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Safety of Hydroxychloroquine in Patients with COVID-19: The Experience in the District of Piacenza, Preliminary Data

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In December 2019, a new pathogen enveloped RNA beta-coronavirus has been identified and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes severe pulmonary disease in about 14% of infected people (Lu 2020; Wu 2020). On March 2020, the World Health Organization (WHO) has characterized coronavirus infection disease-19 (COVID-19) as a public health emergency of international concern and defined it a pandemic (WHO, 2020). In Italy, the most involved regions by COVID-19 are Lombardy, Emilia Romagna and Veneto. The city of Piacenza (Emilia Romagna Region) is very near to the epicenter of the outbreak of COVID-19, and the catastrophic nature of Lombardy's outbreak has been widely publicized (Berrardi 2020; Horowitz 2020).

In the District of Piacenza, a week later 21 February 2020, the Emergency Department of the Piacenza Hospital was overcrowded with COVID-19 infected people, already in serious condition. Noninvasive ventilation was attempted in the majority of these patients, but the rapidity of lung deterioration in most severely affected patients was quickly worsening.

No vaccine or specific antiviral treatment for COVID-19 has yet been demonstrated to be effective in phase III randomized clinical trials, however hydroxychloroquine with or without antiviral treatment has been incorporated in national guidelines to treat COVID-19 (SIMIT 2020; Geleris 2020).

Hydroxychloroquine (HCQ) and Chloroquine (CQ) are antimalarial drugs and their role in the treatment of COVID-19 is not well defined, given that they, principally, deploy antimicrobial and anti-parasitic effects. Furthermore, these drugs have been proven beneficial in treating rheumatological and immunological diseases, because of the modulation they exert on immunity and proinflammatory cytokines (Yu 2020). However, a carefully monitoring is required when using chloroquine-based drugs, as these drugs can cause QT prolongation and might put patients at increased risk of torsade de pointes and sudden cardiac death (Geleris 2020).

We report the preliminary results on safety of the first 96 patients with COVID-19, treated at the Azienda Sanitaria of Piacenza (Northern Italy) with HCQ.

The treatment was based on a loading dose of 800 mg of hydroxychloroquine for the first day, followed by 200 mg twice daily for six more days.

In this series no arrhythmia was registered. It must be emphasized, however, that ECG was not performed as a daily monitoring program, but only when clini cally required. The median age of our patients was 56 years

Variables	All patients N. (%)
	96 (100%)
Male N. (%)	49 (51%)
Female N. (%)	47 (49%)
Age medians years (range)	56 18-83
Survival at 30 days of treatment HCQ	96 (100%)
Survival at 60 days of treatment HCQ	96 (100%)
Treatment	800 mg of hydroxychloroquine for the first day, followed by 200 mg twice times daily for 6 more days

Table 1: Clinical Demographic characteristics and outcome of the 96 COVID-19 patients treated with HCQ.

Patient without any adverse event	86/96	(89,6%)
Patient with adverse event possible related to the treatment (grade 1-2)	10 /96	(10,4%)
Diarrhea	6	(60%)
Abdominal pain	3	(30%)
Headache	4	(40%)
Vomiting	2	(20)

Table 2: Adverse Events of the 96 COVID-19 patients treated with HCQ.

(range 18-83), while other clinical demographic characteristic, and outcome are reported in Table 1.

In this series of patients no deaths were registered after two months from the treatment. The majority of these patients improved after some days from the beginning of the treatment, thought several cases showed severe type of COVID-19 pneumonia.

In our experience, treatment with HCQ for patients with COVID-19 at the loading dose of 800 mg for first day followed by 200 mg twice times daily for six more days showed to be safe and beneficial. We believe that this shorten regimens used to treat COVID-19 may be suitably adopted, given the reduced rate of significant side effects (Table 2). In addition to the aforementioned cluster of Covid-19 patients, we have already reported data on 25 additional cancer patients suffering from COVID-19 infection. Treatment with HCQ of this group of high-risk patients did not entail any significant burden of side effects (Stroppa, 2020). A further observational study on additional 51 cancer patient affected by COVID-19, showed no significant side effects (Cavanna, submitted 2020).

Conclusively, Chloroquine and hydroxychloroquine are old drugs and have been widely used in the treatment of rheumatic disease and malaria. The current COVID-19 pandemic poses an urgent need to identify effective treatments. It is worth of noting that repurposing of old, off-label drugs, has gaining momentum, providing new exciting insights in pharmacology. Accordingly, HCQ has been "rediscovered" as a useful remedy in managing Covid-19 patients, thus becoming common practice among physicians (Rodriguez-Martinez 2020). Up to now, HCQ has been used in many thousands of patients with COVID-19 around the world (Geleris 2020). However, though this drug is inexpensive and readily available, a number of scientists and physicians are seriously concerned by the hypothetical burden of side effects, usually more "perceived" than actually proven. Namely, the occurrence of cardiac negative events, including the association of QT prolongation and torsade de pointes (ToP) - especially in patients with heart, hepatic or renal disease – has raised fear and suspicion. However, very recently M. Saleh (Saleh 2020) reported that effects of Chloroquine, Hydroxychloroquine and Azithromycin on the Corrected QT Interval in Patients with SARS-CoV-2 Infection are very limited. Two hundred-one patients have been treated for COVID-19 with chloroquine/hydroxychloroquine, with only seven patients (3.5%) requiring discontinuation of treatment due to QTc prolongation. Moreover, no arrhythmogenic deaths related HCQ treatment have been reported (Saleh 2020).

We are currently performing a retrospective study on additional several hundreds of COVID-19 infected patients followed and treated at home or admitted to the hospitals of the district of Piacenza (North Italy) and treated with HCQ. Preliminary data – at a glance – are unable in evidencing clinical significant side effects, as well as treatment-related deaths. We believe that HCQ can be an effective repurposed, "weapon" against COVID-19, with acceptable toxicity when administered according to our proposed model.

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