Letter to the Editor

Azithromycin, a questionable treatment for COVID-19

Editor: Jean-Marc Rolain

We read the recent article entitled 'Safety and effectiveness of azithromycin in patients with COVID-19: an open-label randomized trial' by Sekhavati et al. regarding the treatment of patients with coronavirus disease 2019 (COVID-19) with azithromycin [1]. We wish to highlight some points regarding this trial based on our clinical experience and review of the current literature.

The authors did not mention any specific admission criteria for patients, the duration of symptoms or how long patients had been symptomatic before admission. It is not clear when medications were started during the course of the disease in either study group. For COVID-19, it is known that patients at the end of the viral phase or pulmonary phase can show improvement in their symptoms without any further treatment [2].

It is important to note that the mean age of the control group was approximately 5 years older compared with the case group. Upon admission, mean oxygen saturation (SpO_2) of the control group was lower compared with the case group (89.51 ± 6.84 vs. 89.61 ± 2.98, respectively). SpO_2 worsened on day 3 of admission for both groups, but the control group showed more deterioration. These findings suggest that patients in the control group were sicker upon hospital admission, which could have overestimated the effect of azithromycin in the case group. Furthermore, an inclusion criterion was radiographic evidence of COVID-19 pulmonary involvement on computed tomography (CT) scan [1]. However, no details of the CT scan findings were provided for either group. For better comparison of the two study groups, it is imperative to risk-stratify patients based on the severity of pulmonary involvement on CT scan. Baseline characteristics of the two arms of the study, including smoking status, diabetes mellitus, pulmonary disease, cardiovascular disease and other underlying comorbidities, could explain why the clinical status of the patients in the control group on admission was worse, which possibly resulted in a longer hospital stay, higher rate of intensive care unit admission, and need for intubation in the control group.

The aim of this trial was to assess if the addition of azithromycin to hydroxychloroquine and lopinavir/ritonavir improved patient prognosis. However, the study did not address why those four medications were chosen for this trial, and there is no established platform for these medications in the treatment of COVID-19 [3]. Also, there was no elaborate discussion on the possible adverse effects of the medications used to justify starting the regimen.

The authors cited studies that demonstrated the effectiveness of azithromycin against Zika and Ebola viruses. However, the studies were conducted on ZIKV-infected Vero cells rather than human subjects [4]. The authors cited another study stating that azithromycin has high affinity for the binding interaction site of the SARS-CoV-2 spike protein and angiotensin-converting enzyme 2 [5]. However, this study can only be found on ChemRxiv and is not available on PubMed [5]. We believe that lack of evidence, as mentioned in the references, should be considered seriously as the efficacy and safety risks of these actions are not based on a scientific approach [5].

Although methylprednisolone was prescribed upon deterioration, there is no mention of how many patients received methylprednisolone in each group. It is also not clear whether symptoms such as haemoptysis, cough and dyspnoea were present prior to receiving therapy. In addition, we would like to report a miscalculation, as the number of patients who reported myalgia in the control group was 22 of 55 patients, which is 40% but was incorrectly reported as 74%. It is worth noting that the lowest SpO_2 values at discharge in the case and control groups were 91.81% and 87.82%, respectively, but according to the study discharge criteria, patients were discharged only after they achieved stable SpO_2 >92%.

References

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