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COMMENTARY

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Hydroxychloroquine, dermatology, and SARS-CoV-2: Updating an old association

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On 31 December 2019, the Chinese city of Wuhan, Hubei, confirmed the first case of "atypical ARDS/interstitial pneumonia." On 11 February 2020, the World Health Organization (WHO) officially announced the name of the emergent disease associated with a new coronavirus identified as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): Coronavirus Disease 2019 (COVID-19).[1]

On 13 February, 72 000 cases are officially reported in China, among which 15 000 were registered in Hubei province only, with 242 deaths in a single day. Following this, the Republic of China ordered drastic containment measures to fight the spread of the SARS-CoV-2 virus.[1]

On 11 March 2020, the WHO relayed that the international outbreak of the new SARS-CoV-2 coronavirus infection was now a pandemic. As of 28 May, 2020, 217 countries have been affected worldwide, with approximately 5 556 679 confirmed cases and 351 866 deaths since the epidemic outbreak.[2]

The demand for effective drugs for the treatment and control of the COVID-19 pandemic was given top priority by the health and political authorities, specifically in scenarios with high infection rates and in severe and potentially fatal cases.[3-7] This is particularly important as the first COVID-19 vaccine is not expected to be ready for clinical trials before the end of this year.[8]

Anti-malarial aminoquinoline (chloroquine and hydroxychloroquine) drugs have been used for the treatment of inflammatory diseases for more than 70 years by dermatologists and rheumatologists.[9] Hydroxychloroquine (HCQ) is currently used for the treatment of rheumatoid arthritis, systemic lupus erythematosus, discoid lupus erythematosus (DLE), and photodermatosis, due to its immunomodulatory effect. For example, in the treatment of chronic cutaneous lupus erythematosus, the use of HCQ has a healing rate of more than 85%, proving to be equally effective as 50 mg acitretin but with fewer side effects.[9]

Though the mechanisms of action of HCQ are not fully understood, some important aspects are well-known. Chloroquine (CQ), a weak base with a large distribution volume, accumulates at high concentrations in most body tissues, including the lungs.[10] After oral administration, CQ is efficiently absorbed and is present in the blood as a protonated molecule. However, the unprotonated circulating portion easily crosses cell membranes and accumulates in acidic organelles such as lysosomes, Golgi vesicles, and endosomes due to its basic charge. Here, these molecules bind to the free protons, significantly increasing intracellular pH. Thus, many enzymes contained in these organelles that optimally work in an acidic environment, become inhibited.[11] This mechanism is presumably based on the direct antiparasitic, antiviral, and immunomodulatory effects of CQ. Although most of the evidence in this field is regarding CQ, some studies show similar effects when treated with HCQ. Additionally, current data support that the mechanisms of action of these two molecules are similar and that HCQ appears to be significantly less toxic, effectively replacing the use of CQ in the treatment of rheumatic, inflammatory, and autoimmune diseases.[12,13]

Recently hydroxychloroquine has been considered as a potential therapy for COVID-19.[7,13,14] Both CQ and HCQ have been shown to inhibit the SARS-CoV-2 replication in vitro. Additionally, a Chinese clinical trial with more than 100 patients has demonstrated the effective role of chloroquine phosphate (500 mg/day) against COVID-19, inhibiting the exacerbation of pneumonia, improving lung-imaging findings, promoting a virus-negative conversion, and shortening the disease course.[14] However, the N-hydroxyethyl substituted derivative

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of chloroquine, HCQ, is less toxic, more soluble, and has similar or even higher activity towards COVID-19 inhibition.[13,15] Based on these results, CQ and HCQ are currently recommended for the treatment of hospitalized COVID-19 patients in several countries.[8] In fact, HCQ was recommended by the National Health Commission of the People's Republic of China for treatment of COVID-19, and presently, is under investigation by the US Food and Drug Administration (FDA) as a treatment for COVID-19.[8] Therefore, the therapeutic use of HCQ is truly experiencing an unexpected rebirth.

Moreover, the French open-label, non-randomized clinical trial, which reported 20 cases treated for 6 days with HCQ at a dosage of 600 mg/d plus azithromycin, was the first clinical trial testing these medications against COVID-19 with promising results. In fact, the trial showed a significant reduction in the viral carriage compared with that of the controls. The combination of azithromycin with HCQ was suggested to significantly increase the efficiency of virus elimination.[7]

Although these medicines have shown promising activity against SARS-CoV-2, they are not free of side effects, specifically causing retinal and cardiovascular toxicity (retinopathy and cardiomyopathy or with conduction system abnormalities), which depend critically on daily dosage and duration of use.[16] Careful considerations should be given before the use of these medications at higher cumulative dosages in patients with known QT prolongation or are at higher risk of arrhythmia. It is recommended that these medicines be used primarily for suspected/confirmed COVID-19 cases and be restricted to hospitalized patients.[17]

To date, antimalarials are one of the medications with the largest, albeit limited, scientific background, warranting their use in COVID-19 treatment protocols. Soon, a significant amount of data should be available from clinical trials to verify whether the theoretical strong effects of the drug has a real impact on the survival and recovery of COVID-19 patients. Until then, due to the excellent safety profile and vast experience, their use remains a pillar of current treatment protocols.[13] Particularly in United Hospital of Ancona, Italy, because of the establishment of a task force composed of dermatologists and rheumatologists,[18,19] HCQ was included in the treatment protocols of patients affected by SARS-CoV2.

Briefly, among the 50 patients hospitalized for COVID-19 from March 19th to April 6th, 43 (86%) received HCQ as part of active treatment (Table 1). Of note, the median duration of treatment was 12 days, and 25 (50%) patients received HCQ together with azithromycin. Three deaths were observed in all elderly patients with SARS-CoV-2 pneumonia and several comorbidities. Other treated patients experienced a slow but progressive improvement, until healing. All patients were taking HCQ, but not azithromycin. In our cohort, there were no emerging arrhythmias that could be related to QT prolongation.

Despite this encouraging experience, The Lancet recently published an observational study on HCQ and CQ and their effects on COVID-19 patients who have been hospitalized. Among 100 000 patients receiving the drug, alone or with a macrolide, the estimated mortality rate and the frequency of irregular heartbeats were increased.[20] For this reason, the Executive Group of the Solidarity Trial, representing 10 of the participating countries, has decided to start a comprehensive analysis and critical appraisal of all evidence available globally to adequately evaluate the potential benefits and harms from HCQ. Finally WHO has assessing the use of hydroxychloroquine on COVID-19 patients within the Solidarity Trial and the hydroxychloroquine arm has been paused as a precaution while the safety data is being reviewed by the Data Safety Monitoring Board.[21] In Italy, the AIFA (Agenzia Italiana del Farmaco) has currently revoked the authorization for the use of HCQ for the treatment of SARS-CoV-2 infection, out of clinical trials.

In conclusion, despite the encouraging experience of our centre and other centres around the world, the relative weight of

TABLE 1 Demographic, clinical, and radiological characteristics of patients with COVID-19

Variables	N = 50
Age, y, m (SD)	66.1 (12.7)
Gender (male) n (%)	36 (72)
Ethnicity (Caucasian), n (%)	49 (98)
Comorbidity, n (%)	
Hypertension	7 (14)
Diabetes	4 (8)
Ischemic heart disease	3 (6)
Atrial fibrillation	5 (10)
Symptoms, n (%)	
Fever (>38°C)	45 (90)
Dyspnoea	28 (56)
Cough	36 (72)
Fatigue	15 (30)
Myalgia	8 (16)
Nausea/vomiting	4 (8)
Diarrhoea	10 (20)
Headache	2 (4)
Dysgeusia	4 (8)
Hyposmia	3 (6)
Confusion	5 (10)
Time from symptoms to hospitalization, d, – median (IQR)	8 (5-11)
Chest X-ray findings, n (%)	
Normal	5 (10)
Interstitial pneumonia	32 (64)
Ground glass opacity	3 (6)
Bilateral consolidation	10 (20)
Treatment	
HCQ	43 (86)
Azithromycin	25 (50)
Lopinavir/ritonavir	27 (54)
Tocilizumab	8 (16)
Corticosteroids	9 (18)
Other antibiotics	31 (62)
Cumulative mortality, n (%)	3 (6)

hydroxychloroquine in the treatment or prevention of COVID-19 disease, either alone or in association with macrolides, has not be established yet.[22,23] Recent studies also highlight the misleading nature of anecdotal experiences reported when contrasted with the controlled clinical trials.

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