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Hydroxy Chloroquine in COVID-19 Diseases: What Points of Controversy?

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Abstract

Hydroxychloroquine (HCQ) is an analogue of chloroquine, with fewer side effects. This antimalarial was proposed in the early phase of COVID-19 pandemic as a potential treatment. HCQ is an old drug used for several chronic diseases such as systemic lupus erythematosus. It has been confirmed that HCQ effectively inhibits the entry step and the post-entry stages of SARS-CoV-2. It also suggested that HCQ blocked the transport of SARS-CoV-2 from endosomes to endolysosomes, which is essential to release the viral genome as in the case of SARS-CoV-2. But it prescription in COVID-19 disease garnered exceptional interest. For that, many studies were carried all over the word to assess its efficiency compared to standard care. The current paper is a quick view on the main discussion corners about HCQ in COVID-19 disease.

Results of *in vitro* researches stimulate retrospective and observational studies. Findings concerning the efficiency were inconsistent between these studies, which requires clinical trials. A lot of randomized controlled trials were conducted then, but conclusions were opposite. The optimal dose regimens and the need for HCQ monitoring also constitute a point of discord between these studies.

Keywords: Hydroxychloroquine; COVID-19 efficiency; *In vitro* study; Retrospective study; Clinical trials

Introduction

The World Health Organization (WHO) declared COVID-19 a public health emergency of international concern on 30 January 2020, and a pandemic on 11 March 2020 [1]. That stimulates the search for safe and effective COVID-19 therapies. Umifenovir, remdesivir, fevipiravir, Hydroxychloroquine (HCQ) and other substances were suggested [2]. HCQ analogue of Chloroquine (CQ) was proposed as a potential drug for COVID-19 following preliminary reports on its *in vitro* activity against the virus [3]. This antimalarial drug is known to be used for several chronic diseases such as Systemic Lupus Erythematosus (SLE) with low adverse effects [4]. HCQ used off label, garnered exceptional interest and initiated a profound debate fed by the many studies carried over the word to evaluate its efficiency.

The current paper is a brief overview of the main points that were the topic of this debate.

Discussion

HCQ is a weak base that is known as well as chloroquine (**Figure 1**) to elevate the pH of acidic intracellular organelles, such as endosomes/lysosomes, essential for membrane fusion which confers antiviral effects. It has been confirmed in the time-of-addition experiment that HCQ effectively inhibits the entry step and the post-entry stages of SARS-CoV-2. It also suggested that HCQ blocked the transport of SARS-CoV-2 from endosomes to endolysosomes, which appears to be a requirement to release the viral genome as in the case of SARS-CoV-2. It can also inhibit nucleic acid replication, glycosylation of viral proteins, virus assembly, new virus particle transport, virus release, and other processes to achieve its antiviral effects [5-7] (**Figure 2**). HCQ has demonstrated its effectiveness in rheumatic diseases such as SLE for its antioxidant activities, and it performs in the regulation of cytokines (Interleukin-1 and Interleukin-6, for example). That suggests the benefice of HCQ in COVID-19 patients since a higher pro-inflammatory cytokine storm reported in patients with a severe or critical illness [8].

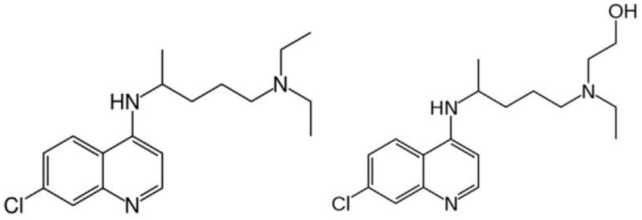
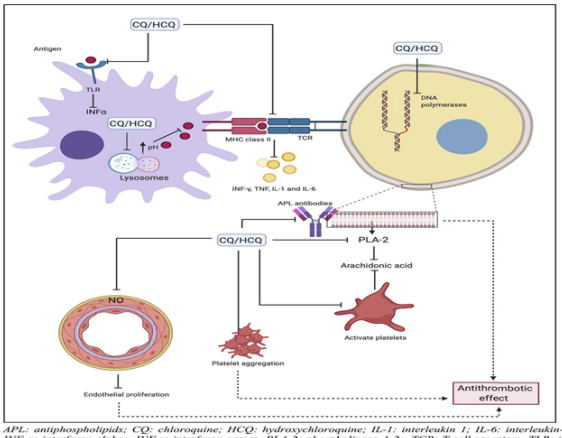


Figure 1: Chemical structure of chloroquine and hydroxychloroquine [9]. Note: Chloroquine (CQ), CAS number: 54-05-7, Formula: C18H26ClN3, Mol. mass: 319.872 g/mol, Hydroxychloroquine (HCQ), CAS number: 118-42-3, Formula: C18H26ClN3O, Mol. mass: 335.872 g/mol.



APL: antiphospholipids; CQ: chloroquine; HCQ: hydroxychloroquine; IL-1: interleukin 1; IL-6: interleukin-6; INF-α: interferon alpha; INF-γ: interferon gama; PLA-2: phospholipase A-2; TCR: T cell receptor; TLR: toll like receptor; TNF: tumor necrose factor

Figure 2: Proposed mechanisms of action of antimalarial (chloroquine and hydroxychloroquine) [10]. Abbrevations: APL: Antiphospholipids; CQ: Chloroquine; HCQ: hydroxychloroquine; IL-1: Interlukin-1; IL-6: Interlukin-6;INF-α: Interferon Alpha; INF-γ: Interferon Gama; PLA-2: Phospholipase A-2; TCR: T Cell Receptor; TLR: Toll Like Recertor; TNF: Tumor Necrose Factor.

Results from the *in vitro* studies conducted by Yao, et al. showed that HCQ have good antiviral activity. It decreases the viral replication in a concentration-dependent manner [7]. The same study finds that HCQ has an anti-virus activity when added before viral challenge [7]. HCQ antiviral activity was also proved *in vitro* study by Jia et al. [5].

Many retrospective studies and clinical trials were conducted to evaluate efficiency of HCQ in COVID-19 patient's treatment. Gautret, et al. report through a pilot observational study a beneficial effect of co-administration of HCQ and azithromycin in the treatment of COVID-with few adverse effects (7/80). Patients received treatment with HCQ (200 mg 3X/d) and azithromycin) for at least 3 days and were followed-up for at least 6 days. The time between the onset of symptoms and hospitalization was on average 5 days. The first primary outcome of this study was requiring oxygen therapy or transfer to the Intensive Care Unit (ICU). Only 15% of inpatients required oxygen therapy and just 3 were transferred to IUC [9]. But in this study, among 80 patients, only 41% suffered from upper respiratory tract infection symptoms, while 59% presented with lower symptoms or asymptomatic [10,11]. A retrospective study realized by million and al. enrolled 1061 patients receiving HCQ 600 mg/d for 10 days plus azithromycin for 5 days. The mean time between the symptoms onset and treatment initiation was 6.4 days. The majority of patients (90.7%) had a good outcome and only 2.4% presented mild side effect [10]. But it is important to note, that all recruited patients in this study have mild disease (95%) or asymptomatic (5%) [12].

The results of these two studies are inconsistent with reported in a retrospective, observational study carried by Lopez and al, including 29 patients following HCQ regimen of 800 mg loading dose of HCQ and maintenance dose of 400 mg for 9 days, showed that no statistical difference was found between the patients with HCQ plasma concentration above the target concentration of 0.1 mg/L, and whom below this target. That concerns nasopharyngeal swab PCR results at Day 15 (p=0.77), length of mechanical ventilation (p=0.92), use of vasopressor (p=0.95) and 15-days mortality (p=0.16) [13]. Sample size analysed was small (n=29) and non-representative. But an observational study on 1376 hospitalized patients conducted by Geleris, et al. showed that the risk of intubation or death was not significantly different between patients who received HCQ and those who did not (hazard ratio, 1.04). In this study 811 (58.9%) received hydroxychloroquine (loading dose of 600 mg twice on day 1, then 400 mg daily for 4 days) and 565 (41.1%) did not. The time between symptom onset and treatment initiation was not indicated but patients received HCQ 48 hrs after hospitalization at most [14].

Results of retrospective and observational studies lead to clinical trials. A Chinese randomized clinical trial conducted by Chen, et al. on 62 COVID 19 disease patients assigned in two groups [8]. Both received the standard treatment. HCQ group (31/62) received in addition HCQ 400 mg/d for 5 days. Time to clinical recovery was significantly shortened in HCQ group in which none sever side effect reported [8]. In his open-label non-randomized clinical trial, Gautret, et al. described that HCQ treatment is significantly associated with viral load reduction/ disappearance in COVID-19 patients. This survey recruited 36 hospitalized patients with confirmed COVID-19. 20/36 in HCQ group (200 mg 3X/day for 10 days) were compared to 16/360 control patients. Time between onset of symptoms and inclusion was short (4.0 ± 2.6) in this trial [15]. Additionally to the small size of the samples in both trials, the patients enrolled are only with mild illness (Chen's study) and having upper respiratory tract infection symptoms only in 61% (Gautret's study).

Regarding mortality in patients with COVID-19 diseases, a study carried on 568 critically ills by Tang et al. [16] HCQ treatment (200 mg 2X/d for 7-10 days) is significantly associated with a decreased mortality. Only 18.8% (9/48) of patients died in the HCQ group against 45.8% (238/520) in the control group. Interestingly, this study report that inflammatory cytokine IL6 level significantly decreases from 22.2 pg/ml at the beginning of the treatment to 5.2 pg/ml (p=0.002) at the end of the treatment in the HCQ arm, but there is almost no change in the control arm (21.3 to 20.2; p=0.05). Furthermore, hospital stay time from hospitalization to death was longer in HCQ patients than control subjects (p=0.021) [16].

Contrary to results of these researches, Tang, et al. [16] in multicenter, open label randomized trial, noted no significant difference between HCQ arm (75/150) and control arm (75/150) concerning the negative conversion of COVID 19 disease by 28 days. Non additional benefit of HCQ in this study was shown despite the high dose regimen followed (1200 md/d for 3 days then 800 mg for 2 to 3 weeks) and the fact that the majority of participants suffered from middle to moderate disease [16]. Long delay between the onset of symptoms and the initiation of treatment (mean 16.6 day; range 3-41 days) may be an influencing factor. Adverse events were reported in 7/80 (9%) control group subjects and in 21/70 (30%) HCQ group subjects [16]. That may be due to high dosage applied. The results of this study are consistent with those of multicenter randomised controlled trial realized by Mitjà, et al. [17] with shorter onset

time (median=3 days) and lower dose regime (800 mg on day 1 followed by 400 mg once daily for 6 days). All participants presented mild disease and no differences were found between the control group (157/293) and intervention one (136/293) concerning reduction of viral load, risk of hospitalization the time symptom resolution. No relevant adverse events were reported in this study [17].

Concerning mortality and contrary to Horby et al. [18] study result, preliminary results from randomized controlled trial conducted at 176 hospitals showed that HCQ failed to reduce 28 day mortality. Furthermore, in HCQ arm time of hospitalization was prolonged and risk of progressing to invasive mechanical ventilation or death were increased. Patients were assigned in a ratio of 2:1, 3155 patients in usual care group and 1561 patients received a loading dose of 800 mg at zero and 6 hours, followed by 400 mg starting at 12 hours after the initial dose and then every 12 hours for 9 days. Interestingly, there were no significant differences in the frequency cardiac arrhythmia between the group and only one case of serious adverse effect was reported in HCQ arm (torsade de pointe) [18]. But in this large sample size study (N=4716), participant were stratified according to time between onset symptom and initiation of treatment: patients receiving treatment before day 7 and those receiving it over 7 days. Consequently, there was not the identical onset time even within the same subgroup.

HCQ dosage regimen was also subject to controversy. Many regimens were suggested essentially 200 mg 3X/day which is the standard dosage used for treating Systemic Lupus Erythematosus (SLE). Perinel, et al. [19] study enrolled 13 Intensive Unit Care (IUC) patients receiving HCQ 200 mg three times daily dosing regimen. Only 61% of cases reached blood target levels 1-2 mg/L, 15% exceeded a concentration of 2 mg/L with a mean time to reach the minimum therapeutic level 2.7 days [19]. The same result was found by Saadi, et al. study [20] in which 61% (11/18) of patients monitored on day 2 had HCQ serum concentration between 0.1 and 1 mg/L [20]. However, a study conducted by Million and al. with a significantly large sample size revealed that more than 88% of patients monitored on day 2 (n=263) and following the same regimen reached the therapeutic target of 0.1-1 mg/L [12]. Interestingly, we note that several cases in Perinel's study reached the minimum therapeutic target from the second day even in IUC patients. All patients (n=13) following 200 mg HCQ 3X/d for 10 days regimen in Giame, et al. study reached the minimum serum target level (0.1 mg/L) [21]. But these results are limited by the small size sample. However a loading dose was suggested to attain the minimum effective concentration more rapidly than when using only the maintenance dose from the start. In the Discovery trial, HCQ dose regimen of 800 mg Day 1 followed by 400 mg once daily for 9 days was determined to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients [22]. But this suggestion has been criticized by Megarbane and al.due to uncertainties related to the need of *in vitro* model reliability, choose of anti-SARS-CoV-2 activity marker EC50 instead of EC90 and physiologically based pharmacokinetic models chosen that did not mirror HCQ PK complexity at the intracellular target level [23]. Interestingly, in retrospective study conducted by Blondel, et al. [24] HCQ concentrations measured in COVID-19 patient show that HCQ exposure tends to be low even with high dose regimen and with load dose [24]. That confirm the complexity of HCQ pharmacokinetic and it large inter individual variability and lead to another subject: The HCQ monitoring in COVID-19 patients is indicated or not.

Perinel, et al. [19] in his prospective study report that the therapeutic drug monitoring is essential to individualize the optimal dose regime [19]. In same article, QT interval prolongation was reported in two patients which the blood concentrations were wide different; one in infra-therapeutic range (0.03 mg/L) and the other in therapeutic level (1.74 mg/L). Giame, et al. in theirs study cited above, reported no interest of HCQ plasma concentration monitoring to prevent cardiac toxicity. They instead recommend ECG and potassium monitoring. But, furthermore the small sample size studied, only 1 patient presented a long QTc syndrome (QTc>500 ms) in which HCQ concentration was therapeutic [21]. Comparable results reported by Painvin, et al. study where side effects were recorded while patients' blood concentrations were in therapeutic range [25].

Conclusion

This mini review has given a rapid synthesis regarding the use of HCQ in treatment of COVID-19 disease. Finding of both retrospective or observational and clinical trials were contradictory. Polemic concerns the performance or not of HCQ in this illness, the optimal dose regimen and the matter of drug monitoring. But regardless it efficiency or not, HCQ has shown according to studies findings a good tolerance and with few severe side effect.

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