Do calcineurin inhibitors influence the serum concentrations of mizoribine?

Takahisa Hiramitsu*, Makoto Tsujita, Takayuki Yamamoto, Norihiko Goto, Shunji Narumi, Yoshihiko Watarai, Takaaki Kobayasi

INTRODUCTION

Mizoribine (MZR) is an antimetabolite that inhibits inosine-monophosphate dehydrogenase just like mycophenolate mofetil (MMF), and has been used for preventing rejection in renal transplantation. It has been reported that the pharmacokinetics of MMF shows large variations among individuals, depending on the concomitant use of a calcineurin inhibitor (CNI), steroid, etc. On the other hand, the pharmacokinetics of MZR is known to be influenced strongly by the renal function. But, there are as yet no reports in the literature of clinical investigations of the effect of CNIs on the pharmacokinetics of MZR. These data were evaluated by population pharmacokinetic (PPK) analysis.

METHODS

This study was approved by our Ethics Committee and in accordance with Helsinki Declaration of 1975 (as revised in 1983).

ABSTRACT

Background: Mizoribine (MZR) is an antimetabolite that inhibits inosine-monophosphate dehydrogenase and has been used for preventing rejection in renal transplantation. However, the effect of calcineurin inhibitors (CNIs) on the pharmacokinetics of MZR has not been shown. This study was performed to show the influence of CNIs (tacrolimus [Tac] or cyclosporine [CyA]) on the serum concentration of MZR.

Methods: Thirty-four living-donor renal transplant recipients administered a four-drug immunosuppressive therapy regimen (steroid, CNIs, basiliximab and MZR 6 mg/kg/day) were investigated. 20 recipients were treated with Tac and 14 were with CyA. Serum concentrations of MZR were obtained retrospectively at 464 points and at 243 points for each. Population pharmacokinetic (PPK) analysis was used to make pharmacokinetic models of serum MZR. After statistically evaluating the correlation of the pharmacokinetic models with the actual data, areas under the curves (AUCs) of each CNI were also estimated in these models and statistically evaluated.

Results: The mean values of the PPK parameters (absorption lag time, absorption rate constant [Ka], apparent volume of distribution [V/F] and oral clearance of MZR [CLₘₐₓ/F]) were 0.600 hr and 0.643 hr, 1.14/hr and 0.911/hr, 0.732×body weight (WT) (L) and 0.784×WT (L), and 1.64×creatinine clearance (CLᶜ) (L/hr) and 1.81×CLᶜ (L/hr), respectively. Moreover, the serum concentrations of MZR at all-time points were estimated with these parameters. The correlation coefficients between the individual actual and estimated serum concentrations of MZR in the Tac group and the CyA group were 0.988 and 0.992, respectively. The average value of the AUCs of MZR corrected by the CLᶜ in the Tac group, and the CyA group were 0.988 and 0.992, respectively. The average value of the AUCs of MZR corrected by the CLᶜ in the Tac group, and the CyA group were 0.61±0.21 and 0.55±0.19 (average value±standard deviation) for each (p<0.19).

Conclusion: These findings suggest the pharmacokinetics of MZR were well-described by 1-compartment model with first-order absorption. Moreover, concomitant use of CNIs, e.g., Tac and CyA, may have no significant influence on the pharmacokinetics of MZR.

Keywords: Mizoribine, Calcineurin inhibitors, Population pharmacokinetics
Selection and description of participants

A total of 34 recipients performed living-donor renal transplantation between October 2006 and December 2010 were administered with steroid, CNIs (tacrolimus [Tac] or cyclosporine [CyA]), basiliximab and MZR 6 mg/kg/day. Of these 34 recipients, 20 patients were administrated with Tac 0.2 mg/kg/day and 14 patients were with CyA 8 mg/kg/day.

Technical information

Blood samples were collected from therapeutic drug monitoring (TDM) study at 0 hr, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 9 hr, 12 hr, after the administration of MZR during the induction period. A total of 464 blood samples and 243 samples were obtained in each group.

Analysis of the serum MZR concentration

The serum MZR concentrations were determined by high-performance liquid chromatography method. In this measuring method, the intra- and inter-day precisions in terms of coefficient of variation were lower than 5.0% and 6.5%, respectively. The accuracy in terms of % relative error ranged from −1.7% to 4.4% (0.25-4.0 µg/mL), detection range was from 0.01 to 10 µg/mL and lower limit of quantitation was 0.01 µg/mL.

Statistical techniques

Significant difference of recipients between two groups was tested by means of Chi-square test and Student’s t-test (SPSS software, version 19 [SPSS Chicago, IL, USA]). The serum MZR concentration-time data were fitted by PPK analysis, with the NONMEM computer program (ADVAN2 TRANS2). The following individual parameters of \( i \)th were estimated: absorption lag time (ALAG) \( _i \), \( Ka_i \), \( V/F_i \), \( CL/MZR/F_i \).

These parameters were defined by following equations.

\[ ALAG_i = A_1 \]
\[ KA_i = A_2 \times \exp(\eta_{ka_i}) \]
\[ \eta_{ka_i} \]: random effect variable distributed normally with means of zero and variance of \( \sigma_{ka_i}^2 \).

\[ V/F_i = \theta_1 \times WT \times \exp(\eta_{v/f_i}) \]
\[ CL/MZR/F_i = \theta_2 \times CL_{cr} \times 60/1000 \times \exp(\eta_{cl/f_i}) \]
\[ WT \]: body weight
\[ CL_{cr} \]: creatinine clearance

RESULTS

Recipients

Recipients’ characteristics of two groups are shown in Table 1. There were no significant differences in gender, age, weight, post-transplant serum creatinine level, and dose of MZR.

PPK analysis

The mean values of the PPK parameters for the basic structural model of MZR are shown in Table 2. These parameters (\( Ka \), \( V/F \) and \( CL/F \)) in both groups were nearly identical to those reported among healthy adults. The mean values of ALAG, \( Ka \), \( V/F \), and \( CL/F \) were 0.34 hr, 0.869/hr, 0.834969 L/hr, respectively in the healthy adults.
Validity of the PPK parameters

The regression lines between the predicted serum MZR concentration based on these parameters and actual serum MZR concentration were plotted on Figure 1. Each correlation coefficient in Tac group and CyA group was 0.988 and 0.992 respectively. These results showed that there was a strong relationship between the estimated serum MZR concentration and actual serum MZR concentration. According to these results, the mean values of the PPK parameters were proved to be valid.

AUCs of MZR

Average values of AUCs adjusted by CLcr are shown in Figure 2. Adjusted average values of AUCs for Tac group and CyA group were 0.61±0.21 and 0.55±0.19 (average value±standard deviation) respectively, and there was no significant difference (p=0.19).

DISCUSSION

MZR is an antimetabolite that inhibits inosine-monophosphate dehydrogenase just like MMF. It is widely used in kidney transplantation as an antimetabolite combined with steroids, CNI and basiliximab in Japan.

The efficacy and safety of MZR compared with MMF had already been reported. Acute rejection rate of MZR is almost the same as that of MMF when administered with CyA and CyA in the CyA group. The efficacy and safety of MZR are comparable to MMF when administered with CyA.

### Table 1: Recipients’ characteristics.

<table>
<thead>
<tr>
<th>Tac group</th>
<th>CyA group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of recipients</td>
<td>20</td>
</tr>
<tr>
<td>Measurement point (total)</td>
<td>464</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7/13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.55±13.46</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55.90±14.24</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.32±0.52</td>
</tr>
<tr>
<td>Mean treatment dose of MZR (mg/day)</td>
<td>348.71±76.15</td>
</tr>
</tbody>
</table>

Tac: Tacrolimus, CyA: Cyclosporine, MZR: Mizoribine.

### Table 2: PPK parameters.

<table>
<thead>
<tr>
<th>Tac</th>
<th>CyATac</th>
<th>CyA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Measurement points</td>
<td>464</td>
<td>243</td>
</tr>
<tr>
<td>ALAG (hr)</td>
<td>0.600</td>
<td>0.643</td>
</tr>
<tr>
<td>Ka (hr⁻¹)</td>
<td>1.14</td>
<td>0.911</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>0.732×WT</td>
<td>0.784×WT</td>
</tr>
<tr>
<td>CLMZRF/L/hr</td>
<td>1.64×CLcr</td>
<td>1.81×CLcr</td>
</tr>
<tr>
<td>ωALAG</td>
<td>Not determined</td>
<td>Not determined</td>
</tr>
<tr>
<td>ωKa</td>
<td>0.562</td>
<td>0.821</td>
</tr>
<tr>
<td>ωV/F</td>
<td>0.393</td>
<td>0.533</td>
</tr>
<tr>
<td>ωCL/F</td>
<td>0.344</td>
<td>0.345</td>
</tr>
<tr>
<td>ωV/F, CL/F</td>
<td>0.888</td>
<td>0.875</td>
</tr>
<tr>
<td>σ (μg/ml)</td>
<td>0.256</td>
<td>0.18</td>
</tr>
</tbody>
</table>


Figure 1: Estimation accuracy from the parameters calculated in the Population pharmacokinetic analysis (all time points).
It is used to observe samples randomly collected from it, and to estimate a population from the results conversely.

In conclusion, the results of this study illustrates that concomitantly CNI use exerts little influence on the serum concentration of MZR.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES