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LETTER TO THE EDITORS

Decreased tacrolimus concentration following a temporal increase during interferon-free therapy with asunaprevir and daclatasvir in patients with recurrent hepatitis C after liver transplantation

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Drug–drug interactions (DDIs) are an important issue to consider when using direct-acting antivirals (DAAs) in transplant recipients, as most DAAs are substrates of cytochrome P450 3A4, an enzyme responsible for the metabolism of tacrolimus. Since November 2014, we have administered interferon-free therapy using the NS3/4A inhibitor asunaprevir and NS5A inhibitor daclatasvir for transplant recipients with genotype 1b hepatitis C virus (HCV). The DDIs of combination treatment using asunaprevir and daclatasvir with tacrolimus are largely unknown. In our institution, patients who start interferon-free regimen have their dose of tacrolimus adjusted by therapeutic drug monitoring (TDM). In this study, we evaluated the changes in the concentration/dose (C/D) ratio of tacrolimus during this interferon-free therapy in 10 cases, by measuring the blood concentration of tacrolimus at least three times a week in the first 2 weeks and twice a month thereafter. Six of the 10 patients were men, and the median age was 63 years (range, 43–67 years). The median time to treatment initiation after liver transplantation was 122 months (2–153 months). Three patients were treatment-naïve, three had peginterferon plus ribavirin therapy, and four had triple therapy with simeprevir, peginterferon, and ribavirin after the liver transplantation. Before the treatment, 3, 6, and 1 patients had METAVIR fibrosis scores of F1, F2, and F4, respectively, as determined by liver biopsy. In addition to tacrolimus, mycophenolate mofetil and prednisolone were used in 7 and 2 patients, respectively. The median serum HCV-RNA load before treatment was 7.0 logIU/ml (5.9–7.9 logIU/ml). The median serum creatinine level was 0.93 mg/dl (0.68–1.41 mg/dl).

The time course of the blood concentration of tacrolimus in a typical case is shown in Figure 1a. A 64-year-old woman received asunaprevir (200 mg/day) and daclatasvir (60 mg/day) 11 years after liver transplantation. The concentrations of tacrolimus were elevated in the first week but decreased thereafter, necessitating an increase in the dose of tacrolimus. The median C/D ratio of tacrolimus in the first week was elevated in eight of the 10 patients; compared to the last three C/D ratios before the initiation of the interferon-free treatment, the C/D ratio was significantly increased in four patients. Significant decreases in the C/D ratio 2–6 weeks after treatment compared to the C/D ratio in the first week were observed in six of 10 cases, and these decreases necessitated dose increases of tacrolimus compared to before treatment in five patients. Using TDM, neither rejection nor infection episodes occurred in this study period. The median C/D ratios of tacrolimus before, in the first week after, and 2–6 weeks after asunaprevir and daclatasvir administration in the 10 cases are shown in Figure 1b. The median C/D ratio significantly increased from 3.95 ng/mL per mg before to 5.2 ng/mL per mg in the first week after asunaprevir and daclatasvir administration, but significantly decreased to 2.975 ng/ml per mg after 2 weeks of administration. Serum HCV-RNA levels rapidly decreased by 2.5–5.5 $\log_{10}$ after 7 days of treatment and became undetectable within 6 weeks in five patients; however, HCV-RNA levels in three patients then increased again (Figure 1c). Serum alanine aminotransferase levels significantly decreased at day 7 and were maintained at low levels at 6 weeks (Figure 1c). Serum albumin levels were significantly increased after 6 weeks of treatment, suggesting that liver function improved with asunaprevir and daclatasvir administration (Figure 1c).

The findings of this study revealed the dynamic changes in tacrolimus concentration in transplant recipients undergoing interferon-free therapy with asunaprevir and daclatasvir. During the first week, the elevation of the C/D ratio was considered to be caused by the DDIs of the DAAs with tacrolimus. Notably, the C/D ratio was significantly decreased after 1 week of interferon-free therapy. A decrease in the concentration of calcineurin inhibitors during anti-HCV therapy has similarly been reported in transplant recipients treated with interferon-containing therapy

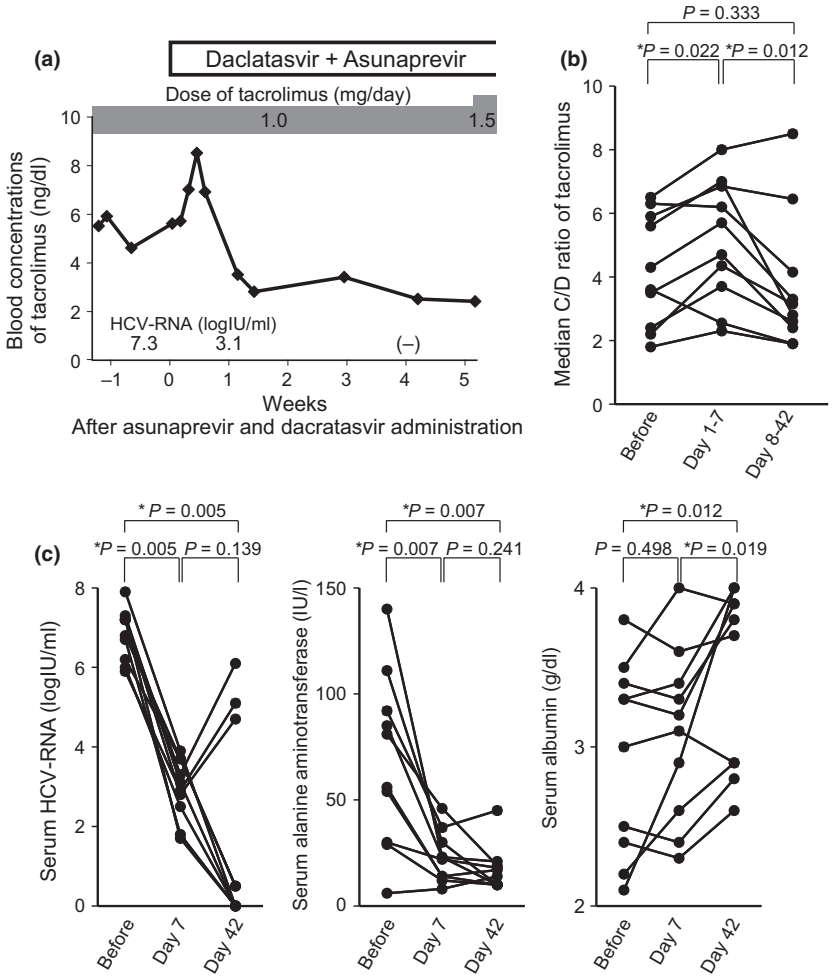

Figure. 1 (a) Typical time course of the blood concentration of tacrolimus for a patient who received interferon-free therapy with asunaprevir and daclatasvir for recurrent hepatitis C after liver transplantation. The fine line represents the blood concentration of tacrolimus (ng/mL). The dose of tacrolimus is shown in gray boxes. The top box indicates the duration of daclatasvir and asunaprevir treatment, and the serum hepatitis C virus (HCV) RNA levels (logIU/mL) are shown as the exact values or as (-), which indicates undetectable levels. (b) Median concentration/dose (C/D) ratio of tacrolimus in 10 patients treated with interferon-free therapy with asunaprevir and daclatasvir after liver transplantation. Significant differences between two time points are indicated by *, with P values determined using the Wilcoxon signed-rank test. Differences among the three time points were also significant, as determined by the Friedman test ($P = 0.025$). (c) Serum HCV-RNA, alanine aminotransferase, and albumin levels in 10 patients before, at 7 days, and at 42 days after asunaprevir and daclatasvir administration. Significant differences between two time points are indicated by *, with P values determined using the Wilcoxon signed-rank test.

[1, 2], as well as in those treated with interferon-free therapy with sofosbuvir and ribavirin [3]. The mechanism of the decreased concentration of calcineurin inhibitors upon effective anti-HCV therapy is hypothesized to be the increased metabolism of these calcineurin inhibitors as a result of improved liver function [1, 2]. In this study, the serum alanine aminotransferase and albumin levels significantly decreased and increased, respectively, even in the three patients whose serum HCV-RNA increased, suggesting that liver function was improved. In turn, this improved liver function resulted in the decreased concentration of tacrolimus. The dynamic changes in tacrolimus concentration during anti-HCV therapy indicate that TDM is necessary throughout antiviral therapy, even if the DAAs being used do not show DDIs with tacrolimus.

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Conflicts of interest

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