



EDITORIAL COMMENT

Two years later, azithromycin for COVID-19 and the effect on the heart, is it still relevant?

Dois anos mais tarde, azitromicina para Covid-19 e os seus efeitos cardíacos ainda é relevante?

Sérgio Matoso Laranjo ^{a,b}

^a Serviço de Cardiologia Pediátrica, Hospital de Santa Marta, Centro Hospitalar e Universitário de Lisboa Central, Portugal

^b Comprehensive Health Research Center, Universidade NOVA de Lisboa, Lisboa, Portugal

Available online 21 April 2022



COVID-19 is an ongoing global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus was first identified from an outbreak in the Chinese city of Wuhan in December 2019.¹

For the first two years of the pandemic, no specific effective treatment or cure was available. In the first months of the pandemic, antiviral and immunomodulatory agents were proposed as potential treatments. Drugs such as hydroxychloroquine, lopinavir/ritonavir, ivermectin and azithromycin were reported and tested as potential therapeutic options.² Azithromycin presented in vitro activity against SARS-CoV-2 and was able to act in different points of the viral cycle, with the main antiviral effect of azithromycin being due to its intracellular alkalinizing effect. However, the evidence of its clinical use was always scarce and of low quality. A recent systematic review of the available clinical trials revealed that the routine use of azithromycin as therapy in Covid-19 patients was not justified, due to its lack of efficacy and potential risk of bac-

terial resistance that was not offset by an increased clinical benefit.^{3,4}

The proarrhythmic effects of azithromycin are well known,⁵ resulting in prolonged ventricular repolarization, which associated with the tropism of SARS-CoV-2 for cardiomyocytes, has raised well-founded concerns regarding the use of this drug, particularly in association with hydroxychloroquine, as it could potentially lead to a severely prolonged QTc interval.⁶ Several of the therapeutic protocols even proposed the serial electrocardiographic monitoring of these patients. Several studies have since demonstrated the safety of the drug, within therapeutic doses, despite its ineffectiveness for its primary objective.

Regardless of these premises, and reporting from the last two years, the mass use of azithromycin has served as a laboratory experiment to assess the impact of the drug on certain electrocardiographic properties. In the current issue of this journal, Sunkak and et al.⁷ seek to detail the effects of azithromycin on ventricular repolarization in children with COVID-19. The study included 105 pediatric patients who were hospitalized between June and August 2020 in a single center Pediatric Infection Diseases Clinic, with a positive COVID-19 PCR test and treated with oral azithromycin. In

E-mail address: sergiolaranjo@gmail.com

<https://doi.org/10.1016/j.repc.2022.04.005>

0870-2551/© 2022 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

this study, oral azithromycin had no effect on QTc, Tp-ec, QTc, or Tp-ec dispersion or the Tp-ec/QTc ratio in children with COVID-19. Hence, in the authors experience, oral azithromycin treatment alone did not affect ventricular repolarization in children with COVID-19 and appeared to be safe in asymptomatic or mildly symptomatic patients.

Nevertheless, as we have previously stated, for hydroxychloroquine to be used in pediatric patients in the same setting,⁸ the direct cardiac toxicity of SARS-CoV-2 and the relative contribution of concomitant drugs to the reported cardiac adverse effects in COVID-19 patients needs to be further studied and be better evaluated.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. WHO Statement on the Second Meeting of the International Health Regulations (2005). Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). [https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-\(2005\)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-\(2019-ncov\)](https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)).
2. Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for COVID-19: living systematic review and network meta-analysis. *BMJ (Clin Res Ed)*. 2020;370:m2980, <http://dx.doi.org/10.1136/bmj.m2980>.
3. Kamel AM, Monem M, Sharaf NA, et al. Efficacy and safety of azithromycin in COVID-19 patients: a systematic review and meta-analysis of randomized clinical trials. *Rev Med Virol*. 2022;32:e2258.
4. Johnston C, Brown ER, Stewart J, et al. COVID-19 Early Treatment Study Team. Hydroxychloroquine with or without azithromycin for treatment of early SARS-CoV-2 infection among high-risk out-patient adults: a randomized clinical trial. *EClinicalMedicine*. 2021;33:100773.
5. Giudicessi JR, Ackerman MJ. Azithromycin and risk of sudden cardiac death: guilty as charged or falsely accused? *Cleveland Clin J Med*. 2013;80:539–44.
6. Mercurio NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for Coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5:1036–41.
7. Suleyman S, Argun M, Celik B, et al. Effects of azithromycin on ventricular repolarization in children with COVID-19. *Rev Port Cardiol*. 2022;41.
8. Hormigo I, Silva TM, Laranjo S, et al. Protocol-based cardiotoxicity monitoring in hydroxychloroquine medicated COVID-19 pediatric patients. *Rev Portug Cardiol*. 2021, <http://dx.doi.org/10.1016/j.repc.2021.01.018>. Advance online publication.