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.

Tacrolimus: Unlikely Harmful and Perhaps Helpful in Liver Transplant Recipients with COVID-19

See "Protective role of tacrolimus, deleterious role of age and comorbidities in liver transplant recipients with Covid-19: results from the ELITA/ELTR multi-center European study," by Belli LS, Fondevila C, Cortesi PA, et al, on page 1151.

Now almost 1 year into the coronavirus disease-2019 (COVID-19) pandemic, medical recommendations for patients infected with its causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continue to evolve. The impact and management of chronic immunosuppressive medications, such as those required after liver transplantation (LT), has been 1 such topic of deliberation. Experts recommend consideration of lowering the overall level of immunosuppression, as is the recommendation for managing severe infections in general.[1,2] A contrasting consideration has been the hypothesis that COVID-19 can cause dysregulated, excessive inflammatory activity, in which immunomodulators could potentially be beneficial and that dexamethasone has become a mainstay for the treatment of hospitalized patients with COVID-19.[3] To complicate things further, this "cytokine storm" association has been called into question because studies have shown lower levels of key inflammatory cytokines in cohorts with COVID-19 compared with those with acute respiratory distress syndrome,[4,5] and in a randomized, placebo-controlled trial, interleukin (IL)-6 inhibitor tocilizumab and sarilulimab failed to improve outcomes in patients with COVID-19.[6,7]

Compared with the general population, solid organ transplant recipients seem to have higher rates of SARS-CoV-2 infection, but of those hospitalized, short-term outcomes are similar.[8–11] This also seems to be true in nontransplant populations on immunosuppressive medications; in a large cohort of patients with inflammatory bowel disease and COVID-19, chronic treatment with tumor necrosis factor antagonists was not a risk factor for severe COVID-19.[12] However, all immunosuppressants are not equal. Mycophenolate-containing immunosuppression has been found to be a predictor of severe COVID-19, an effect not observed with calcineurin inhibitors or mammalian target of rapamycin inhibitors.[9] This finding may be related to its potential to cause lymphopenia, which has been found to be predictive of poor outcomes in those with COVID-19.[13] Given the lack of clear evidence, how should we consider immunosuppressants in LT recipients with COVID-19?

To help answer this question, in this issue of *Gastroenterology*, Belli et al[14] present the results from a multicenter study of adult LT recipients with confirmed SARS-CoV-2 infection. The study, using data from the European Liver Transplant Association and European Liver Transplant Registry, included 243 LT recipients with symptomatic COVID-19 from 36 centers in 9 countries—the largest cohort of its kind in the literature. A multivariate analysis found that tacrolimus was associated with lower mortality (hazard ratio, 0.55; 95% confidence interval, 0.31–0.99) as compared with other immunosuppressive agents, including cyclosporine, mycophenolate mofetil, and mammalian target of rapamycin inhibitors. On the initial analysis, advanced age (>70 years) was the only factor independently associated with increased mortality; however, given the association between advancing age and comorbidities, a second model excluding age showed diabetes and chronic kidney disease as independent risk factors for mortality as well.

This study may be the first to show an independent association between tacrolimus and improved survival in patients with COVID-19. Tacrolimus, a calcineurin inhibitor, exerts its immunosuppressive effect by inhibiting the transcriptional activation of multiple cytokine genes, including those for IL-2 and tumor necrosis factor-alpha. Tacrolimus and cyclosporine have also been shown to inhibit coronavirus replication in vitro,[15,16] so perhaps the benefit is due to a direct antiviral effect rather than an immunomodulatory one; however, an antiviral effect has not yet been confirmed in vivo.

Although this observed association between tacrolimus and survival is certainly intriguing, more studies are needed before recommending switching LT recipients with severe COVID-19 to tacrolimus yet empiric dose reductions of tacrolimus seem unwarranted. It must be interpreted, like all observational studies, with caution. In the early days of the pandemic, hydroxychloroquine was promoted as a treatment for COVID-19, and even gained emergency approval from the US Food and Drug Administration, based on very limited data from observational studies. This approval led to the widespread use of a medication that was ultimately found to have no mortality benefit once more thoroughly evaluated in randomized trials.[17] But with appropriate caution, this study by Belli et al[14] does provide a rationale for further investigation into the impact of calcineurin inhibitors in COVID-19. Relatedly, a recent pilot study found a mortality benefit in patients (without a history of transplantation) hospitalized with COVID-19 and hypoxemia or elevated inflammatory markers who were treated with cyclosporine and steroids as compared with steroids alone.[18]

The work by Belli et al[14] also strengthens the case that older age and chronic comorbidities, such as diabetes, chronic kidney disease, and obesity, are the most important determinants of short-term outcomes in COVID-19. This has been observed previously in transplant recipients and in the general population.[8–12,19]

Overall, this study by Belli et al[14] is an important addition to the literature on LT recipients with COVID-19. Furthermore, it adds to emerging evidence for

immunomodulation in the treatment of COVID-19, more generally, in transplant recipients and nontransplant recipients. As the data on this topic continue to move quickly, clinicians need to use the best available information to care for patients while avoiding quick reactions that could lead to harm. With this in mind, tacrolimus seems to be safe to continue in LT recipients with COVID-19 and perhaps future prospective trials will be able to confirm the possible benefit. Whether or not this study's findings are generalizable to all solid organ transplant recipients or patients on tacrolimus for reasons other than transplant is unknown. Safe and effective vaccines for the prevention of COVID-19 in transplant recipients and nontransplant recipients will undoubtedly change the landscape for these questions.

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Conflicts of interest
The authors disclose no conflicts.

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