JIM Letter to the Editor

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Inhibition of SARS-CoV-2 replication using calcineurin inhibitors: are concentrations required clinically achievable?

Dear Editor,

We read with great interest the article by Galvez-Romero et al. entitled 'Cyclosporine A plus low-dose steroid treatment in COVID-19 improves clinical outcomes in patients with moderate to severe disease. A pilot study' published in the Journal of Internal Medicine.[1]

This study aimed to assess the added benefit of cyclosporine A (CsA) to steroids in the treatment of life-threatening COVID-19, according to the two pathological mechanisms that appear to coexist in severe SARS-CoV-2 infections, the first triggered by the virus itself and the second by the host-immune response. The study is a nonrandomized observational investigation with 209 hospitalized patients with COVID 19, showing better outcomes in patients treated with CsA plus steroids, compared to patients treated with steroids alone. Furthermore, a significantly lower death rate across all grades of severity was observed, even more marked in those with moderate-to-severe lung injury.

The authors hypothesize that this beneficial effect may be due to both the anti-inflammatory and the antiviral properties of CsA. Accordingly, they report that, in addition to the well-known role as immunomodulatory agent, CsA shows an interesting certain antiviral activity, inhibiting in vitro the replication of several coronavirus, including SARS-CoV and MERS-CoV.[2-4]

In this regard, we would like to remark that, although calcineurin inhibitors have been shown to inhibit SARS-CoV replication in cell cultures, the 50% effective concentrations (EC_{50}) of CsA in Vero cells have been reported to be 3.3 μM (corresponding to plasma levels of 3968 ng/mL),[2] which is 10-fold higher than the recommended therapeutic range in humans, and 6.9 μM (corresponding to plasma levels of 5540 ng/mL)[5] in the case of tacrolimus, which is 1000-fold.

Therefore, we agree that the use of CsA might be justified in those severe COVID-19 patients at risk to transit into the second stage of the disease, by blocking the excessive inflammatory response, but not at the early stages, when viral growth and spread occurs. In this regard, we have recently launched a randomized controlled trial (RCT) using tacrolimus to treat severe COVID-19 patients,[6] and we encourage the development of new other RCTs to assess the efficacy and safety of calcineurin inhibitors, at recommended dose, focused on to tackle the systemic host-immune hyperinflammatory response present in severe COVID-19.

Conflicts of interest

All authors declare no competing interests.

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Author contribution

Xavier Solanich: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing-original draft (equal); Writing-review & editing (equal). Nuria Padullés: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Writing-original draft (equal); Writing-review & editing (equal). Jordi Niubó: Conceptualization (equal); Supervision (equal); Writing-review & editing (equal). Sebastià Videla: Conceptualization (equal); Writing-review & editing (equal). Arnau Antolí: Writing-review & editing (equal). Gemma Rocamora-Blanch: Writing-review & editing (equal). Xavier Corbella: Writing-review & editing (equal).

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