Received: 30 April 2020 | Revised: 16 June 2020 | Accepted: 22 June 2020

DOI: 10.1002/dmrr.3379

COMMENTARY

WILEY

Hydroxychloroquine, COVID-19 and diabetes. Why it is a different story

Anca Pantea Stoian[1] | Doina Catrinoiu[2] | Manfredi Rizzo[3,4] | Antonio Ceriello[5]

[1]Diabetes, Nutrition and Metabolic Diseases Department, "Carol Davila" University of Medicine, Bucharest, Romania

[2]Faculty of Medicine, Clinical Center of Diabetes, Nutrition and Metabolic Diseases, Ovidius University of Constanta, Constanta, Romania

[3]Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of South Carolina, Columbia, South Carolina

[4]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy

[5]IRCCS MultiMedica, Milan, Italy

Correspondence
Antonio Ceriello, IRCCS MultiMedica, Via Gaudenzio Fantoli, 16/15, 20138 Milan, Italy.
Email: antonio.ceriello@hotmail.it

Abstract

Hydroxychloroquine has been proposed for the cure of the COVID-19 due to its anti-inflammatory and anti-viral action. People with diabetes are more prone to severe outcome if affected by COVID-19 and the use of Hydroxychloroquine might have some benefit in this setting. However, the use of Hydroxychloroquine in diabetes deserves particular attention for its documented hypoglycemic action.

In the context of the current COVID-19 pandemic, solutions are being sought worldwide in order to identify the most appropriate treatment for the patients with SARS-COV-2. Hydroxychloroquine (HCQ) or chloroquine have been widely used for the treatment of COVID-19.[1] The use of this class of drugs for COVID-19 was based on a small number of anecdotal experiences that have shown variable responses in uncontrolled observational analyses.[2] HCQ is a well-known antimalarial drug, also used as anti-rheumatic therapy in the systemic lupus erythematosus, rheumatoid arthritis, etc.[1] Chloroquine (CQ) was the first drug that was used as prophylaxis as well as treatment in malaria.[1] HCQ is the most soluble and least toxic metabolite of CQ.[1]

There are two possible mechanisms of action through which CQ/HCQ might combat the SARS-CoV-19 infection: the effect on angiotensin-converting-enzyme-2 (ACE2) receptor and the anti-inflammatory activity.[3,4] The penetration of the SARS-CoV-19 inside the host cells is achieved through the super expression of the ACE2 on the cell surface, in the lung, heart, kidneys and several other tissues. The virus links to this enzyme and in this way its penetration into the host cell is facilitated.[5] CQ/HCQ blocks the glycosylation of ACE2 by modifying the lysosomal PH, thus preventing the intracellular penetration of the virus, and the effect on sialic acid binding linked to the ganglioside domain on the cell surface.[3,4] Via MAP-kinase pathway, HCQ interferes with SARS-CoV-2 at an intimate molecular level, modifying the architecture of the virion and facilitating the process of proteolysis of the M protein.[3,4]

The second kind of action is the anti-inflammatory effect.[3,4] This effect plays a major role in blocking the inflammatory cytokine production, especially IL-6, thus significantly diminishing the "cytokine storm," which is responsible for elevated morbidity, as well as mortality, due to the development of multiorgan dysfunction including the "Acute Respiratory Distress Syndrome" (ARDS).

Based on this data, it has been hypothesized that HCQ could be used as a therapy for the SARS-CoV-19 infection.[2] Preliminary data were contradictory[6,7] and more recent evidence is even more controversial.[8] However, it is worth to mention that the question might be still open. The typical clinical course of COVID-19 infection suggests that the virus load in the respiratory tract increases stepwise starting with mild symptoms and ending in up to 15% of patients with severe and potentially life-threatening pneumonia.[9] Therefore, the treatment with a drug that inactivates the cell receptor for the virus should start after exposition with high risk, for example, when one person has been infected very recently with the virus or is in the early phase of the disease.[9] This hypothesis is new because the major assumption in ongoing clinical studies and actual recommendations is that HCQ and CQ should

be used in patients with severe COVID-19 pneumonia and only when other treatment strategies have failed.[9]

Smith et al in 1987 were the first describing a significant improvement of glycaemic values in few people with type 2 diabetes mellitus treated with HCQ.[10] Quatraro et al then sustained this observation in 1990, with a study in type 2 diabetes treated with insulin or glibenclamide associated with HCQ for 6 months.[11] HCQ treatment produced a significant decrease of HbA1C by 3.3% and a reduction of the insulin dose by 30%, among the group treated with insulin, compared to placebo.[11] A recent systematic review evaluating the effect of HCQ in diabetes, including 55 776 study participants, has shown a significant improvement of lipid profile and insulin levels and substantial diminution of haemoglobin A1c, fasting plasma glucose and postprandial blood glucose levels.[12]

The mechanisms through which HCQ produces its anti-hyperglycaemic effects seems to be the increase in insulin action and the alterations in insulin metabolism and signalling through cellular receptors.[13] Anyhow, the management of the anti-diabetic therapy when HCQ is used should be reassessed, because its hypoglycaemic effect may precipitate severe episodes of hypoglycaemia.[11] This possibility was firstly mentioned by Smith et al in 1987.[10]

Unfortunately, it not surprising that during the COVID-19 pandemic emerged that people with diabetes have a worse prognosis, particularly those with uncontrolled glycaemia.[14,15] It is emerging that the presence of hyperglycaemia worsens the prognosis of people infected with COVID-19. On this basis, it is clear that an optimal glycaemic control is mandatory in people with diabetes to reduce their risk of a complicated COVID-19.[15] Considering the studies described above, it should make sense to implement the first-line treatment in people with diabetes with HCQ. This, however, will require a strict monitoring of other concomitant anti-hyperglycaemic treatments, in order to avoid severe hypoglycaemia.

It is interesting that due to the low costs and to the anti-diabetic efficiency, HCQ in India is officially recognized in the clinical practice guidelines as an anti-hypoglycaemic therapy of third or fourth line.

However, even though the evidence about HCQ and diabetes opens an exciting therapeutic line, the treatment with HCQ in patients with diabetes and COVID-19 does not seem interesting, because, at the moment, there are over 90 clinical studies evaluating the potential therapeutic effects of HCQ, but no one clinical trial looking at the efficiency and efficacy of this treatment in people with diabetes.

The literature search was completed for the terms “COVID-19,” “SARS-COV-2,” “Chloroquine,” “Hydroxychloroquine,” “Diabetes.” The database used was PubMed.

References retrieved were reviewed and selected manually according to their relevance to the aims of this article. Except for the key historical references on the topic, priority for inclusion has been given to relevant literature studies published in the last 3 years (2017 and onwards).

ACKNOWLEDGEMENTS

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. A.P.S., D.C., M.R. and A.C. equally contributed to the paper.

CONFLICT OF INTEREST

A.P.S., D.C. do not have conflict of interests to declare for this article. M.R. is currently Director, Clinical Medical & Regulatory Department, Novo Nordisk Europe East. A.P.S. is currently Vice-President, National Diabetes Commission, Ministry of Health, Romania.

ORCID

Antonio Ceriello https://orcid.org/0000-0001-8122-3203

REFERENCES

1. Principi N, Esposito S. Chloroquine or hydroxychloroquine for prophylaxis of COVID-19. *Lancet Infect Dis*. 2020;S1473-3099(20):30296-6.
2. Brufsky A. Hyperglycemia, hydroxychloroquine, and the COVID-19 epidemic. *J Med Virol*. 2020;92:770-775. https://doi.org/10.1002/jmv.25887.
3. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents*. 2020;55:105938.
4. Amin M, Abbas GJ. Docking study of chloroquine and hydroxychloroquine interaction with SARS-CoV-2 spike glycoprotein-an in silico insight into the comparative efficacy of repurposing antiviral drugs. *Biomol Struct Dyn*. 2020;1-11. https://doi.org/10.1080/07391102.2020.1775703.
5. Brufsky A, Lotze MT. DC/L-SIGNs of hope in the COVID-19 pandemic. *J Med Virol*. 2020;6. https://doi.org/10.1002/jmv.25980.
6. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients mainly with mild to moderate COVID-19: an open-label, randomized, controlled trial. *BMJ*. 2020;369:m1849.
7. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. *J Zhejiang Univ (Med Sci)*. 2020;49:215-219.
8. Mehra MR, Ruschitzka F, Patel AN. Retraction-hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet*. 2020;395(10240):1820. https://doi.org/10.1016/S0140-6736(20)31324-6.
9. Klimke A, Hefner G, Will B, Voss U. Hydroxychloroquine as an aerosol might markedly reduce and even prevent severe clinical symptoms after SARS-CoV-2 infection. *Med Hypotheses*. 2020;142:109783.
10. Smith GD, Amos TA, Mahler R, Peters TJ. Effect of chloroquine on insulin and glucose homeostasis in normal subjects and patients with non-insulin-dependent diabetes mellitus. *Br Med J*. 1987;294:465-467.
11. Quatraro A, Consoli G, Magno M, et al. Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus. A new job for an old drug? *Ann Intern Med*. 1990;112:678-681.
12. Wondafrash DZ, Desalegn TZ, Yimer EM, Tsige AG, Adamu BA, Zewdie KA. Potential effect of hydroxychloroquine in diabetes mellitus: a systematic review on preclinical and clinical trial studies. *J Diab Res*. 2020;2020:1-10. https://doi.org/10.1155/2020/5214751.
13. Mercer E, Rekedal L, Garg R, Lu B, Massarotti EM, Solomon DH. Hydroxychloroquine improves insulin sensitivity in obese non-diabetic individuals. *Arthritis Res Ther*. 2012;14:R135.
14. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020;e3319. https://doi.org/10.1002/dmrr.3319.
15. Ceriello A, De Nigris V, Prattichizzo F. Why is hyperglycemia worsening COVID-19 and its prognosis? *Diabetes Obes Metab*. 2020. https://doi.org/10.1111/dom.14098.