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Chikungunya Disease and Chloroquine Treatment

Ilenia Delogu and Xavier de Lamballerie*

Unité des Virus Emergents, UMR190 (Aix-Marseille 2 University-IRD-EHESP), Marseille, France

In a recent issue of the Journal of Medical Virology, Khan et al. [2010] presented an "assessment of in vitro prophylactic and therapeutic efficacy of chloroquine against Chikungunya virus in Vero cells." This article mentions the fact that chloroquine, a well-known drug developed for the treatment of malaria in the 1930s, was considered previously as a potent antiviral drug in a number of viral diseases (HIV, HBV, influenza A virus, SARS, and others) but makes no reference to previous studies of the antiviral activity of chloroquine against alphaviruses (and more specifically Chikungunya virus) suggesting that the authors had identified a new and promising field of investigation. Their presentation deserves significant qualification.

First, the in vitro antiviral effect of chloroquine is not a recent discovery. It was first reported some 40 years ago [Inglot, 1969; Shimizu et al., 1972]. A clinical antiviral application of the molecule has been assessed over time for a number of viral pathogens, and the concrete benefits or risks of such treatment is still debated [Boelaert et al., 1999; Seth et al., 1999; Fredericksen et al., 2002; Savarino et al., 2006].

Regarding alphaviruses, in cellulo inhibition of Sindbis and Semliki Forest virus replication was reported 30 years ago [Coombs et al., 1981; Helenius et al., 1982], but these results were balanced by those obtained from a mouse model, which suggested that chloroquine may enhance viral replication in vivo and aggravate the disease [Maheshwari et al., 1991].

Soon after the beginning of the Chikungunya outbreak in 2005, in the Indian Ocean, the question of the possible use of chloroquine was raised. It is a matter of fact that, in many tropical areas, chloroquine is used as a symptomatic treatment of febrile illnesses and thus, the health authorities had to face its actual—non-evaluated—use during the acute phase of Chikungunya disease. The (confusing) reasons why a part of the local population utilized chloroquine also possibly included the fact that immunomodulatory effects of chloroquine have been used for a long time in autoimmune and rheumatological diseases [Cooper and Magwere, 2008], including chronic Chikungunya arthritis [Brighton, 1984].

Early studies of the emerging Indian Ocean Chikungunya virus (CHIKV) variant demonstrated in vitro inhibition of virus replication by chloroquine [Charrel, 2006; de Lamballerie et al., 2008, 2009; Gould et al., 2010]. Sourisseau et al. [2007] reported that chloroquine inhibited potently the appearance of CHIKV-positive cells and CHIKV-associated cytopathic effect and noted that the therapeutic (antiviral) index of chloroquine in cell cultures is rather narrow and thus, one should be cautious when proposing the use of chloroquine as an antiviral treatment in infected individuals.

These early results led to the careful design of a clinical trial in the French Reunion Island (Indian Ocean) (CuraChik, http://clinicaltrials.gov/ct/show/NCT00391313), which was performed at the end of the 2006 outbreak [de Lamballerie et al., 2008]. In this double-blind placebo-controlled randomized trial, 27 patients (diagnosed within <48 hr) received chloroquine and 27 other patients received a placebo treatment. The chloroquine treatment consisted of 600 mg at day 1, 600 mg at days 2 and 3, and 300 mg at days 4 and 5 (and not 250 mg daily as reported by Savarino et al. [2007]). The results did not provide justification for the use of chloroquine to treat acute Chikungunya infections.

In conclusion, the issue of chloroquine treatment of Chikungunya virus infection has been examined for years. Whilst in vitro inhibition of CHIKV replication is strongly established, the narrow therapeutic index and the absence of obvious biological or clinical improvement during a clinical trial do not argue in favor of a curative use in non-complicated cases. Whether chloroquine may be useful as a prophylactic treatment, or in the case of severe, sustained Chikungunya infections deserves further investigations that could take advantage of the availability of a relevant non-human primate animal model [Labadie et al., 2010].

*Correspondence to: Xavier de Lamballerie, Unité des Virus Emergents, UMR190, Medical University, 27 Bd Jean Moulin, 13005 Marseille, France.
E-mail: xavier.de-lamballerie@univmed.fr

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