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Antiviral Research 177 (2020) 104762

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Commentary

Of chloroquine and COVID-19

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ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
2019-nCoV
Chloroquine
Antiviral

ABSTRACT

Recent publications have brought attention to the possible benefit of chloroquine, a broadly used antimalarial drug, in the treatment of patients infected by the novel emerged coronavirus (SARS-CoV-2). The scientific community should consider this information in light of previous experiments with chloroquine in the field of antiviral research.

Recent publications have brought attention to the possible benefit of chloroquine, a broadly used antimalarial drug, in the treatment of patients infected by the novel emerged coronavirus (SARS-CoV-2) (Colson et al., 2020; Gao et al., 2020). The scientific community should consider this information in light of previous experiments with chloroquine in the field of antiviral research.

The sulfate and phosphate salts of chloroquine have both been commercialised as antimalarial drugs. Hydroxychloroquine has also been used as an antimalarial, but in addition is now broadly used in autoimmune diseases such as lupus and rheumatoid arthritis. Of note, chloroquine and hydroxychloroquine are considered to be safe and side-effects are generally mild and transitory. However, the margin between the therapeutic and toxic dose is narrow and chloroquine poisoning has been associated with cardiovascular disorders that can be life-threatening (Frisk-Holmberg et al., 1983). Chloroquine and hydroxychloroquine use should therefore be subject to strict rules, and self-treatment is not recommended.

The *in vitro* antiviral activity of chloroquine has been identified since the late 1960's (Inglot, 1969; Miller and Lenard, 1981; Shimizu et al., 1972) and the growth of many different viruses can be inhibited in cell culture by both chloroquine and hydroxychloroquine, including the SARS coronavirus (Keyaerts et al., 2004). Some evidence for activity in mice has been found for a variety of viruses, including human coronavirus OC43 (Keyaerts et al., 2009), enterovirus EV-A71 (Tan et al., 2018), Zika virus (Li et al., 2017) and influenza A H5N1 (Yan et al., 2013). However, chloroquine did not prevent influenza infection in a randomized, double-blind, placebo-controlled clinical trial (Paton et al., 2011), and had no effect on dengue-infecteds patient in a randomized controlled trial in Vietnam (Tricou et al., 2010). Chloroquine was also active *ex vivo* but not *in vivo* in the case of ebolavirus in mice (Dowall et al., 2015; Falzarano et al., 2015), Nipah (Pallister et al., 2009) and influenza virus (Vigerust and McCullers, 2007) in ferrets.

The case of chikungunya virus (CHIKV) is of specific interest: chloroquine showed promising antiviral activity *in vitro* (Coombs et al., 1981; Delogu and de Lamballerie, 2011), but was shown to enhance alphavirus replication in various animal models (Maheshwari et al., 1991; Roques et al., 2018; Seth et al., 1999), most probably because of the immune modulation and anti-inflammatory properties of chloroquine *in vivo* (Connolly et al., 1988; Katz and Russell, 2011; Savarino et al., 2003). In a nonhuman primate model of CHIKV infection, chloroquine treatment was shown to exacerbate acute fever and delay the cellular immune response, leading to an incomplete viral clearance (Roques et al., 2018). A clinical trial conducted during the chikungunya outbreak in 2006 in Réunion Island showed that oral chloroquine treatment did not improve the course of the acute disease (De Lamballerie et al., 2008) and that chronic arthralgia on day 300 post-illness was more frequent in treated patients than in the control group (Roques et al., 2018). Altogether, the assessment of previous trials indicates that, to date, no acute virus infection has been successfully treated by chloroquine in humans.

Chloroquine has also been tested in chronic viral diseases. Its use in the treatment of HIV-infected patients has been considered inconclusive (Chauhan and Tikoo, 2015) and the drug has not been included in the panel recommended for HIV treatment. The only modest effect of chloroquine in the therapy of human virus infection was found for chronic hepatitis C: an increase of the early virological response to pegylated interferon plus ribavirin (Helal et al., 2016) and, in a small sample size pilot trial in non-responder HCV patients, a transient viral load reduction (Peymani et al., 2016) were observed. This was not enough to include chloroquine in the standardised therapeutic

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https://doi.org/10.1016/j.antiviral.2020.104762
Received 29 February 2020; Received in revised form 2 March 2020; Accepted 2 March 2020
Available online 05 March 2020

protocols for hepatitis C patients.

Recently, Wang and colleagues (Wang et al., 2020) evaluated *in vitro* five FDA-approved drugs and two broad spectrum antivirals against a clinical isolate of SARS-CoV-2. One of their conclusions was that "chloroquine (is) highly effective in the control of 2019-nCoV infection *in vitro*" and that its "safety track record suggests that it should be assessed in human patients suffering from the novel coronavirus disease". At least 16 different trials for SARS-CoV-2 already registered in the Chinese Clinical Trial Registry (ChiCTR2000029939, ChiCTR2000029935, ChiCTR2000029899, ChiCTR2000029898, ChiCTR2000029868, ChiCTR2000029837, ChiCTR2000029826, ChiCTR2000029803, ChiCTR2000029762, ChiCTR2000029761, ChiCTR2000029760, ChiCTR2000029741, ChiCTR2000029740, ChiCTR2000029609, ChiCTR2000029559, ChiCTR2000029542) propose to use chloroquine or hydroxychloroquine in the treatment of COVID-19 ("Chinese Clinical Trial Register" (ChiCTR)). In a recent publication (Gao et al., 2020), Gao and colleagues indicate that, "according to the news briefing", "results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course".

This would represent the first successful use of chloroquine in humans for the treatment of an acute viral disease, and is undoubtedly excellent news, since this drug is cheap and widely available. However, it should be considered carefully before drawing definitive conclusions, since no data has been provided yet to support this announcement. Results were produced in ten different hospitals and possibly from a number of different clinical protocols among those listed above, which include various designs for control groups (none, different antivirals, placebo, etc.) and various outcome primary indicators. The final interpretation is therefore technically demanding, and in the absence of published data, it is difficult to reach any firm conclusion. It will be of the utmost importance to know if the observed efficacy is associated specifically with chloroquine phosphate, or if this includes other salts (e.g., sulfate) of chloroquine, and hydroxychloroquine. It is also necessary to determine if the benefit of chloroquine therapy depends on the age class, the clinical presentation or the stage of the disease.

In conclusion, the option of using chloroquine in the treatment of SARS-CoV-2 should be examined with attention in light of the recent promising announcements, but also of the potential detrimental effect of the drug observed in previous attempts to treat acute viral diseases. We urge Chinese scientists to report the interim trial results currently running in China as soon as they are available. This should be preferentially done in a peer-reviewed publication with detailed information to allow the international scientific community to analyse the results, to confirm in prospective trials the efficacy of the proposed treatment and to guide future clinical practice.

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