

# Exposure-Effectiveness and –Nephrotoxicity Relationships of Everolimus and Cyclosporine

## INTRODUCTION

The principle objective of the present analysis is to build exposure-response models using data from the B253 trial for learning the quantitative relationship between drug exposure and safety/efficacy responses and assisting in selecting a suitable dosage regimen for testing in a future heart transplant trial. The criteria for the dosage regimen selection are to maintain the effectiveness of everolimus and reduce the renal toxicity associated with the combined use of everolimus and cyclosporine (CsA/RAD).

## METHODS

### Data

All the data (from the azathioprine control and everolimus groups) collected up to 6 months in the study B253 were employed to develop a CsA-CrCL model. The observed cyclosporine (CsA) and everolimus (RAD) concentrations and calculated renal creatinine clearance (CrCL) based on the Cockcroft and Gault equation were used for model building.

### Models

To describe the relationship between renal creatinine clearance (CrCL) and cyclosporine (CsA) and everolimus (RAD) concentrations, an indirect response model (Eq. 1) was used, assuming the renal toxicity is reversible (best case scenario).

$$\frac{dCrCL}{dt} = K_{in} \cdot (1 + E_{heart}) - K_{out} \cdot (1 + CsA \cdot \beta) \cdot CrCL \quad (\text{Eq. 1})$$

where  $\beta = \alpha_0 + \alpha_1 \cdot \text{RAD}$

$K_{in}$ : input rate for CrCL,

$K_{out}$ : decay rate for CrCL

$E_{heart}$ : beneficial effect due to a new heart

$\beta$ : slope for cyclosporine (CsA) effect

$\alpha_0$ : slope for Azathioprine (AZA) group (RAD=0)

$\alpha_1$ : change in slope due to everolimus (RAD)

An exponential error model was used to describe the inter-individual variability in the following parameters:  $K_{in}$ ,  $K_{out}$ ,  $E_{heart}$ , and  $\beta$ . For example, for  $K_{in}$ :

$$K_{in_i} = TVK_{in} \cdot \exp(\eta_{i\_Kin}), \quad (\text{Eq.2})$$

where  $\exp(\eta_{i\_Kin})$  denotes the difference (proportional) between the true individual parameter ( $K_{in_i}$ ) and the typical value ( $TVK_{in}$ ).  $\eta_{i\_Kin}$  was assumed to follow a normal distribution with mean 0 and variance  $\omega^2_{\_Kin}$ . An exponential model was also used for the residual error model in the following form:

$$Y_{ij} = F_{ij} \cdot \exp(e_{ij}) \quad (\text{Eq. 3})$$

where  $Y_{ij}$  was the observed CrCL level at time  $j$  for individual  $i$ ,  $F_{ij}$  was the predicted CrCL level at time  $j$  for individual  $i$  and  $e_{ij}$  was assumed to follow a normal distribution with mean 0 and variance  $\sigma^2$ .

An Emax model was also attempted to describe  $\beta$  ( $\beta = \alpha_0 + E_{max} * RAD / (EC_{50} + RAD)$ ).

To include as many observations as possible, any record that contained CrCL observation was included in the dataset. As a result, some records have missing values for RAD levels, which were treated as zero in NONMEM if not marked as missing data. These missing values were imputed based on the following rules for each subject:

- A1. If there were observations right before and after the missing value in the dataset, the missing value was calculated as the mean of these two adjacent observations.
- A2. If there were observations before two adjacent missing values, the first missing value will take the preceding observation. This rule applies until situation described in rule A1 happens.
- A3. If there was no observation before the missing values, all the missing values were calculated to be half of the first observation.
- A4. If there was no observation at all, all the missing values were assigned the median observed RAD levels (4.505 for RAD 1.5mg group and 7.874 for RAD 3mg group).

There are 2327 records for RAD groups, of which 236 records were missing and imputed. All the records for AZA group were assigned 0 for RAD concentration. Both the original dataset and the imputed dataset were fitted with a non-linear mixed-effects modeling approach with First Order (FO) estimation method in the NONMEM program (double precision, Version V, Level 1.1) via WINGS for NONMEM (Version 408).

For effectiveness evaluation, the logistic model (Eq. 3) without interaction developed by the sponsor was used during the simulation process. The primary endpoint was the dependent variable.

Logit (p) =  $\beta_0 + \beta_1 * LRAD + \beta_2 * LCSA$ , (Eq. 3)

where  $\beta_0 = 1.9857$ ,  $\beta_1 = -0.3632$ ,  $\beta_2 = -0.4064$ ,  $LRAD = \log(\text{arithmetic mean of RAD concentration before 6 month})$  and  $LCSA = \log(\text{arithmetic mean of CsA concentration before 6 month})$ . Even though in the original model building process, LRAD and LCSA were calculated based on time-normalized mean, arithmetic mean was used to calculate the simulated mean exposure to put more weight on earlier exposure of CsA based on the result that earlier CsA exposure is more important for primary effectiveness endpoint than later exposure (day 1-225 analysis versus day 15-225 analysis).

### **Model Evaluation**

The CsA-CrCL model was evaluated based on 200 non-parametric bootstrap runs. The parameter estimates with successful covariance step were summarized as a histogram plot and compared with the parameter estimates based on the original dataset.

### **Simulation**

The CsA-CrCL model was used to simulate various different regimens and explore for a regimen with better risk/benefit profile to be tested in a future heart transplant study. The patient characteristics in B253 are assumed to be identical in this future trial. Specifically, the individual CsA-CrCL model parameters estimated from B253 data were used to simulate clinical trial outcomes for the new trial. The first month CsA levels were maintained the same in the new trial as those observed in B253 while the CsA levels during months 2-6 were reduced at various degrees in the two RAD groups compared to those observed in B253. The RAD levels were maintained the same in the new trial as in B253, assuming the doses of RAD can be adjusted to achieve this. The creatinine clearance profiles were then simulated for each individual in NONMEM based on the CsA-CrCL model.

### **Analysis**

The simulated creatinine clearance data was summarized at the end of 6 months to compare the control group (AZA) with the two RAD groups. The therapeutic failure rate (primary effectiveness endpoint) was calculated for RADL and RADH groups based on the equation 4:

$$\log it(p) = \log it(p_0) + \beta_1 \cdot (LRAD - LRAD_0) + \beta_2 \cdot (LCSA - LCSA_0) \quad (\text{Eq. 4})$$

where p is the therapeutic failure rate during 6 months for RADL and RADH groups in

the new trial,  $\log it(p_0) = \log\left(\frac{p_0}{1 - p_0}\right)$ ,  $p_0=0.38$  for RADL group and  $0.28$  for RADH

group based on the results from study B253,  $\beta_1 = -0.3632$ ,  $\beta_2 = -0.4064$ ,  $LRAD_0$  and  $LCSA_0$  are the log mean exposure of RAD and CSA observed for the two RAD groups in study B253,  $LRAD$  and  $LCSA$  are the log mean exposure of RAD and CSA simulated for the two RAD groups in the new trial. SAS 8.02 was used for all the analysis.

## **RESULTS AND DISCUSSION**

### **CsA-CrCL Model**

It is well known that CsA can cause nephrotoxicity [Olyaei, A.J. et al., Curr Opin Crit Care. 2001; 7(6): 384-389]. Various mechanisms are involved in CsA renal toxicity. It is believed that acute/early nephrotoxicity due to vasoconstriction is reversible while progressive nephrotoxicity due to chronic structural change such as interstitial fibrosis is irreversible. Even for early renal toxicity, there may be a threshold that, once suppressed, is irreversible and leads to chronic renal failure [David, A.B. et al., Am J Cardiovasc Drugs 2004; 4(1): 21-29]. Therefore, reversibility of the renal toxicity plays a very important role in determining the impact of CsA tapering on renal function. Due to the lack of quantitative matrices to incorporate the irreversible renal toxicity, reversible renal toxicity was assumed for the dosage regimens studied as the best case scenario.

The mismatch of maximum CsA exposure and the maximum renal toxicity suggested a delayed drug effect, consistent with the CsA renal toxicity mechanisms that involve multiple intermediate factors [Olyaei, A.J. et al., Curr Opin Crit Care. 2001; 7(6): 384-389]. Therefore, an indirect response model was adopted to model the renal toxicity of

CsA. Even though RAD alone did not cause renal toxicity, the renal toxicity of CsA was boosted when CsA was used together with RAD. Pharmacodynamic interaction and/or local pharmacokinetic interaction between CsA and RAD could be the mechanism for this observation. RAD's boosting effect on CsA's renal toxicity was also incorporated in the model. In the comparator group (azathioprine, AZA) in study B253, an initial improvement in renal function was observed after transplantation. This could be due to the better cardiac function after the surgery and was modeled as a heart effect ( $E_{\text{heart}}$ ) on the input rate in the model. Since this initial improvement was mainly observed in AZA group, the heart effect was modeled with the AZA data alone and the parameter estimate for heart effect was fixed when all the data in study B253 were used to estimate other parameters. The final parameter estimates and their precision are listed in Table 2 for models with missing RAD values=0 (Model 1A) or imputed RAD values (Model 1B). The objective function reduction was 8.1 for Model 1A or 7.6 for Model 1B ( $p < 0.01$  for  $\chi_1^2$ ) if the RAD effect ( $\alpha_1$ ) was included in the model, suggesting a significant boosting effect of RAD exposure on CsA's renal toxicity. An Emax model was also attempted to describe the RAD effect on CsA's renal toxicity. The final parameter estimates were listed in Table 3. The estimation variability for these parameters could not be evaluated due to the failure of covariance step in NONMEM. Very similar fitting results were obtained when either linear model or Emax model was used for RAD effect (Figure 1). The models describe the median change in CrCL for the 3 groups well and the individual predictions agree closely with the observations. No efforts were applied to search for covariates since the individual parameters were expected to contain sufficient information about the unknown covariate effects on each parameter and the same population would be used for prediction. The large inter-individual variability for  $E_{\text{heart}}$  is due to a bimodal distribution (Figure 2) and also reflecting various sources of potential covariates that will impact this parameter, including the donor conditions, the recipient conditions and the surgery operation. Even though  $E_{\text{heart}}$  was not expected to be related to treatment groups, the posthoc summary of  $E_{\text{heart}}$  for the 3 treatment groups (Figure 3) indicated that RAD groups had less  $E_{\text{heart}}$  than AZA group, suggesting  $E_{\text{heart}}$  contained treatment information. As a result, patient assignment pattern in B253 was maintained in simulation for the new trial.

Model 1A was selected for further simulation because: A). it had successful covariance convergence to evaluate the parameter estimation precision; B). the estimate of RAD effect on CsA's renal toxicity is conservative (relative to Model 1B). Simulations based on other models were also conducted to assess the sensitivity of the simulation results on the model selected.

Table 2. Parameter estimates and their precision (SE%) based on linear model

Parameter	Missing RAD values=0 (Model 1A)		Missing RAD values imputed (Model 1B)	
	Estimate (SE%)	Inter-Indiv. Variability (SE% for variance)	Estimate (SE%)	Inter-Indiv. Variability (SE% for variance)
$K_{\text{in}}$	0.983 (20%)	27% (68.2%)	0.988 (20.5%)	27% (68.5%)
$E_{\text{heart}}$	0.0107 (fix)	2198% (32.5%)	0.0107 (fix)	2220% (31.6%)

$K_{out}$	0.0142 (20.1%)	24% (81.0%)	0.0143 (20.6%)	24% (84.6%)
$\alpha_0$	1.47 (15%)	82%* (24.9%)	1.43 (16.9%)	81%* (25.0%)
$\alpha_1$	0.0521 (52%)		0.0531 (55.7%)	
$\sigma$	0.177 (2.7%)		0.177 (2.7%)	

\*: inter-individual variability for  $\alpha_0 + \alpha_1 * RAD$

Table 3. Parameter estimates and their precision (SE%) based on  $E_{max}$  model

Parameter	Missing RAD values=0 (Model 2A)		Missing RAD values imputed (Model 2B)	
	Estimate	Inter-Indiv. Variability	Estimate	Inter-Indiv. Variability
$K_{in}$	0.961	30%	0.964	30%
$E_{heart}$	0.0107 (fix)	2109%	0.0107 (fix)	2124%
$K_{out}$	0.0139	20%	0.0139	20%
$\alpha_0$	1.58	84%*	1.57	83%*
$E_{max}$	0.176		0.176	
$EC_{50}$	0.248		0.559	
$\sigma$	0.2		0.2	

\*: inter-individual variability for  $\alpha_0 + E_{max} * RAD / (EC_{50} + RAD)$

Figure 1: The diagnostic plots for CsA-CrCL population model

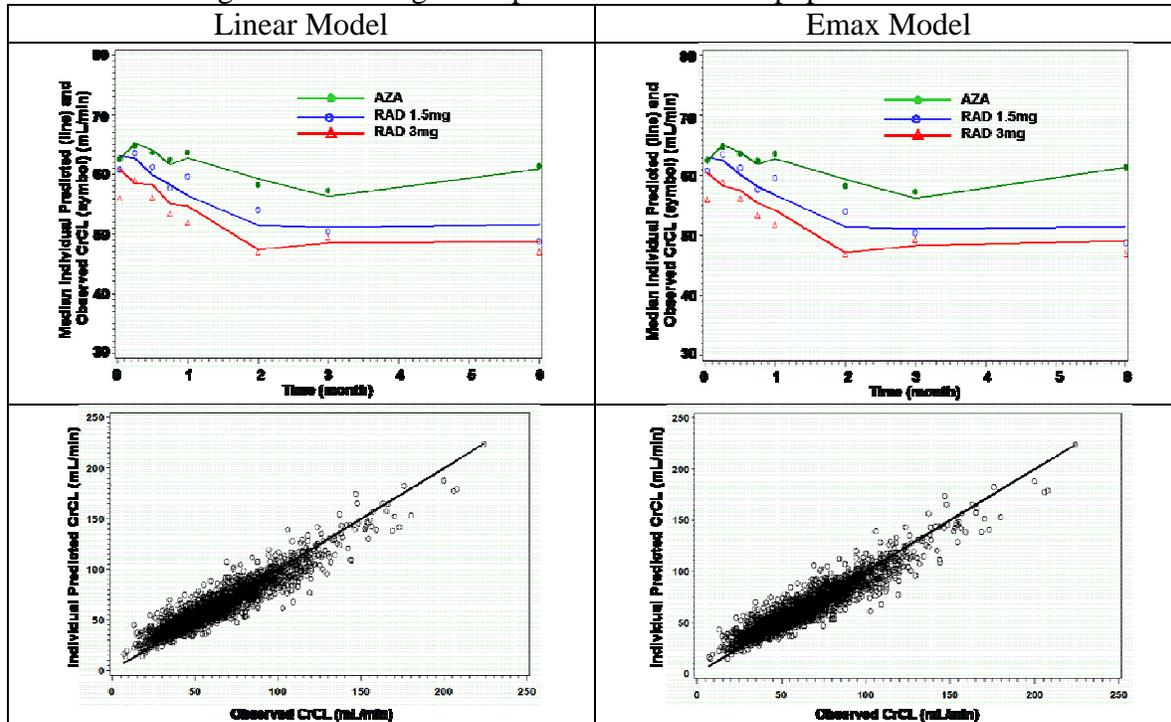


Figure 2: The histogram of inter-individual variability for  $E_{\text{heart}}$  displays a bi-modal distribution

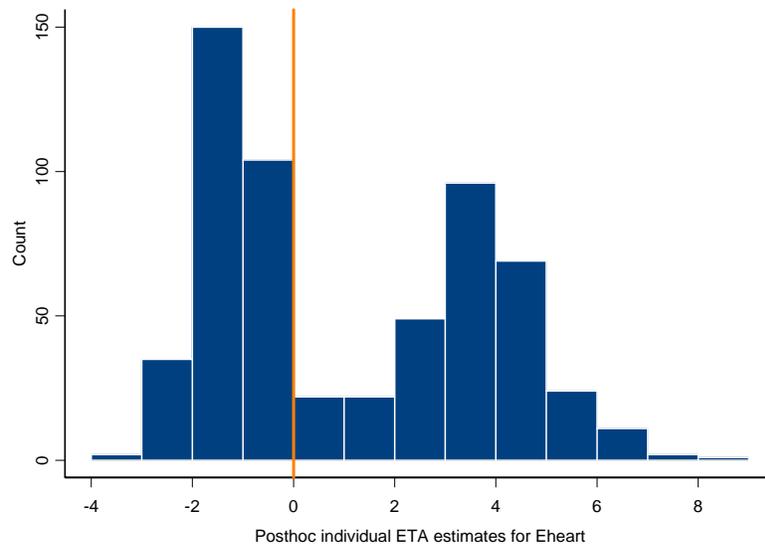
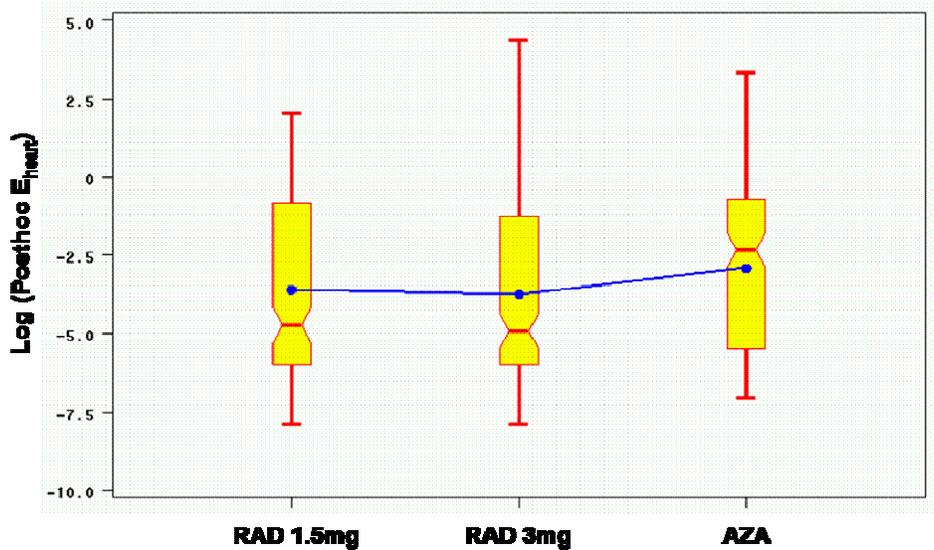


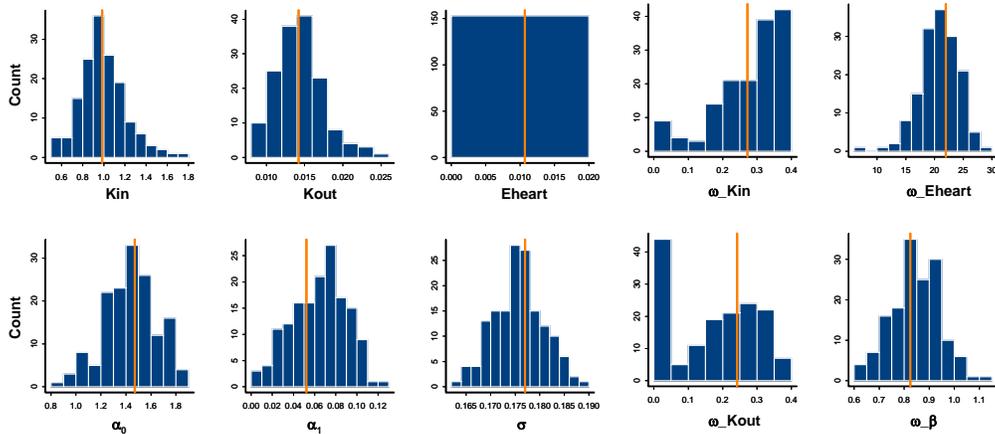
Figure 3: The comparison of posthoc  $E_{\text{heart}}$  across treatments (means are connected)



### CsA-CrCL Model Evaluation

Since Model 1A was selected for later simulation purpose, 200 non-parametric bootstrap runs were conducted for this model. All 200 runs had successful estimation convergence while 155 had successful convergence for both estimation and covariance steps. The histogram (Figure 4) of the parameter estimates from those 155 runs showed that the parameter estimates based on the original dataset are fairly robust.

Figure 4: The histograms of 155 bootstrap parameter estimates and the original parameter estimates (orange lines)



**Simulation**

Following a faster CsA tapering schedule (45% and 65% reduction during 2-6 months for the low dose RAD group and the high dose RAD group, respectively) shown in Figure 5, the mean CrCL changes at month 6 in the two RAD groups were comparable to that observed in AZA group of B253 even though the failure rate increased from 27% to 28% for the low dose RAD group and 36% to 37% for the high dose RAD group (Table 5). Similar simulation results were obtained if an Emax model was used for RAD effect on CsA’s renal toxicity or the missing RAD concentrations were imputed. Other feasible alternate regimens, such as multiple-step tapering of CsA exposure combined with therapeutic drug monitoring of RAD, may show even better risk/benefit profiles. The interpretation of these results should be combined with the assumption that renal toxicity is reversible. If significant irreversible renal toxicity happens, especially in RAD groups, the impact of faster CsA tapering may be reduced.

Figure 5: The Recommended and Observed CsA Distributions

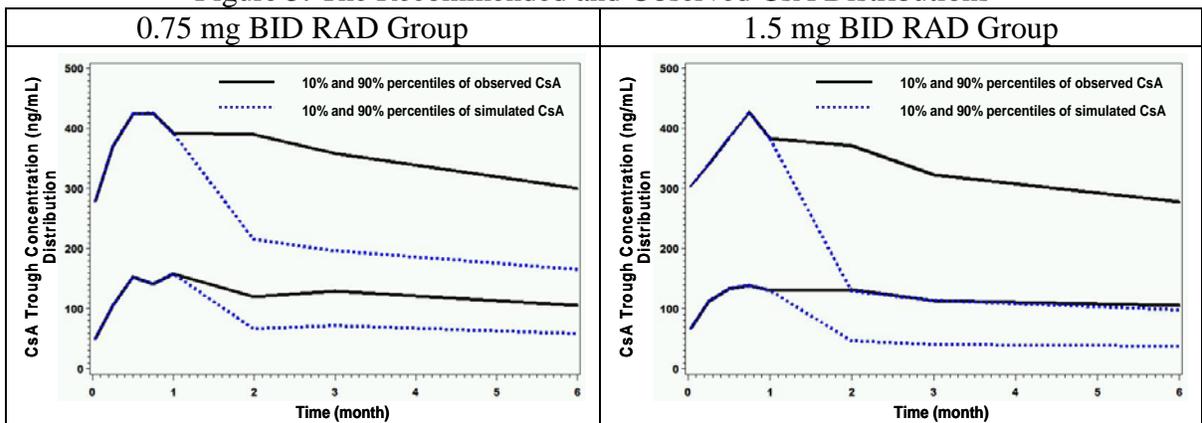


Table 5. Observed and simulated benefit (failure rate) and risk (mean change from baseline in CrCL at 6 months) between the Everolimus groups (47% of the patients in the azathioprine group had at least one of the composite effectiveness events. The mean change in CrCL for the azathioprine group was -4.6 mL/min at 6 months)

<b>Treatment</b>	<b>Benefit</b>	<b>Risk</b>
	<b>Primary efficacy events in 6 mo.</b>	<b>Mean change in CrCL (mL/min) from baseline at 6 mo.</b>
<i>Observed results with standard CsA trough concentrations from Study B253</i>		
0.75 mg BID Everolimus	36%	-13
1.5 mg BID Everolimus	27%	-19
<i>Simulated results with lower target cyclosporine concentrations during 2-6 months post transplantation</i>		
0.75 mg BID Everolimus with CsA ↓45%	37%	-5
1.5 mg BID Everolimus with CsA ↓65%	28%	-5

## CONCLUSIONS

The CrCL model described the observed data in study B253 reasonably well. The simulations using the CrCL model suggest that a faster CsA tapering in RAD groups could reduce the renal toxicity while still maintaining acceptable efficacy results. This conclusion is based on the assumption that renal toxicity is reversible under the proposed dosage regimens. Significant irreversible renal toxicity may reduce the impact of faster CsA tapering on improving the renal function. Therefore, such a new regimen should be prospectively tested in a new trial.