SLE) and other autoimmune diseases
190 (such as rheumatoid arthritis, dermatomyositis, systemic scleritis, Sjögren's syndrome), the
191 antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by
192 recurrent venous or arterial thrombosis with or without pregnancy morbidity in the presence
193 of persistent antiphospholipid (aPL) autoantibodies including the lupus anticoagulant (LA) or,
194 anticardiolipin (aCL) or anti-beta 2glycoprotein (anti β 2-GPI) autoantibodies. In 53% of
195 patients it exists alone as primary APS (PAPS) ^{80, 81}. The presence of antibodies directed
196 against CL and/or β 2-GPI has been observed in a percentage of healthy individuals without
197 clinical symptoms of APS ranging from 4.5 to 5.5% ^{82, 83}. There is still controversy about
198 whether pharmacologic primary thromboprophylaxis is indicated in asymptomatic carriers of
199 aPL antibodies ⁸⁴.

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

206 By opposite, HCQ (grade 1B recommendation) and low-dose aspirin are proposed in SLE
207 with LA or isolated persistent aCL ⁸⁶. Indeed, several studies suggest that beside its anti-
208 inflammatory effects, HCQ could play a role in lowering antiphospholipid titers and
209 potentially be anti-thrombotic through several mechanisms involving inhibition of platelet
210 adhesion, intravascular aggregation of red blood cells, interactions between platelets and
211 coagulation factors, and binding of antiphospholipid (aPL) antibodies phospholipid surface <sup>91-
212 93</sup>. In antiphospholipid syndrome (APS) an important risk of thrombosis relapse should be
213 considered ⁹⁴. HCQ benefit to protect against thromboembolism was described more than 30-
214 years ago, with reported reduction of erythrocyte aggregation *in vitro* and thrombus size ^{95, 96}.
215 *In vitro*, CQ at 1 mM inhibit both ADP-stimulated platelets aggregation and thrombin-
216 stimulated platelets aggregation ⁹⁷. Jancinova and colleagues hypothesized that CQ, as a

217 cationic amphiphilic molecule, might inhibit platelets aggregation either through interaction
218 with membrane phospholipids, membrane receptor such as ADP receptor, induce the
219 displacement of membrane-bound calcium, or pass membrane and directly act on platelets
220 phospholipase A2, phospholipase C or calmodulin, or the production of aggregating-
221 amplifying substances such as histamine, serotonin and adenine nucleotides. HCQ
222 administration to patients was found to significantly reduce the thrombus size and duration ⁹⁸.
223 Similar observations were reported using mouse models of APS in which administration of
224 HCQ limited aPL binding on target cells decreased pro-inflammation, and reduced the size
225 and duration of the thrombus ^{98, 99}. Miranda and colleagues ⁹⁹, found that HCQ increased the
226 p-eNOS/e-NOS ratio leading to an improvement in the production of NO. A protective effect
227 of HCQ against thrombosis in asymptomatic aPL-positive APS individuals was reported ¹⁰⁰.
228 In the LUMINA observational cohort of 442 SLE patients HCQ was found
229 thromboprotective ¹⁰¹. These encouraging preliminary reports lead to the organization of an
230 international consortium (APS ACTION) with the aim to set up a randomized controlled trial
231 of HCQ in the primary thrombosis prevention of persistently aPL-positive but thrombosis free
232 patients without other systemic autoimmune diseases ¹⁰²; they had the objective to investigate
233 a cohort of 1,000 patients age 18-60 years, without pharmaceutical support, but 6-years only
234 20 patients had been included in the cohort and the trial was stopped ¹⁰³. However, there are
235 evidences that HCQ could be beneficial to APS patients. Among asymptomatic aPL-positive
236 patients with SLE, primary prophylaxis with HCQ appears to reduce the frequency of
237 thrombotic events ¹⁰⁴. HCQ could reduce subclinical atherosclerosis and its use may provide
238 survival benefit ¹⁰⁵. HCQ was found to protect patients against both venous and arterial
239 thromboses ¹⁰⁶. HCQ is considered to have several antithrombotic effects ¹⁰⁷⁻¹¹⁰. Rand and
240 colleagues ^{108, 109}, demonstrated that HCQ reduces the binding of aPL autoantibodies/ β 2GPI
241 complexes (responsible for the thrombotic effect) to phospholipid bilayers, and protect the
242 anticoagulant annexin A5 (AnxA5) from disruption by aPL autoantibodies. Interestingly, HCQ
243 blocks platelet aggregation and adhesion and improves cholesterol profiles ¹¹¹. Schmidt-
244 Tanguy and colleagues ¹¹², reported that in patients with clinical history of venous thrombosis
245 (one or two episodes) 6/20 patients treated with oral anticoagulants (fludione) alone showed
246 recurrent venous thromboses whereas no recurrent venous thromboses (0/20) in patients who
247 received HCQ (400 mg daily) in addition to oral anticoagulants (fludione). The long term
248 administration of HCQ to PAPS patients reduced aPL antibodies ⁹². HCQ also partially
249 reverse the aPL-induced impaired trophoblast migration ¹¹³. This is consistent with the
250 observation that addition of HCQ to conventional treatment may be associated with a

251 reduction of first-trimester miscarriages in pregnant patients ¹¹⁴.

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

261

262 **Anti-thrombotic effect of HCQ in COVID-19 ?**

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

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

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

277 Thrombosis is common during critical illness especially in the oldest patients who had
278 preexisting cardiovascular disease and it was reported in COVID-19 patients ^{49, 52, 54}. There is
279 currently a debate whether or not the number of patients who experience arterial thrombotic
280 events in COVID-19 is higher rate compared to critically ill patients without SARS-CoV-2

281 carriage ¹²⁰. Whatever the answer, COVID-19 appears to induce a hypercoagulable state with
282 elevated fibrinogen and the fact remains that clinicians must prevent and/or treat thrombosis.
283 In patients with previous thrombosis attributable to APS, anticoagulation has formed the
284 cornerstone of treatment. Inflammation in the presence of aPL, is associated with an increased
285 thrombotic risk, that requires rapid treatment with anticoagulant to reduce mortality. This is
286 very similar to what is observed in COVID-19 (inflammation and thrombosis), which
287 suggests that in this pathology also taking HCQ could have a beneficial effect against
288 thrombotic events and preliminary investigation of such therapy is under evaluation ¹²¹.

289

290 **Conclusion**

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

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315

316 **Authorship**

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

320

321 **Declaration of Competing Interest**

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

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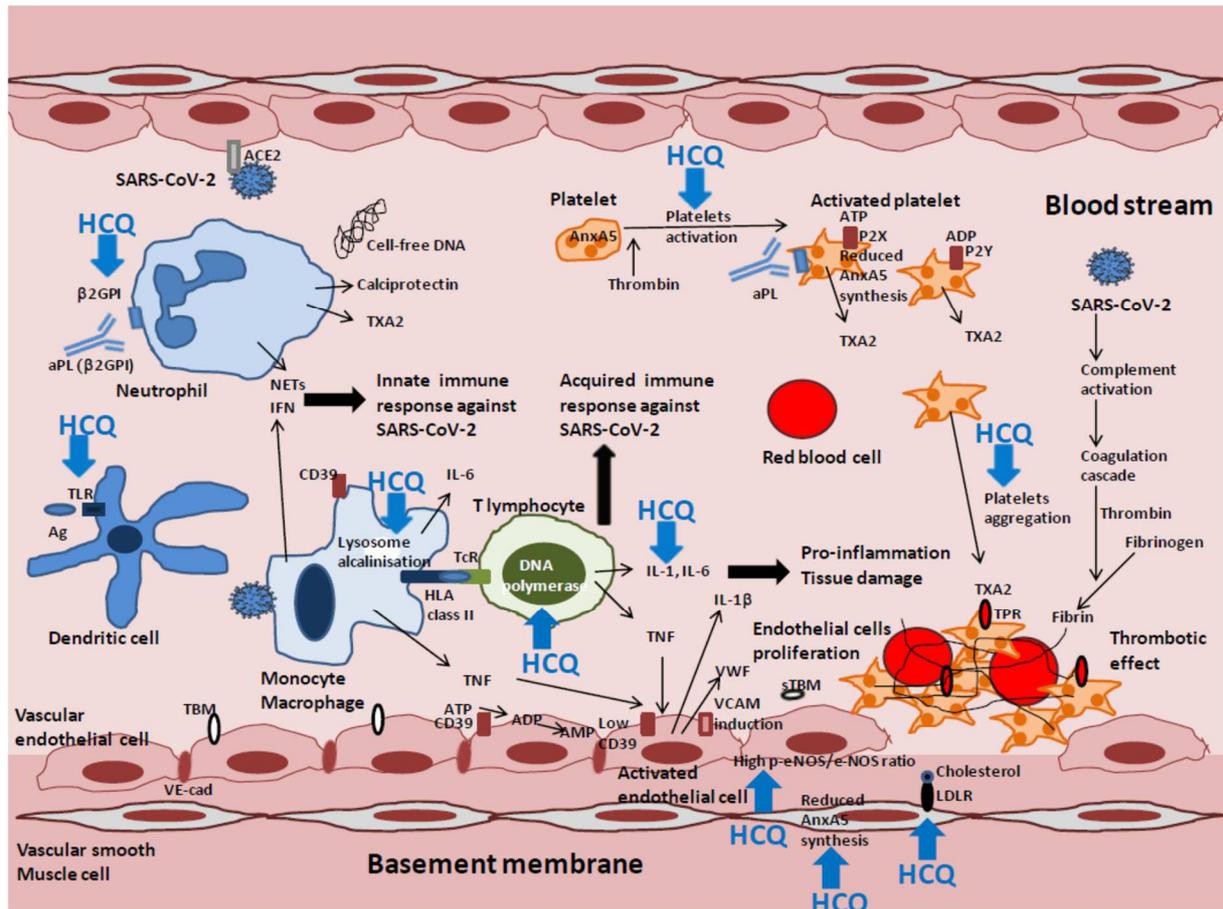
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334 **Figure 1:** Possible mechanisms of action of hydroxychloroquine (HCQ) against COVID-19-
335 associated thrombosis. The vascular endothelium functions as an integral barrier through
336 myriad mechanisms including VE-cadherin, and maintains blood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

368 from blood plasma fibrinogen (produced in the liver) by the action of thrombin; red thrombus
 369 is composed of erythrocytes enmeshed in a fibrin network; LDLR: Low density lipoprotein
 370 receptor (bind LDL/cholesterol).



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