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Letter

Cyclosporine A and COVID19 – The COQUIMA cohort – Author's reply

Pablo Guisado-Vasco[a,*], Daniel Carnevali-Ruiz[a], Israel John Thuissard Vasallo[b], On behalf of COQUIMA study members

[a] Department of Internal Medicine. Hospital universitario quironsalud Madrid, Universidad Europea (Madrid), Pozuelo de Alarcon, Madrid, Spain
[b] Statistical section, Faculty of Biomedical Science and Health, Universidad Europea (Madrid), Villaciosa de Odon, Madrid, Spain

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Dear Dr Macé M Schuurmans and Dr René Hage,

Thank you for your gentle comments about our manuscript under the format of a letter to the editor.

These comments give positive feedback to our research. They also contribute to a scientific debate to boost the research on cyclosporine A for COVID-19.

We thank Dr Macé M Schuurmans and Dr René Hage for their comments about our manuscript under the format of a letter to the editor. These comments give positive feedback to our research. They also contribute to a scientific debate to boost the research on cyclosporine A for COVID-19.

Firstly, CsA might use in those patients in the second stage of SARS-CoV-2 infection, the pulmonary phase1 [1]. Hypoxemia and bilateral lung infiltrates or ground-glass opacities characterizes this phase. Most hospitals admit patients into wards during this disease phase. The hypoxemia -as mentioned in the manuscript- should be defined as saturation of oxygen below 94% or PaO_2 /FiO_2 < 300 mmHg. Typically, blood tests detect lymphopenia or transaminitis. A rise of inflammatory parameters, such as d-dimer, ferritin, and C-protein reactive, is also identified. Those cases in stage III, systemic hyperinflammation, are, of course, also suitable for CsA therapy. The transition between both phases is rather dynamic, and probable most hospitalized cases share features of both pulmonary and hyperinflammatory stages.

Secondly, in our opinion, CsA therapy should start as soon as possible in hospitalized patients. It also might work as rescue therapy in those cases which do not improve after supportive measures. Nowadays, the best standard of care might include dexamethasone 6 mg q. i.d. intravenously [2] - and thrombosis prophylaxis with low-molecular-weight heparin.

Thirdly, CsA can have a clear advantage when used as an intravenous formulation in severely ill cases. In our paper, we referenced an effective accumulative therapeutic dose of CsA to the oral administration of 300 mg or more. It is known that a factor of 3 (1:3) should be applied to convert any intravenous to the oral dosage of CsA in the solid-organ transplant recipients. Nevertheless, we used two principles to keep a balance between effective therapy and to avoid side effects. For these purposes, we considered a factor of 2 for the conversion of intravenous to oral CsA formulations [3]. A total daily dose of CsA was set on 2·5–3 mg/kg/day, approximately. Thereby, this low-dose of CsA seemed to be safe and successful for COVID-19.

Finally, in our hospital, we stopped CsA therapy if a patient was transferred to the intensive care unit. We agree that this population deserves the design of specific protocols of CsA therapy. Thus, a clinical trial should include this severely ill population in the protocol. CsA schedules might be different for specific clinical scenarios.

Dear Dr Olga Sánchez Permaute,

Thank you for your comments about our manuscript under the format of a letter to the editor.

They contribute to a scientific debate to boost the research on cyclosporine A for COVID-19.

We thank Dr. Olga Sánchez Permaut for her proposed some interesting points, which give to our research about cyclosporine A for COVID-19 a positive inside. All these comments are relevant to a reasoning scientific debate about this repurposed drug. These comments are mainly focusing on those severely-ill cases of COVID19. We would like to underscore some data already reported in the manuscript.

First, our research aimed to describe the characteristics and outcomes of the whole cohort (as previously published manuscripts of similar scope). We reported in-hospital mortality (or other cohort features, as suitable), using relative mortality rates [4]. This statistical approach is widespread used in the scientific literature and validated elsewhere. We showed all available data in the manuscript, and supplementary material, so that readers could easily make whichever percentage (including crude mortality rates) they consider.

In-hospital crude (or relative) mortality rates might vary according to the design of the research: total hospital admissions [5] due to severe COVID-19, or just those transferred to the intensive care unit (ICU) [6]. In both researches, unfortunately, the final outcome of all included patients was not available. The authors reported that a relevant percentage of cases were still in ICU at the moment of the publication.

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* Corresponding author.
E-mail address: pablo.guisado@quironsalud.es (P. Guisado-Vasco).

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However, the issue is interesting. Most of our patients admitted to ICU received mechanical ventilation. The reported crude mortality of previous reports in the same population was 70% [7–9]. In our cohort, the in-hospital absolute mortality rate in those cases admitted to ICU was lower (48·98%).

As we reported, we stopped cyclosporine A (CsA) treatment if a patient transfers to ICU. Some of them had already been treated with CsA and reached the minimum accumulative dose of 300 mg. Table 2S summed up the impact of CsA in the outcome of these cases. This table shows the mortality rate of those cases treated or not with CsA 300 m.c.d. The proportion of patients admitted to ICU in the group of CsA 300 mg m.c.d. was lower, compared to the group without CsA 300 mg m.c.d (4·52% versus 10·10% per treatment cohort). Furthermore, the in-ICU crude mortality rate was again lower among those treated with CsA 300 m.c.d. (20% versus 56·41%). Of course, we consider it is a small sample to settle categorical conclusions about CsA therapy and ICU admissions and related outcomes. Perhaps, CsA could have a clear advantage when used as an intravenous formulation in severely ill cases. Thus, specific protocols of CsA therapy should schedule considering the singular characteristics of this population.

Second, we chose broadly extended criteria of severe COVID-19 pneumonia (oxygen saturation (SaO2) at or below 94% while breathing ambient air, or a ratio of the partial pressure of oxygen (PaO2) to a fraction of inspired oxygen (FiO2) (PaO2/FiO2; or PAFI) at or below 300 mmHg). The emergency department discharged most of the mild COVID-19 cases, and none of them were treated with CsA. We carried out all CsA treatment under in-hospital observation. We applied similar exclusion criteria for all explored therapies (including early discharge or supportive care due to the unfitted condition of the patient). CsA therapy protocols for outpatients might entail further research around this issue.

Finally, to confirm our findings and to assess the real impact of CsA therapy against severe COVID-19, an adequately powered, randomized, double-blind, and placebo-controlled clinical trial must be carried out.

Declaration of Competing Interest

None.

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