Practical Consideration for Drug Monitoring of Tacrolimus in Liver Transplantation Recipients with SARS-CoV-2 Infection

TO THE EDITOR:

Previous studies have shown that infection-related cytokine increase of interleukin 6 (IL6) and tumor necrosis factor α (TNF-α) can cause suppression of cytochrome P450 3A4 (CYP3A4) enzymes.[1] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been associated with increased cytokine levels, which may suggest suppression of CYP3A4 enzymes and downstream interaction with CYP-mediated drug metabolism including calcineurin inhibitors.

Tacrolimus (Tac), the most used immunosuppressive agent for orthotropic liver transplantation (LT), is a calcineurin inhibitor metabolized via CYP3A4 primarily in the liver and intestinal mucosa.[2] This potential effect of CYP3A4 inhibition on immunosuppression (IS) management with Tac in LT recipients with SARS-CoV-2 infection has yet to be evaluated. We sought to characterize and evaluate our experience with Tac-based immunosuppressive management among LT recipients hospitalized for SARS-CoV-2 infection.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CYP3A4, cytochrome P450 3A4; IL6, interleukin 6; IS, immunosuppression; LT, liver transplantation; MMF, mycophenolate mofetil; PCR, polymerase chain reaction; Pred, prednisone; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Tac, tacrolimus; TNF-α, tumor necrosis factor α.

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Patients and Methods

We retrospectively evaluated a consecutive series of adult LT recipients who were hospitalized with SARS-CoV-2 infection at our institution between June 1, 2020, and December 31, 2020. Clinical and laboratory data were evaluated prior to and during hospitalization. Patients on Tac-based regimen had a serum trough level (ng/mL) within 72 hours of confirmed SARS-CoV-2 infection based on a positive polymerase chain reaction test result. Baseline Tac levels were calculated as mean trough levels within the preceding 6 months. Medications prior to hospitalization were reviewed and no drug-drug interactions with Tac-based therapy were found. Standard IS protocol included Tac and prednisone (Pred), with Pred tapered off within the first year. Stable IS was defined as a Tac-based regimen that had not be altered in the 6 months prior to presentation. This study was approved by the institutional review board at Baylor College of Medicine.

Results

In total, 18 posttransplantation recipients were hospitalized with SARS-CoV-2 infection during the study period. Patients were predominantly White and male, with a median time from LT of 4.5 years (interquartile range, 1.4-9.4). Of these,16 patients were on Tac-based IS. To this date, 4 patients died due to complications related to SARS-CoV-2 infection.

A total of 14 patients had baseline and serial Tac trough levels as an outpatient (baseline) and serial daily trough levels during hospitalization. Immunosuppressive management during hospitalization is presented in Table 1. A total of 9 (64.3%) patients presented with diarrhea or had elevated serum aminotransferase levels at the time of admission, with only 1 patient having aminotransferase level over 3-fold higher than normal. All patients experienced a decrease in baseline albumin levels and 7/10 had an elevated ferritin level within 72 hours from admission.

Thirteen of the 14 patients (92.8%) on Tac IS experienced an increase in their trough level on admission; with an average increase of 105.6% (standard deviation 81.7). Nine patients (64.3%) had at least a 50% increase from baseline trough levels noted on their first trough upon admission. Ten (71.4%) patients were on stable IS prior to admission and 3 were maintained on Pred beyond the first year after transplantation. To avoid complications related to supratherapeutic levels, Tac daily dose was reduced by an average of 45.4%. Steroid use did show a positive correlation ($r = 0.57$; $P = 0.03$) with an increase above baseline Tac trough level. There was no correlation with diarrhea ($r = -0.04$; $P = 0.88$), respiratory failure requiring intubation ($r = 0.04$; $P = 0.88$), or other clinical parameters.

Discussion

In this consecutive series of LT recipients hospitalized with SARS-CoV-2 infection, we found that most patients on Tac had supratherapeutic trough at initial presentation. Nearly all patients were on a stable immunosuppressive regimen prior to hospitalization. There was an average 2-fold increase in Tac trough levels compared with baseline, with 64.3% (n = 9) of patients experiencing at least a 50% increase. This increase in trough levels in recipients with active infection led to a nearly 50% reduction in daily Tac dosing. These observations suggest close monitoring in LT recipients with SARS-CoV-2 infection on calcineurin inhibitors. Supratherapeutic concentrations also raise concern for infection-related complications and development of multiorgan toxicities including neurotoxicity, nephrotoxicity, and gastrointestinal toxicity.

This is the first study to describe these findings and provide observational data as evidence toward a possible underlying direct mechanism. None of these patients had severe liver dysfunction, and the mild elevations in aminotransferase levels do not indicate substantial hepatocyte loss; therefore, liver dysfunction would be unlikely to explain the decreased Tac metabolism. There are compelling data demonstrating that the proinflammatory "cytokine storm," with increased levels of IL6 and TNF-α, inhibits CYP3A4 enzyme expression. This inhibitory effect alters drug metabolism, increasing plasma levels and decreasing elimination of calcineurin inhibitors.[1] IL6 levels are increased in SARS-CoV-2 infection and support this potential inhibitory mechanism.[3] Moreover, we noted elevated ferritin levels and acute hypoalbuminemia, which are frequently seen in a cytokine-mediated hepatic acute-phase response from inflammation.[4]

Supratherapeutic Tac levels may negatively impact the ability to produce a robust antibody response. In the setting of an active infection, maintenance IS should be closely monitored and evaluated. Options include reducing the daily Tac dose, as shown in this study, until obtaining a trough level in those with confirmed SARS-CoV-2 infection. In addition, following infection resolution, vigilant monitoring is necessary to ensure an adequate level of IS is maintained. This may warrant increased number of clinic visits with more frequent laboratory monitoring.

There are several limitations to these data including the retrospective nature of the study. We did not longitudinally evaluate Tac concentrations during hospitalization because drug-drug interactions would have a confounding effect via CYP3A4 inhibition.[5] There was also heterogeneity in collection and testing for Tac concentrations in the outpatient and inpatient settings. Trough levels were not collected uniformly after symptom onset; however, all patients had trough levels within 3 days of confirmed infection. Our data also did not evaluate mild or asymptomatic infection. Deviation from standard IS protocol as noted in 3 of our patients may play a contributory role in altering trough levels and severity of infection.

In conclusion, our study provides compelling evidence to closely monitor Tac levels during acute infection and adjust dosing accordingly. Increasing vaccination efforts for these patients may mitigate potential challenges in IS. Prospective studies are needed to further evaluate these findings and the potential mechanism and implications involved.

TABLE 1. Tac-Based Immunosuppressive Management Among LT Recipients Hospitalized with SARS-CoV-2 Infection

Age, Sex, Status	Diarrhea	Intubated	Time From LT, Years	Daily IS as Outpatient*	Stable IS for 6 Months†	Baseline Trough, ng/mL‡	First Trough, ng/mL	Outpatient to First Trough, Days§	Infection to First Trough, Days‖	Second Trough, ng/mL	Change in IS¶	AST, U/L#	ALT, U/L#
56, male, alive	No	No	0.3	Tac 9 mg, Pred 15 mg	Yes	5.2	14.7	18	1	6.4	Tac 9 to 5 mg, Pred 15 to 10 mg	13	12
35, male, alive	No	No	15 days	Tac 8 mg, Pred 20 mg	Yes	8.1	19.2	8	1	11.8	Tac 8 to 5 mg, Pred no change	186	170
77, male, dead	No	Yes	21.5	Tac 2 mg	Yes	3.7	6.9	8	2	5.1	No change	50	32
72, female, alive	Yes	No	11.8	Tac 2 mg, Pred 5 mg	Yes	4.8	18.7	124	1	9.0	Tac 2 to 1 mg, Pred no change	19	14
68, male, alive	Yes	No	4.9	Tac 3 mg	No	6.8	14.9	16	3	8.5	Tac 3 to 0.5 mg	44	29
66, male, dead	Yes	Yes	2.6	Tac 2 mg	Yes	6.0	7.9	36	3	9.1	Tac 2 to 1 mg	48	28
69, male, alive	Yes	No	0.9	Tac 4 mg, Pred 7.5 mg	Yes	6.1	7.2	33	2	3.8	Tac 4 to 2 mg, Pred no change	21	15
53, female, dead	Yes	Yes	14.8	Tac 10 mg, Pred 5 mg	No	2.5	6.3	153	1	2.6	Tac 10 to 1.5 mg, Pred no change	28	6
62, male, alive	No	No	0.4	Tac 2 mg, Pred 5 mg	Yes	5.0	10.8	14	2	6.8	Tac 2 to 1 mg, Pred no change	67	72
63, male, alive	Yes	No	4.3	Tac 2 mg	Yes	7.1	9.9	76	1	6.9	Tac 2 to 1 mg	61	39
54, male, alive	Yes	No	4.6	Tac 5 mg	Yes	6.5	6.3	163	1	4.5	Tac 5 to 1 mg	82	31
71, male, alive	No	No	5.3	Tac 2 mg	Yes	3.7	4.1	112	1	3.6	No change	33	40
60, male, alive	No	No	3.7	Tac 3 mg	Yes	4.9	11.0	55	2	7.9	Tac 3 to 1 mg	20	20
30, female, dead	Yes	Yes	22.9	Tac 3 mg, Pred 20 mg, MMF 250 mg	No	6.7	18.4	82	1	7.4	No change	70	66

*Daily IS: Daily outpatient IS regimen prior to admission.
†Stable IS regimen defined as a Tac-based therapy regimen that had not been altered in the 6 months prior to presentation.
‡Baseline trough: calculated as mean trough levels collected in the outpatient setting prior to admission within the preceding 6 months.
§Time (days) between last outpatient and first hospitalization troughs.
‖Time (days) between positive SARS-CoV-2 PCR nasal swab and the first hospitalization Tac trough.
¶Change in IS: change in daily IS therapy from the outpatient regimen was made as a response to first Tac trough levels obtained during hospitalization.
#AST and ALT values at the time of admission.

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