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LETTER TO THE EDITORS

Fluctuations in the concentration/dose ratio of calcineurin inhibitors after simeprevir administration in patients with recurrent hepatitis C after liver transplantation

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Dear Sirs,

As the efficacy of dual therapy with peginterferon and ribavirin for recurrent hepatitis C after liver transplantation is limited, direct-acting antiviral agents (DAA) should be considered. First-generation NS3/4A inhibitors, such as telaprevir or boceprevir, for liver transplant recipients are problematic because of their inhibitory action on cytochrome P450 3A (CYP3A), an enzyme responsible for the metabolism of calcineurin inhibitors including tacrolimus and cyclosporine. In fact, administration of telaprevir resulted in elevation of blood concentrations and increase in the elimination half-life of calcineurin inhibitors (CNI) [1]. Therefore, when telaprevir is used for recurrent hepatitis C after liver transplantation, the dose of the CNI needs to be reduced to maintain proper blood concentrations, resulting in a significant increase in the concentration/dose (C/D) ratio of the CNI after the administration of telaprevir [2].

Since January 2014, we started using the second-generation NS3/4A inhibitor simeprevir along with peginterferon

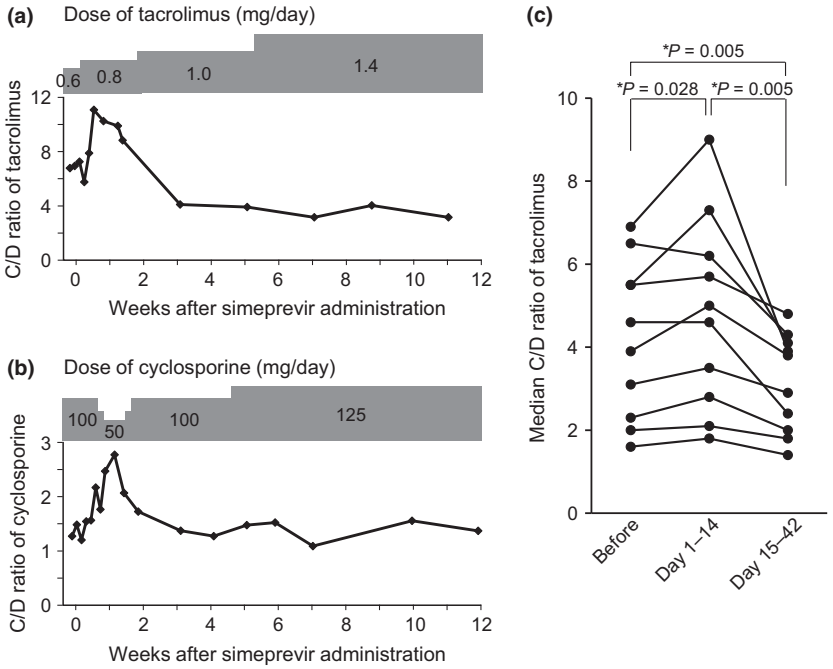

Figure 1 (a,b) Time course of the concentration/dose (C/D) ratio of a calcineurin inhibitor for case 1 (a) and case 2 (b), both of which involved triple therapy with simeprevir, peginterferon, and ribavirin for recurrent hepatitis C after liver transplantation. The fine line represents the C/D ratio of tacrolimus (ng/ml per mg) in a or cyclosporine (ng/ml per mg) in b. The dose of calcineurin inhibitors is shown in gray boxes. (c) Median C/D ratio of tacrolimus in 10 patients with simeprevir-based triple therapy after liver transplantation. Significant differences between the 2 groups are indicated by * with *P* values analyzed by Wilcoxon's signed-rank test. Difference among the 3 groups is also significant by Friedman's test ($P < 0.001$).

and ribavirin for patients with recurrent hepatitis C after liver transplantation. The dose of the CNI was adjusted using therapeutic drug monitoring (TDM) of either tacrolimus or cyclosporine. In 11 cases, we identified fluctuations in the C/D ratio during the simeprevir-based triple therapy. Six of the 11 patients were men, and the median age was 64 years (range, 46–73 years). Before the treatment, fibrosis scores F1 and F2 based on the METAVIR score was found in five and six patients, respectively. Tacrolimus-based immunosuppression with (n = 4) or without (n = 6) mycophenolate mofetil was administered to 10 patients, and cyclosporine with mycophenolate mofetil was administered to one patient. Median serum alanine aminotransferase (ALT) level before treatment was 51 IU/l (range, 21–115), and ALT of all patients decreased to the normal range in the first 2 weeks of treatment.

For the first 2 cases, the time course of the C/D ratio of tacrolimus in case 1 and cyclosporine in case 2 is shown in Fig. 1a and b. Blood concentrations of tacrolimus and cyclosporine were adjusted to trough levels 6–8 and 150–200 ng/ml, respectively, using TDM after simeprevir administration (100 mg/day). The C/D ratio of calcineurin inhibitors were elevated in the first 2 weeks in both cases, but decreased thereafter, necessitating an increase in the dose of the calcineurin inhibitor. The median C/D ratio of tacrolimus before, the first 2 weeks after, and 3–6 weeks after simeprevir administration in the 10 consecutive cases of patients receiving tacrolimus and simeprevir-based triple therapy in our hospital is shown in Fig. 1c. The median C/D ratio significantly increased from 4.25 ng/ml/mg before simeprevir administration to 4.8 ng/ml per mg in the first 2 weeks, but significantly decreased to 3.35 ng/ml per mg after 3 weeks of simeprevir administration.

These findings revealed the importance of TDM of CNI in transplant recipients undergoing simeprevir-based triple therapy. During the first 2 weeks, elevation of the C/D ratio would be caused by the interaction of simeprevir with CNI, because simeprevir is metabolized by the enzyme CYP3A, which is responsible for the metabolism of CNI. Notably, the C/D ratio was significantly decreased after 2 weeks of simeprevir-based triple therapy, despite continuous simeprevir administration at the same dose. The mechanism for the decrease in concentration of CNI with effective antiviral therapy has been proposed to be due to an increased metabolism of CNI by improvement in liver function [3]. Changes of CNI concentrations would be more dynamic using DAA, because of the drug–drug interaction and strong anti-HCV effect. Therefore, we should be cautious of the fluctuations in the CNI concentrations especially during DAA-based therapy and thus recommend TDM during the entire period of antiviral therapy.

Yoshihide Ueda[1], Toshimi Kaido[2] and Shinji Uemoto[2]
1 Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
2 Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan
e-mail: yueda@kuhp.kyoto-u.ac.jp

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Conflict of interest

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