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Treatment of COVID 19—Repurposing drugs commonly used in dermatology

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Abstract

For the last two decades, the outbreaks of diseases caused by coronaviruses and intermittent worldwide public health emergences have reminded us that they still represent a severe threat to global health. The recent outbreak of corona virus disease 19 (COVID-19) highlighted the urgent need for effective treatment, and initiated rapid search for therapies, able to counter the most severe disease effects. Many aspects of COVID-19 pathogenesis are unknown, but complex interplay of direct viral damage and immune response dysregulation is underline. Intensive research is undergoing for therapeutic targets of virus and high-efficiency and low toxicity targeted drugs. There is no available specific antiviral treatment of this disease, therefore repurposing of drugs already available for the treatment of other viral and autoimmune diseases has been a part of research efforts. Well known anti-inflammatory properties of chloroquine and hydroxychloroquine, agents widely used in dermatology, made them potential candidates for the treatment of COVID-19. We review pathogenesis and clinical characteristic of COVID-19, as well as treatment options that have been under evaluation in past several months. In addition, we focus more on chloroquine and hydroxychloroquine, their pharmacological properties, clinical utility, and current recommendations for their use in COVID-19.

KEYWORDS

antiviral treatment, chloroquine, COVID 19, hydroxychloroquine, SARS-CoV-2, side effects

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pulmonary infection caused by novel Coronavirus (2019-nCoV).[1-4] It has been declared as a public health emergency of international concern by The World Health Organization (WHO) since January 2020,[5] after its outbreak in Wuhan, Hubei province, central China, at the end of 2019.[6] After China, an increasing number of countries has been affected and issued the alert of the highest level.[4] Up to now, coronavirus COVID 19 has affected 213 countries, with 4 088 848 confirmed cases.[7] The disease is potentially zoonotic, but person-to-person transmission occurs through contact and respiratory transmission or probable fecal-oral route.[4,8] COVID-19 has spread rapidly since it was first identified and has been shown to have a strong contagious capacity, high morbidity, a wide spectrum of severity, and estimated mortality rate of 2% to 14%.[3,4,9,10]

There is no definite and specific treatment for COVID 19, disease with spectrum of clinical manifestation that could progress to acute respiratory distress syndrome (ARDS) and involvement of multiple organs and in some cases result in death.[1] Pathogenesis is still unclear and some potential drugs are under investigation.

2 | CHARACTERISTICS OF COVID-19

2.1 | Immunopathological evidence of COVID-19

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), at the beginning called the 2019-novel coronavirus (2019-nCoV), is a single-stranded RNA virus, a member of *Betacoronavirus* genera of *Coronaviridae* family. Seven types of coronaviruses can cause diseases

in humans, ranging from mild common cold symptoms (caused by human coronavirus (HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1) to severe illness (caused by Severe Acute Respiratory Syndrome human coronavirus (SARS-HCoV), Middle Eastern respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2).[11,12] Since this is a novel virus, little is known about mechanisms of infection. Phylogenetic studies of SARS-CoV-2 showed similarity of 76% in the spike protein sequence with SARS-CoV, including 73% homology in its receptor-binding domain (RBD) and further suggested that SARS-CoV-2 like SARS-CoV, could use angiotensin converting enzyme 2 (ACE2) as a receptor to enter human cells.[13,14] Further, SARS-CoV-2 RBD binds with greater affinity to ACE compared to SARS-CoV, which could explain stronger contagious potential and more severe disease in COVID-19.[15] Pathogenesis of cell and tissue damage in COVID-19 is also largely unknown. Beside the tissue damage there is indirect evidence of altered immune response as a contributor to the development and severity of disease. Patients with COVID-19 show significant decreased in total number of lymphocytes, B-cells, T-cells (including helper, suppressor, and regulator subsets), and NK-cells, especially in severe forms of the disease.[16] Severe cases had significant increase in several cytokines (IL-2R, IL-6, IL-8, IL-10, and TNFα) compared to non-severe cases.[16] IL-6 level was also increased in patients who developed ARDS, especially in those with poor outcome.[17] Several other cytokines (IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, and VEGF) were higher in COVID-19 patients compared to healthy individuals, but only some of those (IL-2, IL-7, IL-10, GCSF, IP10, MCP1, MIP1A, and TNFα) were significantly increased in patients who required a treatment in an intensive care unit.[6] Decreased lymphocytes in blood and lungs together with such paradoxical hyperactivation of immunity (also called "a cytokine storm") resembles a Macrophage activation syndrome and could be a mechanism of widespread damage of pulmonary vasculature, local impairment of coagulation and a development of full blown diffuse alveolar damage.[18]

2.2 | Clinical presentation/manifestation of COVID-19

Clinical presentation of COVID-19 varies from asymptomatic or mild disease (more often in children and younger adults) to severe, critical and potentially lethal forms, especially in older adults.[4] After an incubation period of 1 to 24 days, mostly ranging from 3 to 7 days,[4,19] symptomatic patients often develop fever (up to 90% or more) and various respiratory symptoms: cough (around 75%), dyspnea (up to 50%) and chest tightness.[2,4,20,21] A minority of patients, especially children, had gastrointestinal symptoms, such as nausea, vomiting, and diarrhea.[4,19] Most patients experience a mild illness with fever, fatigue, and dry cough, accompanied by other symptoms like headache, nasal congestion, sore throat, myalgia, and arthralgia.[2,4] A part of patients may progress to shortness of breath and hypoxemia, usually in the second week of the illness.[4] Severe pneumonia should be considered in patients developing tachypnea, chest indrawing, or inability to feed or drink. In 10% to 20% of patients with severe forms of disease, the respiratory injury will inevitably develop into ARDS, especially if they are in advanced age and have comorbidities (chronic respiratory disease, hypertension, diabetes, cardiovascular disease, cerebrovascular disease and cancers).[4,19] The disease can progress to respiratory failure, septic shock, metabolic acidosis, coagulation dysfunction and multiple organ failure.[4] It was observed that COVID-19 patients with mild/moderate symptoms can quickly transit into severe or critical status without immediate care. However, patients with COVID-19 can also be afebrile and asymptomatic.[2,4]

Laboratory findings can show leukopenia (25%), lymphopenia (25%) and raised aspartate aminotransferase (37%),[2] but majority of COVID-19 patients have normal leukocyte count.[6,21] Patients can also have increased prothrombin, D-dimer and troponin (hypersensitive-troponin I) levels,[2,6,21] lactate dehydrogenase, direct bilirubin,[9] and infection-related serum biomarkers—C-reactive protein, IL-6, and erythrocyte sedimentation rate.[2] Along with clinical symptoms and laboratory abnormalities, chest X rays and computed tomography (CT) abnormalities can be seen in COVID-19 patients.[2,4,6,19] However, the indication for imaging was not specified yet.[2] The clinical features of the infection are not specific and are often indistinguishable from those of other respiratory infections. Currently, diagnosis is based on epidemiological associations, clinical manifestations, laboratory findings, a coagulation profile, cytokine tests,[10] radiological characteristics,[3] and specific molecular tests for SARS-Cov-2 RNA detection (real-time PCR and/or genomic sequencing),[10,19] or serological methods (ELISA detection of SARS-CoV-2 specific IgM and IgG antibodies).[4,19] Preliminary estimates of case fatality are about 2%,[21] with the higher mortality rate in Wuhan, China (14.1%),[10] mostly due to ARDS, acute kidney injury, and myocardial injury.[21] Our understanding why there is such a discrepancy between the severity of COVID-19 cases is still incomplete. One of the explanations could be prior exposure to community circulation of non-SARS-CoVs, and their antigenic epitopes that leads to antibody-dependent enhancement (ADE) of SARS-CoV-2. ADE further elicits lymphopenia, prolonged inflammation or cytokine storm in serious cases and the individuals with fatal outcome. Also, there are assumptions that certain HLA haplotypes are susceptible to develop severe illness while others have capacity of the cellular immune system to avoid severe infection, but these hypotheses need to be confirmed.[22] Another possibility is that SARS-CoV-2 transmission viral burden could have impact on illness severity. If the infection stems from severely affected patients, the viral load is higher and might lead to severe and sometimes lethal infection. So far, no data on the specific role of either humoral or cellular immunity or innate immunity in patients recovering from COVID-19 is available.[22]

Taking all into account it is noticeable that proper management of COVID-19 patients is needed, individual for each patient in regard to all mentioned contexts (disease severity and individual patient status).

3 | MANAGEMENT OF COVID-19

3.1 | Current corona virus treatments

Unfortunately, no targeted therapy for SARS-CoV-2 infection exists. Researchers are trying to find the therapeutic targets of the virus and high efficiency/low toxicity targeted drugs. Many antiviral and anti-inflammatory treatments, used also in dermatology, have been employed, and experience with SARS and MERS or influenza virus infections has been used to guide the clinical practice.[19,20] Although, no specific antiviral drug has been proven, several clinical trials with different pharmaceutical interventions for COVID-19 treatment are identified in the studies at clinical phases 2, 3, or 4.

3.1.1 | Antiviral medications

Several antiviral agents have been proposed for COVID-19 patients' treatment and included in clinical studies like remdesivir,[23,24] umifenovir, lopinavir-ritonavir, oseltamivir, xiyanping, darunavir-cobicistat,[24] and small molecule drugs (tegobuvir, nelfinavir, and bictegravir) interfering with viral replication and proliferation.[24,25] Some of the antiviral drugs have been combined in multidrug treatment. Oseltamivir has been used in combination with antibiotics and corticosteroids, with chloroquine and favipiravir or intravenous peramivir.[19,24] Danoprevir was combined with ritonavir and interferon inhalation, lopinavir-ritonavir, or traditional Chinese medicine (phytotherapeutic formulations such as teas, pills, powders or tinctures) and interferon inhalation.[24]

3.1.2 | Immunomodulatory agents

Along with antiviral treatments, studies have been conducted with different immunomodulatory therapeutics, that act differently, like human immunoglobulins (broadly neutralizing antibodies), recombinant human interferon α2b, and pirfenidone (IL-1b and IL-4 inhibiting agent).[24] Fingolimod (sphingosine-1-phosphate receptor regulator) as an effective immunology modulator, was administered together with ventilator support to prevent the development of ARDS in patients with severe pneumonia.[24] Tocilizumab (humanized IgG1k monoclonal antibody against soluble or membrane-type IL-6 receptors) and thalidomide (acting through TNFα, IL-12 and activation of natural killer cells) have also been used in clinical trials.[19,24] Pirfenidone, small molecule drug that downregulates production of multiple cytokines and blocks fibroblast proliferation and stimulation in response to cytokines has been included in the study with the patients with severe pneumonia.[24] Furthermore, vitamin C (ascorbic acid) with its antioxidant activity had been tested in patients with severe pneumonia caused by 2019-nCoV.[24] Methylprednisolone, one of the major dermatologic therapeutic, has been used in COVID-19 patients in combination with antibiotics, oseltamivir, and oxygen therapy.[6] However, according to current WHO interim guidance on COVID-19 management corticosteroids are not recommended as a routine therapy unless indicated for another reason, because of possible harms and higher risk of mortality identified in studies on other coronaviruses and influenza.[26]

3.1.3 | Other agents

Among other agents, bromhexine hydrochloride, a mucolytic, is currently being investigated in the treatment of respiratory disorders in patients with suspected and mild COVID-19 pneumonia.[24] Furthermore, antibiotics have been implemented in treatment of severely affected patients, along with supportive therapies (ie, oxygen supplementation), with modest outcomes. Prulifloxacin has been used along with inhibitors of key proteases involved in viral replication and proliferation.[25] Also, carrimycin, a macrolide antibiotic, has been combined with lopinavir-ritonavir, umifenoviror, and chloroquine.[24] Additionally, combination of broad-spectrum antibiotics and antifungal agents (voriconazole for *Aspergillus* spp., fluconazole for *Candida* spp. infections) has been administered. In patients with suspected Pneumocystis pneumonia, sulfamethoxazole and caspofungin have been used.[19] Some of these drugs are used for the skin conditions as well. Metronidazole, a biocidal agent, commonly used for skin disorders, due to its immunopharmacological behavior and immunopotentiating effect (decreases levels of IL8, IL6, IL1B, TNFα, IL12, and IFNγ in vitro and in vivo, as well as the CRP levels, neutrophil count, number of circulatory lymphocytes, neutrophil-generated reactive oxygen species, and lymphoproliferative properties) was proposed as a potential candidate to counteract majority of the immunopathological features of COVID-19.[27] Still, clinical trials are necessary to determine its efficacy in this infection. Finally, chloroquine (CQ) and hydroxychloroquine (HCQ), very beneficial for wide spectrum of different dermatoses, warranted particular attention for use in the therapy of COVID-19, because of its broad-spectrum antiviral and immunomodulatory effects.

3.2 | Immunopharmacology of chloroquine and hydroxychloroquine

Chloroquine is a synthetic amine, an acidotropic form of quinine, that has been used as cheap and safe drug for more than 70 years.[28,29] Another member of the same chemical family, hydroxychloroquine, a 4-aminoquinoline, was first developed to treat malaria.[29,30] Along with malaria, as the first and main indication, CQ and HQC have been utilized in the treatment of numerous autoimmune dermatological diseases: systemic and discoid lupus erythematosus (SLE, DLE), dermatomyositis, refractory chronic urticaria, polymorphic light eruption, psoriasis, morphea, lichen planopillaris, leukocytoclastic vasculitis, as well as Crohn's disease, Sjogren's syndrome and numerous rheumatological conditions.[31,32] Due to their immunomodulatory properties, they have been used to prevent skin disease flares and other organ damage as well as to promote long-term survival (especially HCQ) in patients with autoimmune diseases.[29]

The anti-inflammatory mechanisms of CQ and HCQ, highly beneficial in dermatology, are complex and still under investigation, as

comprehensively reviewed by Schrezenmeier and Dörner.[29] Briefly, these molecules exhibit their activity on antigen presenting cells (plasmacytoid dendritic cells and B-cells) and T-cells and mainly affect antigen presentation and cytokine production. Antigen (especially autoantigen) presentation within MHC class II molecules is prevented due to stabilization of lysosomes and decreased antigen degradation, both in case of internal (autophagy delivered) or external (endocytosis/phagocytosis delivered) antigens.[29] Activation of CD4+ T-cell is decreased, as a result of HCQ mediated reduction in expression of co-stimulatory molecule CD154, but it is only partial as HCQ does not affect Jak1 and Jak3/Stat5 pathway.[33] Beside altered antigen presentation and CD4+ T-cell activation, decreased production of cytokines (especially IL1, IL6, TNF, and IFNγ) is a result of interference with Toll-like receptor (TLR) signaling pathways and cyclic GMP AMP (cGAMP) synthase (cGAS) activity. Mechanisms of CQ/HCQ action are probably context-dependent (dependent on the inflammatory conditions and/or affected tissues or organs) and further studies are needed for the explanation of their (in) direct effect cytokine production.[29]

3.3 | Antiviral properties of chloroquine and hydroxychloroquine

Besides their ability to modulate inflammatory processes, CQ and HCQ show a broad-spectrum antimicrobial activity in a range of bacterial, fungal, and viral infections.[34] Chloroquine repurposing was explored against human immunodeficiency virus (HIV) and other viruses associated with inflammation.[35] Prior studies found antiviral activity against multiple RNA viruses including influenza A and B viruses,[36,37] influenza A H5N1 virus,[38] hepatitis A virus,[39] hepatitis C virus,[40] Chikungunya virus,[41] Dengue virus,[42] Zika virus,[43] Crimean-Congo hemorrhagic fever virus,[44] Ebola virus,[45] poliovirus,[46] rabies virus,[47] as well as against some DNA viruses such as hepatitis B virus and herpes simplex virus.[48,49] Furthermore, the potential antiviral effect of CQ was notably reported for several coronaviruses, including SARS-CoV-1.[50-52]

3.4 | Antiviral mechanisms of chloroquine and hydroxychloroquine in SARS-CoV-2 infection

CQ and HCQ have been proposed as potentially effective drugs for COVID-19, and some of their anti-SARS-CoV2 mechanisms have been determined in vitro so far (comprehensively reviewed in Devaux et al. 2020).[30] CQ interferes with ACE2, inhibits viral spike-glycoprotein/ACE2 interaction, and disables ACE2 receptor glycosylation thus limiting viral entry into target cells.[30,53-56] In addition, CQ inhibits quinone reductase-2 and biosynthesis of sialic acids, which are necessary for SARS-CoV-2 ligand recognition and interaction with target cells.[30,57] CQ interferes with post-translational modification of SARS-CoV-2 viral proteins within the endoplasmic reticulum or the trans-Golgi network vesicles.[30] It modifies lysosomal stability and presumably

leads to the formation of the autophagosome which cleaves SARS-CoV-2 spike protein.[23,58] It is hypothesized that CQ can inhibit kinases such as MAPK and interfere with SARS-CoV-2 molecular crosstalk with its target cell.[30] Also, CQ interferes with viral replication cycle, by proteolytic processing of the M protein, and alters virion budding and assembly.[30] Studies revealed that CQ and HQC both act as a weak base that can increase the pH in endosomes and alter membrane fusion required for virus-cell fusion.[38,50,59] Also, it was found that both CQ and HCQ caused noticeable changes in the number and size/morphology of endosomes or endolysosomes, blocked the transport of SARS-CoV-2 from early endosomes or endolysosomes and blocked the release of viral genome.[59] The possible indirect anti-SARS-CoV-2 effect of CQ is through reducing the production of proinflammatory cytokines and/or by activating CD8+ T-cells.[30] In line with that, previously described cytokine storm in severe SARS-CoV-2 infection could be modified or prevented with CQ and HCQ.

3.5 | Clinical utility of chloroquine and hydroxychloroquine in COVID-19

Due to their antiviral activity against SARS-CoV2 in vitro and strong immunomodulatory capacities, especially significant decrease in the production of proinflammatory cytokines, CQ and HCQ have been proposed as potentially effective drugs in COVID-19. The anti-viral and anti-inflammatory actions of CQ and HCQ have led to numerous trials. Study results demonstrated that CQ was optimal for inhibition of the exacerbation of COVID-19 pneumonia, fever reduction, and improvement of lung CT findings.[60] The disease course was shortened compared to control groups and virus-negative seroconversion was promoted, without serious adverse effects.[60] Also, in multicentric study with CQ treatment, the duration of fewer and median time to achieve an undetectable viral RNA was shorter compared with non-CQ group, and without serious adverse events. It has been shown that patients treated with half dose experienced lower rate of adverse events than with full dose, with the same efficacy.[61] A higher dosage of CQ should not be recommended for the treatment, especially if patients have additional treatments (azithromycin and oseltamivir).[62] Moreover, CQ can enhance the effects of other antiviral drugs.[3] The study results showed HCQ to be more potent than CQ in inhibiting SARS-CoV-2 in vitro. Based on these models, HCQ loading dose was recommended.[63] Recent study results demonstrated that HCQ treatment with 800 mg added loading dose increased survival if administrated in early stages of the disease.[64] Hydroxychloroquine clinical safety profile is better than that of CQ (during long-term use) and allows higher daily dose with less concerns about drug-drug interactions.[63] In another recent study, patients received HCQ in addition with standard treatment (oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids). Time to clinical recovery, the body temperature recovery time and the cough remission time were significantly shortened with improved pneumonia in the HCQ treatment group, with just two patients with mild adverse reactions.[65] Likewise, HCQ treatment was

TABLE 1 Guidelines with protocols and dosage regimens for the chloroquine and hydroxychloroquine treatment of COVID-19

Disease/patient characteristics	Treatment regimen	Treatment guidelines
Adults (aged 18-65, body weight over 50 kg)	CQ 500 mg BID for 7 days	National Health Commission & State Administration of Traditional Chinese Medicine, Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)[72]
Adults with body weight below 50 kg	CQ 500 mg BID for day 1 and 2, 500 mg QD for days 3-7	
All symptomatic cases	HCQ 400 mg BID on day 1 then 200 mg BID from day 2-10 CQ 500 mg BID on day 1 then 250 mg BID from day 2-10 +AZM 500 mg for 5 days	The Italian Society for Infectious and Tropical Diseases[73]
Adults	HCQ day 1800 mg BID Day 2-5400 mg BID Initially treat for 5 days, depending on the severity of the patient (maximum up to 10 days).	Spanish Ministry of Health[76]
Children	HCQ loading dose 6.5 mg/kg/dose every 12 hours (max 400 mg/dose); HCQ Maintenance 6.5 mg/kg/day every 12 hours (maximum 400 mg/day), 4 more days Initially treat for 5 days, depending on the severity of the patient (maximum up to 10 days).	
Not specified	CQ loading dose of 600 mg base followed by further treatment after 12 hours with 300 mg base, followed by 4 days 600 mg BID	The Dutch Working Party on Antibiotic Policy[77]
Mild-to moderate disease (no O_2 requirement/no evidence of pneumonia)	HCQ 400 mg at suspicion/diagnosis; 400 mg 12 hours later, followed by 200 mg BID up to day 5 If no HCQ available, CQ base 600 mg (10 mg/kg) at diagnosis and 300 mg (5 mg/kg) 12 hours later, followed by 300 mg (5 mg/kg) BID up to day 5 or CQ phosphate 1000 mg at diagnosis and 500 mg 12 hours later, followed by 500 mg BID up to day 5.	Interim clinical guidance for adults with suspected or confirmed COVID-19 in Belgium[78]
Confirmed COVID-19 Severe disease	HCQ 400 mg at diagnosis; 400 mg 12 hours later, followed by 200 mg BID up to day 5 If no HCQ available, CQ base 600 mg (10 mg/kg) at diagnosis and 300 mg (5 mg/kg) 12 hours later, followed by 300 mg (5 mg/kg) BID up to day 5 or CQ phosphate 1000 mg at diagnosis and 500 mg 12 hours later, followed by 500 mg BID up to day 5	
Adults Patients hospitalized with monitoring of the ECG and plasma concentrations:	600 mg per day (3 tablets of 200 mg per day). The duration of treatment not determined—should not exceed 10 days dose load on day 1400 mg twice a day, then 400 mg once a day for 9 days	The National Agency for the Safety of Medicines and Health Products, France[79]
Pulse oximetry <94% (FiO2 21%) Or CRP > 1.5 mg/L Or Ferritin > 100 ng/mL Or Risk factors Or Infiltratios on CXR or CT	CQ phosphate 500 mg BID for 5-7 day OR HCQ on day1, 200 mg BID for 7 days + AZM 500 mg OD 5-7 days	Hellenic Thoracic Society, Greece[80]
Treatment in uncomplicated* possible/definitive diagnosed COVID-19 cases	HCQ 400 mg BID per oral, 5 day ± AZM 1 day 500 mg, next 4 days 250 mg	General Directorate of Public Health, Turkey
Mild pneumonia** (no severe pneumonia signs) possible/	HCQ Following the 2 × 400 mg loading dose, 2 × 200 mg tablet, oral, 5 days	

(Continues)

TABLE 1 (Continued)

Disease/patient characteristics	Treatment regimen	Treatment guidelines
definitive COVID-19 treatment in patients	± AZM 1 day 500 mg, next 4 days 250 mg	
Treatment in possible/definitive COVID-19 cases with severe pneumonia***	HCQ Following the 2 × 400 mg loading dose, 2 × 200 mg tablet, oral, 5 days ± Favipavir 2 × 1600 mg loading, 2 × 600 mg maintenance ± AZM 1 day 500 mg, next 4 days 250 mg	
Treatment in pregnant women with COVID-19	HCQ 400 mg BID per oral, 5 day	
Adults with COVID-19	Administration of HCQ **ONLY** in the context of randomized trials with appropriate ethical approval.	Australian guidelines for the clinical care of people with COVID-19[82]
	Currently **DO NOT** recommend the routine use of CQ	Interim Treatment Guideline, National Centre for Infectious Diseases, Singapore[83]
	No specific recommendation except that should not use a high dose of 600 mg CQ	National Institute of Health, USA[74]
	HCQ ± AZM **NOT** recommended to treat COVID-19.	Mount Sinai Health System, USA[75]

Abbreviations: AZM, azithromycin; BID, twice daily; CQ, chloroquine; HCQ, hydroxychloroquine; OD, once daily; QD, once a day.

significantly associated with a decreased mortality in critically ill patients with COVID-19 through attenuation of inflammatory cytokine storm.[66] In case of mild and moderate disease, administration of HQC, at a loading dose of 1200 mg daily for 3 days followed by a maintenance dose of 800 mg daily for 2 or 3 weeks, did not result in a significantly higher probability of negative conversion than standard of care.[67] A few studies suggest better clinical outcome in therapies combining HCQ and azithromycin (AZM).[68,69] Their synergistic effect is important for the clearance of viral nasopharyngeal carriage (measured by PCR).[68] Administration of the HCQ and AZM combination before COVID-19 complications has led to good clinical outcome and virological cure in 91.7% of patients within 10 days; poor clinical outcome was associated with older age, severity at admission, and low HCQ serum concentration.[70] In the study of COVID-19 pandemic empirical treatment, in cases suspected of COVID-19 infection with initial flu-like symptoms, HCQ and AZM treatment reduced the need for hospitalization.[71] According to all these results, HCQ and AZM combination is beneficial both for the prevention of severe respiratory complications and early stage disease recovery as well as for prevention of virus transmission.

CQ and HCQ have been included in the SARS-CoV-2 treatment guidelines.[72-83] Recommended CQ and HCQ regiments are presented in Table 1. Different regimes of usage have been recommended, depending on disease severity.

3.6 | Side effects of chloroquine and hydroxychloroquine

Chloroquine has been established as a cheap and safe drug. It is administrated for years for many chronical dermatologic conditions.

CQ is generally well-tolerated and may also be administered to pregnant women. The safety of CQ in addition with AZM is proved to be safe in all trimesters.[84] Likewise, HCQ is even used to control autoimmune disease activity like SLE during pregnancies, without evidence of fetotoxic or embryotoxic effects.[29] HQC binds strongly to melanin and can deposit in the eyes, potentially causing retinopathy.[29] This disadvantage of HCQ is possible in cases of chronic exposure to the drug, such as those of prolonged prophylactic use, and depends on HCQ cumulative dose. Nevertheless, this side effect is reversible at the early stages and can be prevented by regular ophthalmic examination.[85] HCQ is less toxic than CQ, but prolonged and overdose usage can still cause poisoning.[59] Hydroxychloroquine is associated with a lower risk of retinopathy than CQ, possibly due to the lower volume of distribution of HCQ compared with CQ.[29] Rare adverse reactions caused by HCQ include gastrointestinal reactions, cramps, liver dysfunction, itching, headache, dizziness, insomnia, peripheral neuropathy.[29] Nevertheless, short-term application of HCQ is relatively safe, enabling individual treatment plans and timely monitoring of adverse reactions. In multicenter, open label, randomized controlled trial, adverse effects were recorded in 30% HCQ recipients and the most common adverse event was diarrhea, reported in 10% of the patients.[67] In recent study, a total of 2.3% COVID-19 patients treated with HCQ and AZM had mild adverse events (gastrointestinal or skin symptoms, headache, insomnia and transient blurred vision). No cardiac toxicity has been reported.[70] Myopathy as a severe adverse effect has also been associated with the use of CQ. The major complication, even in short regimens, is the potential for QTc interval prolongation, favoring fatal arrhythmias such as ventricular tachycardia and torsades de pointes (TdP).[86] In the largest reported cohort of COVID-19 patients treated with CQ/HCQ with(out) AZM, no TdP or arrhythmogenic death were reported.[87] No data exists in the

literature showing different cardiotoxic effects between CQ and HCQ. Nevertheless, it would be useful to perform an ECG before or at the very beginning of the treatment with both agents. This problem can be solved by hospitalizing patients at risk in a care unit with continuing ECG monitoring allowing early detection and treatment of potential cardiac side-effects.[68]

Hydroxychloroquine binds strongly also to melanin in the skin,[29] another melanin containing tissue, which might explain certain tissue specific mechanisms and its efficacy in the treatment of skin manifestations, but also cutaneous side effects. Of cutaneous HCQ side effects, the most commonly were drug eruption or rash, cutaneous hyperpigmentation, pruritis, acute generalized exanthematous pustulosis, rarely Stevens-Johnson syndrome or toxic epidermal necrolysis, hair loss and stomatitis. Most of skin drug eruptions occur within 4 weeks of initiating HCQ and disappeared within weeks of discontinuation. Since more skin side effects are not life threatening this drug is consider generally efficacious, safe, and well tolerated.[32]

4 | CONCLUSION

Chloroquine and HCQ, are currently among the best available candidates to impact the severity of SARS-CoV-2 infections in humans. Currently, at least 10 clinical trials are testing chloroquine as an anti-COVID-19 therapy. Also, the possibility of its safely but effective combination with the other agents is promising. Mora data is needed for final and detailed suggestion of their use in human patients suffering from the novel coronavirus disease.

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