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LETTER TO THE EDITOR

Reply to: RAAS inhibitors in COVID-19: Not all are created equal!

Resposta a: Inibidores de RAAS na COVID-19: nem todos são iguais!

We acknowledge Kow et al.'s interest and comments on our article[1] and their support for our suggestion of considering angiotensin receptor blockers (ARBs) as potential treatment for early stages of COVID-19 in further studies. However, some corrections are warranted.

The authors presented two points of criticism: (i) the possibility that the effects of telmisartan in COVID-19 could be caused, not only by blockade of angiotensin II receptor type 1 (AT1R), but also by peroxisome proliferator-activated receptor γ (PPARγ) activation, and (ii) their understanding that we suggested disregarding evidence-based medicine in the face of the pandemic.

We agree that telmisartan and other ARBs cause PPARγ activation, but this occurs with concentrations 1000 times higher than their effects on AT1R (pA2 at AT1R=8.4–9.4; EC_{50} at PPARγ=5.02 μM).[2,3] If we look closely at the pharmacokinetics of telmisartan, the plasma levels needed to cause 50% PPARγ activation would correspond to the C_{max} value after the administration of a single dose of 320 mg/telmisartan for a seven-day period.[4] Therefore, it is unlikely that plasma concentrations reached with telmisartan 80 mg twice daily, used in the telmisartan study would be sufficient to cause a sustained activation of PPARγ and explain the beneficial effects in COVID patients.

Kow et al. are correct that telmisartan (up to 80 mg daily) is used in hypertension. This is probably because initial dosing studies of telmisartan showed a relative flat dose–response curve: the anti-hypertensive effect caused by 80 mg was statistically significant higher, but not clinically relevant, when compared to 40 mg.[5,6] As an antagonist, telmisartan 40 mg may be sufficient to block the angiotensin II (ANG2) levels in hypertensive patients. However, when excessive production of ANG2 is expected, as we anticipate in the lungs of COVID-19 patients, the highest ever tested doses of ARBs should be used to block ANG2 binding to AT1R, which supports at least the 80 mg twice daily regime. From a mechanistic point of view, testing low or middle doses of ARBs to reduce the severity of COVID-19 is not only useless, but also should be deemed as unethical because the treatment failure is predictable even before starting the study.

Kow et al. showed some reluctancy to accept our suggestion that, in a pandemic situation, more pragmatic approaches to drug development should be followed. We have never suggested that evidence-based practice should be disregarded. In fact, our research team comprises mechanistic and clinical pharmacologists, some of whom with a large experience in evidence gathering and dozens of published systematic reviews and meta-analyses. It is this combination of mechanistic and clinical approach we are highlighting in our paper when we criticize the simplistic conception of evidence as an exercise of introducing data into a computer to obtain a pooled effect size measure.

We also recognize the important role of randomized controlled trials (RCTs) in feeding evidence, but real-world evidence resulting from robust observational studies should not be ignored, especially in emergency situations such as pandemics. During the long editorial process of our paper (726-day delay), other RCTs and observational studies testing telmisartan or other ARBs in COVID-19 were published. Some of them reported positive effects on hospitalization or mortality[7] but others failed.[8–10] And this is where the combination of mechanistic and clinical pharmacology could play a crucial role, not only in supporting the potential mechanisms of action, but also supporting the results of evidence-gathering exercises. In this case, one could also wonder why a hazard ratio (HR) for death or intubation of 0.64 (95%CI 0.48–0.85; p=0.002) was considered not clinically relevant,[11] when a HR for death or hospitalization of 0.69 (95%CI 0.48–1.01) was sufficient to authorize molnupiravir for COVID-19 in non-vaccinated patients.[12]

In a nutshell, we suggested a mechanistically sound therapeutic option to reduce the severity of COVID-19 using a highly accessible and affordable drug, whose safety profile has been demonstrated over the years. What should now be discussed is how to create more pragmatic approaches to drug development, especially when drugs with a demonstrated safety profile are involved... And not just in times of a pandemic.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Gonçalves J, Santos CD, Fresco P, et al. Potential use of renin–angiotensin–aldosterone system inhibitors to reduce COVID-19 severity. Rev Port Cardiol. 2023;42:373–83.
2. Schupp M, Janke J, Clasen R, et al. Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. Circulation. 2004;109:2054–7.
3. Rothlin RP, Vetulli HM, Duarte M, et al. Telmisartan as tentative angiotensin receptor blocker therapeutic for COVID-19. Drug Dev Res. 2020;81:768–70.
4. Stangier J, Su CA, Roth W. Pharmacokinetics of orally and intravenously administered telmisartan in healthy young and elderly volunteers and in hypertensive patients. J Int Med Res. 2000;28:149–67.
5. Parker AB, Azevedo ER, Baird MG, et al. ARCTIC: assessment of haemodynamic response in patients with congestive heart failure to telmisartan: a multicentre dose-ranging study in Canada. Am Heart J. 1999;138 Pt 1:843–8.
6. Meredith PA. Optimal dosing characteristics of the angiotensin II receptor antagonist telmisartan. Am J Cardiol. 1999;84:7K–12K.
7. Mirjalili M, Soodejani MT, Raadabadi M, et al. Does losartan reduce the severity of COVID-19 in hypertensive patients? BMC Cardiovasc Disord. 2022;22:116.
8. Jardine MJ, Kotwal SS, Bassi A, et al. Angiotensin receptor blockers for the treatment of covid-19: pragmatic, adaptive, multicentre, phase 3, randomised controlled trial. BMJ. 2022;379:e072175.
9. Nouri-Vaskeh M, Kalami N, Zand R, et al. Comparison of losartan and amlodipine effects on the outcomes of patient with COVID-19 and primary hypertension: a randomised clinical trial. Int J Clin Pract. 2021;75:e14124.
10. Puskarich MA, Ingraham NE, Merck LH, et al. Efficacy of losartan in hospitalized patients with COVID-19-induced lung injury: a randomized clinical trial. JAMA Netw Open. 2022;5:e222735 [published correction appears in JAMA Netw Open. 2022 May 2;5(5):e2215958].
11. Loader J, Taylor FC, Lampa E, et al. Renin–angiotensin aldosterone system inhibitors and COVID-19: a systematic review and meta-analysis revealing critical bias across a body of observational research. J Am Heart Assoc. 2022;11:e025289.
12. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med. 2022;386:509–20.

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