Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

on the Newcastle-Ottawa Scale, 2 studies were of high quality, 6 of moderate, and 2 of low quality (Supplementary Tables 2 and 3).

Pooled results showed that tacrolimus use was associated with neither higher risk of severe COVID-19 (OR, 1.31; 95% CI, 0.47–3.69) or increased mortality (OR, 1.11; 95% CI, 0.63–1.92) in SOT patients with COVID-19 infection (Figures 1 and 2). For mortality, similar results were indicated in subgroup analyses of hospitalized SOT patients (OR, 0.61; 95% CI, 0.28–1.30), kidney transplants (OR, 1.22; 95% CI, 0.65–2.30), a sample size of >100 patients (OR, 0.89; 95% CI, 0.52–1.53), and PCR-confirmed cases (3 studies, OR, 0.97; 95% CI, 0.36–2.61). For severe COVID-19, similar results were also observed in hospitalized SOT patients (OR, 3.46; 95% CI, 0.74–16.21), kidney transplant recipients (OR, 1.71; 95% CI, 0.58–5.03), and PCR-confirmed cases (OR, 1.39; 95% CI, 0.30–6.41).

In conclusion, our study found that tacrolimus use is not a risk factor for mortality and severity in SOT patients with COVID-19. Well-designed prospective study is encouraged to verify these findings in the future.

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Data availability: After publication, data and R code are available as supplementary materials.

Funding
Supported by grants from 1.3.5 Project for Disciplines of Excellence Clinical Research Incubation Project, West China Hospital, Sichuan University (ZY2016104).
Saifu Yin and Xianding Wang contributed equally to this work and shared the co-first authorship.

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https://doi.org/10.1053/j.gastro.2021.01.223

Beneficial Effect of Tacrolimus… Cyclosporin A, Still up for Discussion!

To the Editors:

The management of immunosuppression in liver transplant recipients with coronavirus disease 2019 (COVID-19) is a matter of concern in scientific communities. Belli et al[1] published the first multicenter study that demonstrate a beneficial effect of tacrolimus. They described in a large multicenter study that included 243 adult symptomatic cases from 36 centers and 9 countries that the use of tacrolimus was associated with a better survival in liver transplant recipients. Interestingly, they found no beneficial effect of the cyclosporin A (CsA), another calcineurin inhibitor.

An important point should be discussed; tacrolimus and CsA have similar intracellular mechanisms—an indirect immunomodulator activity and a direct antiviral activity, 2 related but independent mechanisms. Briefly, calcineurin is a calcium-calmodulin-activated serine/threonine-specific phosphatase that is a key player in T-cell activation.[2,3] Its phosphatase activity will allow the nuclear factor of activated T cells to be dephosphorylated, allowing nuclear translocation of its substrate, and consequently the expression of immune genes like IL-2, IL-4, and IL-6, the so-called immune response.[4] CsA enters into the cells and forms a binary complex with its intracellular partners, the cyclophilins. In turn, these binaries sequester the calcineurin into a ternary complex and thus inhibit calcineurin activity. In this manner, CsA suppresses the immune response secondary to activation of cytotoxic and helper T cells.[2–4] Tacrolimus is functionally but not structurally related to CsA. The immunosuppressive properties of tacrolimus depend on the formation of binary complex with FKBP proteins, that constitute the immunophilin superfamily together with cyclophilins. These binaries sequester the calcineurin into a ternary complex and thus inhibit calcineurin activity.[2] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication relies on a variety of host factors, and expresses several structural proteins and many nonstructural proteins.[5] Nonstructural protein 1 interacts with different cellular partners (CypA, CypB, CypH, CypG, FKBP1A, FKBP1B), which in turn increases signaling through the nuclear factor of activated T-cell pathway and enhances the induction of IL-2, IL-4, and IL-6.[3,6] CsA and tacrolimus have an antiviral effect by binding to the cyclophilins and FKBP proteins with subsequent inhibition of their peptidyl-prolyl isomerase activity, whose enzymatic activities are supposed to promote coronavirus replication.[3,6] The exact mechanism by which CsA and tacrolimus interact in coronavirus replication are unknown. Based on this information, both drugs should have similar mechanism and in theory they might have the same beneficial effect in SARS-CoV-2 infection.

At present, it is well-known that the risk factors of poor outcome in COVID-19 infection include older age, male sex, and the presence of comorbidities.[5] The lack of beneficial

effect could maybe be explained by the clinical characteristics of the CsA/other group. Indeed, Supplementary Table 3 of the article shows that the CsA/other group had:

a) A higher percentage of male (81.5 vs 64.8%; $P = .0073$).

b) A higher percentage of patients with $\geq$2 comorbidities (61.7% vs 35.2%; $P = .0003$).

c) A higher median time between liver transplantation and COVID-19 infection (12 years vs 7 years; $P < .0001$), which implies that they had a lower residual concentration of immunosuppressor directly related to the effect in the infection (which seems to be dose dependent).

d) A higher percentage of patients co-treated with mycophenolate mofetil (61.7% vs 42.6%; $P = .0049$). Few studies are available, but the use of mycophenolate mofetil in Middle East respiratory syndrome coronavirus had reported high viral loads with more severe or even fatal disease.[7]

e) A lower percentage (but not significant) of patient with steroids (17.2% vs 25.9%; $P = .1316$). The beneficial effect of corticoids has been demonstrated mostly during the second inflammatory phase.[8]

In conclusion, the main message remains that tacrolimus has a beneficial effect in SARS-CoV-2 infection. At this point, available data are not sufficient concerning the effect of CsA, but based on the intracellular mechanisms of both calcineurin inhibitors, a similar beneficial effect could be expected. Switching drugs or even dose adjustment of CsA need further controlled studies before a clinical recommendation could been done.

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Conflicts of interest
The author discloses no conflicts.

Funding
Isaac Ruiz is a recipient of fellowship grants from the CHUM Foundation, Montreal, Canada.

Most current article

https://doi.org/10.1053/j.gastro.2021.02.039

Reply. We read with great interest the letter by Yin et al,[1] where the authors comment the results of our recently published study.[2]

The authors raised some methodologic issues on our study design, suggesting a possible selection bias because we included both patients receiving homecare (survival rate of 100.0%; 82.1% received tacrolimus) and those requiring hospitalization (survival rate of 76.0%; 63.7% received tacrolimus) in the analysis. Against this argument we emphasize that "place of management" indicates the place with the highest intensity of care required by symptomatic patients during their disease course, and it should be considered as an intermediate outcome between onset of coronavirus disease 2019 (COVID-19) and death or recovery or a proxy for disease progression. If we selected patients based on place of management, we would, in contrast, introduce a selection bias that would affect the assessment of any protective effect of the baseline use of tacrolimus. In the end, tacrolimus was used more frequently in patients receiving homecare who never experienced a worsening of the disease, clearly supporting our finding of a protective effect, particularly in younger patients without comorbidities.

A second issue refers to changes of the calcineurin inhibitors (CNI) doses in hospitalized patients. Of the 57 inpatients who underwent withdrawal of CNI or a 25%–50% dose reduction, 18 (31.5%) were on lopinavir therapy, dose modifications being justified by the interference between the 2 drugs. For the remaining 39 patients, the modifications of CNI doses were proportionally distributed between cyclosporine and tacrolimus, making any selection bias unlikely. Further, 12 of 13 patients who stopped tacrolimus had interstitial pneumonitis requiring oxygen supplementation.

An additional issue points to the discordant results between our study and the only other study published on COVID-19 liver transplant patients by Colmenero et al.[3] In this latter study from Spain, a different composite outcome was used, defined by the need of mechanical ventilation, intensive care, and/or death, thereby supporting our previous statement regarding place of management (intensive care unit) as an outcome and not as a risk factor. Notably, Colmenero et al[3] reported a similar protective role of tacrolimus on development of severe COVID-19 with a relative risk of RR 0.54 (95% CI, 0.29–1.07; $P = .08$) in the univariate analysis and a relative risk of 0.19 (95% CI, 0.05–0.68; $P = .011$) in the initial multivariate model. However, a statistically significant association between tacrolimus use and severe COVID-19 was not confirmed in the final multivariate model. In the end, both studies suggest a protective role of tacrolimus, keeping in mind that the ELITA/ELTR study could benefit of a much larger sample size (243 patients vs 111 patients).