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Original Article

Race differences: modeling the pharmacodynamics of rosuvastatin in Western and Asian hypercholesterolemia patients

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Aim: To evaluate race differences in the pharmacodynamics of rosuvastatin in Western and Asian hypercholesterolemia patients using a population pharmacodynamic (PPD) model generated and validated using published clinical efficacy trials.
Methods: Published studies randomized trials with rosuvastatin treatment for at least 4 weeks in hypercholesterolemia patients were used for model building and validation. Population pharmacodynamic analyses were performed to describe the dose-response relationship with the mean values of LDL-C reduction (%) from dose-ranging trials using NONMEM software. Baseline LDL-C and race were analyzed as the potential covariates. Model robustness was evaluated using the bootstrap method and the data-splitting method, and Monte Carlo simulation was performed to assess the predictive performance of the PPD model with the mean effects from the one-dose trials.
Results: Of the 36 eligible trials, 14 dose-ranging trials were used in model development and 22 one-dose trials were used for model prediction. The dose-response of rosuvastatin was successfully described by a simple E_{max} model with a fixed E_0, which provided a common E_{max} and an approximate twofold difference in ED_{50} for Westerners and Asians. The PPD model was demonstrated to be stable and predictive.
Conclusion: The race differences in the pharmacodynamics of rosuvastatin are consistent with those observed in the pharmacokinetics of the drug, confirming that there is no significant difference in the exposure-response relationship for LDL-C reduction between Westerners and Asians. The study suggests that for a new compound with a mechanism of action similar to that of rosuvastatin, its efficacy in Western populations plus its pharmacokinetics in bridging studies in Asian populations may be used to support a registration of the new compound in Asian countries.

Keywords: rosuvastatin; LDL; dose-response relationship; race difference; clinical trial; hypercholesterolemia

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Introduction

Rosuvastatin, the seventh drug in the statin class, is a synthetic and orally active inhibitor of HMG-CoA reductase used for the treatment of hypercholesterolemia. Early research indicated that rosuvastatin may achieve better outcomes than the other drugs in its class[1–6]. The pharmacokinetics of rosuvastatin were evaluated and reported previously. Both the maximum plasma concentration (C_{max}) and the area under the plasma concentration curve (AUC) are proportional to the dose[7–9]. Age, gender, smoking status, weight, body surface area, and lean body mass had no significant effect on rosuvastatin pharmacokinetics[10, 11]. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups[11]. Nevertheless, pharmacokinetic studies of rosuvastatin, including one conducted in North America, have demonstrated an approximate twofold elevation in median exposure (AUC and C_{max}) in Asian subjects compared with Caucasians[12, 13]. In dose-ranging studies, rosuvastatin produced dose-dependent mean reductions in LDL-C in both Western and Japanese hypercholesterolemia patients[1, 14]. Nevertheless, whether there are similar race differences in rosuvastatin pharmacodynamics is unknown because of a lack of clinical research directly comparing Western and Asian

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patients. At present, considering the potential for increases in systemic exposure, it is recommended in the rosuvastatin product monograph that the dose range of rosuvastatin be 5 to 40 mg orally once a day, that the starting dose be 10 mg in Western patients and 5 mg in Asian patients, and that the maximum dose be 40 mg in Western patients and 20 mg in Asian patients[12]. Therefore, studies of the pharmacodynamics of rosuvastatin in Western and Asian patients are of clinical interest, and the results would improve clinical outcomes and optimize drug development.

This study attempted to pool the mean values of LDL-C reduction (%) from the eligible trials to develop a population pharmacodynamic (PPD) model for evaluating race differences in the pharmacodynamics of rosuvastatin in Western and Asian hypercholesterolemia patients.

Materials and methods

Clinical studies included

A comprehensive literature search in the Medline database was performed from January 1990 to June 2009, with the MeSH terms "rosuvastatin", "hypercholesterolemia" and "clinical trials". There were no language restrictions. Studies were eligible for inclusion if the following conditions were met: (1) the study was a randomized trial to investigate treatment with daily dosing of rosuvastatin in patients with hypercholesterolemia; (2) the percentage change in LDL-C from baseline was reported and the number of patients in each group was greater than 10; (3) the intervention duration was at least 4 weeks. Trials including statin-naive and switched-to-rosuvastatin patients were not eligible when they reported the pooled efficacy from only the two groups of patients. In addition, two Chinese clinical trials were available from our department. Of the eligible studies, the dose-ranging trials were used for model development and the one-dose trials were used for model prediction.

Data extraction and data sets

The mean percentage change in LDL-C from baseline, *ie*, the primary efficacy endpoint, was extracted from each eligible study. In the case of a force-titrated trial, only the efficacy of the starting dose with intervention duration greater than 4 weeks was used in this investigation. Variables for which data were collected included intervention duration, baseline LDL-C, race (Western or Asian), and year of publication. The Western patients consisted predominantly of Whites/Caucasians and the Asian patients comprised Chinese, Japanese, and South Asian subjects.

Population model construction

Population pharmacodynamic analysis of rosuvastatin dose-response data was performed using the nonlinear mixed-effect modeling program NONMEM (Version V, Level 1.1; Globo-Max LLC, Hanover, MD, USA) and DAS version 3.0 (Bontz Inc, Beijing, China). A previously reported sigmoidal E_{max} model was used to characterize the dose-response relationship for rosuvastatin[15]:

$$E=\frac{E_{max}\times Dose^{\gamma}}{ED_{50}^{\gamma}+Dose^{\gamma}}+E_0$$

where E_{max} is the maximal drug effect, reflecting the maximal difference in response between placebo and rosuvastatin; Dose is the dose of rosuvastatin; ED_{50} is the drug dose associated with an effect equal to 50% of E_{max}; and γ is the Hill coefficient reflecting the steepness of the dose-response curve. The term E_0 represents the placebo effect.

The following model structure was used for the PPD analysis:

$$Y_{obs}=E+\eta+\varepsilon$$

where Y_{obs} is the observed effect (the percentage change in LDL-C), η is a trial-specific random effect assumed to be normally distributed with a mean of 0 and an unknown variance of ω^2, and ε is the residual error assumed to be normally distributed parameter with a mean of 0 and a variance of σ^2.

The model was established using the forward inclusion-backward elimination method[16, 17]. In the first step, the PPD analysis was conducted without any covariates in the basic model. In the second step, each candidate covariate (baseline LDL-C and race) was screened in turn by incorporating it into the basic model parameters to develop the intermediate and full models and by observing the decrease in the objective function value (OFV). Covariates were cumulatively added to the PPD model in a forward, stepwise manner in order of their contribution to the reduction in the OFV and until there was no further reduction in OFV. The difference in the OFV was maintained as a χ^2 distribution, and an OFV greater than 3.84, associated with a P value of 0.05 (1 degree of freedom), was used for statistical significance. There were also many indicators of improved fit due to the addition of the following parameters to the model: decrease in standard error of the parameter estimates, reduction in intertrial variability, agreement between the observed and predicted effects, reduction in weighted residuals, and uniformity of the scatter plot of weighted residuals (WRES) versus predicted effects. Finally, a backward elimination step was performed by removing covariates one by one that already exited in the model. In the refinement of the PPD analysis, more stringent cutoff values were applied when determining whether to include a certain covariate or not. Covariates were retained in the model if their removal increased the OFV by 6.63, corresponding to a P value of 0.01 (1 degree of freedom).

Baseline LDL-C was included in the model as a continuous covariate. For the categorical covariate race (RACE), the covariate modeling was described by the following example:

$$P=TVP\times\theta^{RACE}$$

where P is one of the pharmacodynamic parameters and TVP is the typical population parameter value of P. The covariate RACE equals 0 for Westerners and 1 for Asians. If θ^{RACE} is significantly different from 1, it indicates that a race difference exists in the two populations.

Validation and prediction method

Model validation and prediction were used to test the robustness of the parameter estimates and the predictive capacity of the model. Validation of the PPD model was performed by the bootstrap method[18] and the data-splitting method[19]. The means of parameter estimates calculated from the 1000 bootstrap replications with successful runs (*ie*, both the estimation and covariance steps successfully converged) were compared with the final parameter estimates obtained from the original data set. For the data-splitting method, data (subsets) were obtained by deleting one trial at a time in the full data set. Each subset was analyzed by NONMEM with the final model to obtain the parameter estimates, which were compared with those resulting from the full data set.

Monte Carlo simulations were performed 1000 times to predict the 50th percentile LDL-C reduction (as an estimator of the population predicted effect) and the 2.5th and 97.5th percentile LDL-C reductions. The predictive performance of the PPD model was evaluated by observing the mean effects with 95% intervals for Westerners and Asians.

Results

Data

The literature search yielded 93 trials (Figure 1). Of the 54 trials retrieved for detailed assessment, 20 were excluded: one because it focused on a special population (postmenopausal women receiving hormone replacement therapy), one because it included a small number of subjects, two because they reported without number of subjects, four because they included patients whose medications had been switched, five for duplicate reporting, and seven for lack of reduction in LDL-C outcomes. Therefore, 34 eligible studies were identified, 12 of which were dose-ranging trials (9 examined Westerners and 3 examined Asians)[1–3, 5, 14, 20–26] and 22 were one-dose trials (18 comprising Westerners and 4 comprising Asians)[27–48]. In addition to the eligible published studies, two eligible dose-ranging trials in Asians were available from our department. All 14 of the dose-ranging trials were randomized, parallel-group studies; among them, 12 were double-blind, three were placebo-controlled, and the majority were multicenter studies. Tables 1 and 2 summarize the Western and Asian dose-ranging trials. A total of 46 effect samples from the 14 dose-ranging trials were available for the development of the PPD model. A summary of the one-dose trials used for model prediction is presented in Table 3.

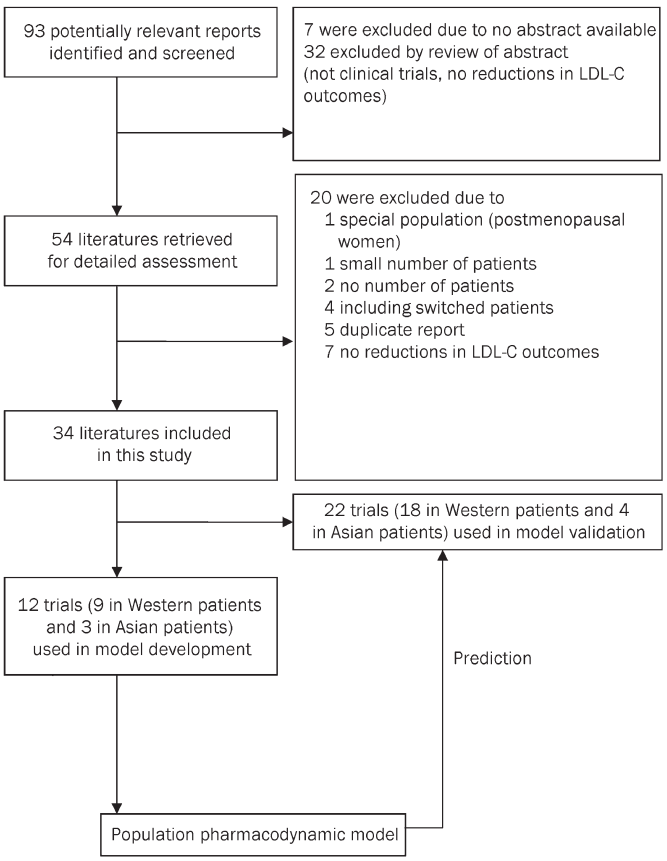

Figure 1. Flow of literatures through the dose-response relationship analysis.

Population pharmacodynamics

In this study, the previously reported sigmoidal E_{max} model described the dose-response relationship for rosuvastatin with incorrect pharmacodynamic parameters. Then, γ was fixed at 1; that is, a simple E_{max} model was used and the estimated parameters were acceptable except for a large relative standard error (RSE) in E_0. Therefore, E_0 was presumed to be -0.802% based on the literature value[15], and the simple E_{max} model was used successfully as the basic model for subsequent covariate analysis. Only the covariate race on ED_{50} produced a small but significant decrease in the OFV (7.095). The resulting population model with the covariate ED_{50} was as follows:

$$ED_{50}=1.74\times0.564^{RACE}$$

The PPD parameters in the final model are listed in Table 4. The RSE values for the parameters were acceptable, with a range from 3.86% to 28.55%. Figure 2 shows the fits of the observed effects with the parameters obtained from the final model. Figure 3 shows the final model-predicted dose-response curves for Westerners and Asians.

The goodness-of-fit plots for the final PPD model are presented in Figure 4. Generally, there was good agreement between observed (OBS) and population model-predicted (PRED) effects, as well as between OBS and individual model-predicted (IPRED) effects, with the magnitude of the WRES being small and randomly distributed over the entire range of PRED. Moreover, the goodness of fit to the model did not vary significantly among the trials.

Validation and prediction

Analysis of each of the 1000 bootstrap samples resulted in 928 samples that successfully converged. The mean values of the parameters after 928 repetitions of the bootstrap estimation were consistent with the parameter estimates of the original data set (Table 5), and the 95% CI was within reasonable

Table 1. Overview of Western dose-ranging trials for model building.

Reference	Year	Duration (week)	Dose (mg)	No of patients	LDL-C baseline (mg/dL)	Reductions in LDL-C (%) Mean	SE
1	2001	6					
			0	29	197.2	3.6	1.7
			1	13	189.4	34.3	2.6
			2.5	13	189.4	40.7	2.6
			5	17	193.4	42.5	2.4
			10	16	189.4	50.5	2.4
			20	13	181.7	57	2.7
			40	34	185.6	62.6	1.5
			80	31	189.4	64.8	2
2	2001	12					
			5	119	190	42	1.3
			10	111	186	49	1.3
3	2002	12					
			5	135	188.0	46	1.3
			10	132	185.9	50	1.3
20	2002	12					
			0	132	187	0	1.2
			5	128	188	40	1.3
			10	129	185	43	1.3
21	2002	12					
			5	121	187.3	39.1	1.3
			10	115	187.0	47.4	1.3
22	2003	6					
			5	38	193	41.5	1.4
			10	45	190	46.6	1.1
			20	38	188	51.7	0.9
			40	44	188	56.8	1.1
			80	42	198	61.9	1.4
5	2003	6					
			10	156	188	45.8	1.0
			20	160	187	52.4	1.1
			40	157	194	55	1.1
23	2004	12					
			5	127	188	39.8	1.1
			10	128	186	47.1	1.1
24	2006	6					
			10	475	172	45.8	0.5
			20	478	173	52.3	0.5
			40	475	173	56.7	0.5

SE, standard error. Dose=0, placebo.

limits.

The values of E_{max}, ED_{50}, and θ (race on ED_{50}) in the full data set and in the subsets are shown in Figure 5. The results indicated that the parameter values for subsets were within the range of the SE of the full data set estimates except for θ (race on ED_{50}) in subset 11.

The visual predictive check using Monte Carlo simulations showed the mean values of LDL-C reduction (%) from the one-dose trials were distributed, in most cases, within the 5th- to 95th-percentile boundaries of the dose-response profiles for both Westerners and Asians (Figure 6).

Discussion

Rosuvastatin is widely used for the treatment of hypercholesterolemia and the recommended doses for Western and Asian patients are different because of a reported race difference in rosuvastatin pharmacokinetics. However, whether there are race differences in rosuvastatin pharmacodynamics remains unclear. In the absence of randomized, controlled studies directly comparing race differences in rosuvastatin pharmacodynamics, an indirect comparison through a model-based meta-analysis was used, characterizing the dose-response relationship for rosuvastatin in Western and Asian patients.

Table 2. Summary of Asian dose-ranging trials for model building.

Reference	Year	Duration (week)	Dose (mg)	No of patients	LDL-C baseline (mg/dL)	Reductions in LDL-C (%) Mean	SE
25	2002	8					
			1	19	219.4	30.0	3.3
			2	16	217.8	36.5	2.2
			4	18	203.8	41.5	3.5
14	2003	6					
			0	12	190.0	3.2	3.2
			1	15	184.0	35.8	2.7
			2.5	17	184.9	45.0	2.6
			5	12	181.3	52.7	3.1
			10	14	182.2	49.7	2.8
			20	18	185.8	58.2	2.5
			40	13	181.0	66.0	2.9
26	2007	6					
			10	183	157	44.7	1.3
			20	171	153	49.5	1.3
NP	2007	8					
			5	82	168.7	42.3	1.8
			10	82	180.3	48.2	1.7
NP	2008	8					
			5	85	157.7	44	1.7
			10	91	163.8	47.4	1.7

SE, standard error. Dose=0, placebo. NP, not published.

Table 3. Summary of one dose trials for model validation.

Reference	Race	Year	Duration (week)	No of patients	Dose (mg)	LDL-C baseline (mg/dL)	Reductions in LDL-C (%)
27	Western	2004	4	12	10	167.6	45.4
28	Western	2004	12	627	10	173.7	46.92
29	Western	2004	6	153	40	257	52.2
30	Western	2005	16	521	10	164.9	47.5
31	Western	2005	12	358	10	171	40.9
32	Western	2005	12	482	10	178.4	45.6
33	Western	2007	8	428	40	189.3	55.9
34	Western	2007	6	230	40	191	57
35	Western	2007	6	152	40	194	54
36	Western	2008	24	17	10	254	47
37	Western	2008	4	25	40	137.8	60
38	Western	2007	8	240	10	131	51
39	Western	2007	12	1230	40	216	54
40	Western	2008	12	252	10	188	42.9
41	Western	2008	48	13	5	153.6	38.2
42	Western	2008	6	498	10	189.2	46.5
43	Western	2008	48	52	10	>200	44.32
44	Western	2009	4	32	10	206.7	37
45	Asian	2004	6	23	10	177.5	43.4
46	Asian	2006	8	40	40	181.73	48.22
47	Asian	2007	12	515	10	166.8	47.5
48	Asian	2009	12	35	10	157.25	47.5

Table 4. Final population pharmacodynamic parameter estimates of rosuvastatin.

Parameters	TVP	SE	RSE (%)	95%CI
E_{max} (%)	57.0	2.2	3.86	52.7, 61.3
ED_{50} (mg)	1.74	0.38	21.8	1.00, 2.48
γ	1			
E_0 (%)	-0.802			
θ (race on ED_{50})	0.564	0.161	28.55	0.248, 0.880
Inter-trial variability	3.0			
Residual error (SD)	3.1			

TVP, typical population parameter value. SE, standard error. RSE, relative standard error, calculated as SE/TVP and expressed as a percentage. 95% CI, lower and upper limits of the 95% confidence interval, calculated as parameter estimates ±1.96 SE. Inter-trials variability was calculated by taking the square root of η. Residual error was expressed as standard deviation. γ was fixed at 1 and E_0 was presumed to be -0.802% based on the literature value.

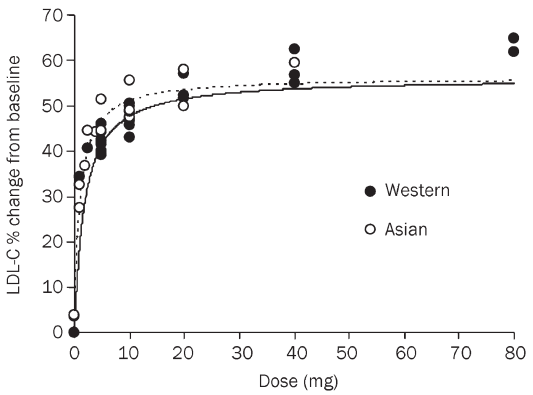

Figure 2. The fits through the observed effects with the parameters obtained from the final model. ●, the observed effects in Western patients; ○, the observed effects in Asian patients. The solid curve is the model-predicted dose-response curve in Western patients and the dashed curve is the model-predicted dose-response curve in Asian patients.

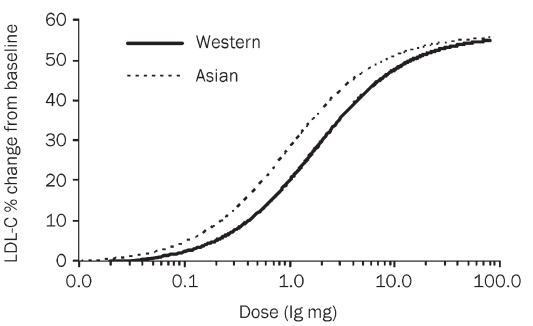

Figure 3. The dose-response logarithmic curve of rosuvastatin in Western and Asian hypercholesterolemic patients. The solid line, LDL-C% change in Western patients; the dashed line, LDL-C% change in Asian patients.

Table 5. Summary of bootstrap validation on the present population pharmacodynamic model.

Parameters	Final estimates	Results of bootstrap simulations		Bootstrap mean/final estimate ratio (%)
		Mean	95% CI	
E_{max} (%)	57.0	57.2	54.8, 59.6	100.4
ED_{50} (mg)	1.74	1.79	1.22, 2.37	102.9
θ (Race on ED_{50})	0.564	0.600	0.334, 0.866	106.4

TVP, typical population parameter value. SE, standard error. RSE, relative standard error, calculated as SE/TVP and expressed as a percentage. 95% CI, lower and upper limits of the 95% confidence interval, calculated as parameter estimates ±1.96 SE. Inter-trials variability was calculated by taking the square root of η. Residual error was expressed as standard deviation. γ was fixed at 1 and E_0 was presumed to be -0.802% based on the literature value.

Because the mean percentage change in LDL-C from baseline is generally accepted as the primary efficacy endpoint for lipid-lowering drugs, the PPD analysis in this study focused on the relationship between dose and LDL-C reduction (%).

The final model in this study successfully provided the pharmacodynamic profile of rosuvastatin in Western and Asian patients. The rosuvastatin-induced reductions in LDL-C were best described by the simple E_{max} model fixing E_0 at -0.802. Race was found to affect the parameter ED_{50} and has a value of 1 for Westerners and 0.564 for Asians. No other significant covariate was found. This finding showed that the ED_{50} was approximately twofold higher in Western patients compared with Asian patients. The result was consistent with the reported race difference in rosuvastatin pharmacokinetics: the AUC_{0-t} values were 2.31-, 1.91-, and 1.63-fold higher and the C_{max} values were 2.36-, 2.00-, and 1.68-fold higher in Chinese, Malay, and Asian Indian subjects, respectively, compared with white subjects[13]. The pharmacodynamics of rosuvastatin with a common E_{max} and a different ED_{50} for Westerners and Asians confirmed that there is no significant difference between these two populations in the exposure-response relationship for LDL-C reduction. It supports the current dosing recommendation for Westerners (10 to 40 mg) and Asians (5 to 20 mg) that was based on pharmacokinetic exposure[12]. Although the dose in Asians is half that in Westerners, the LDL-C reductions (%) are similar in the two populations. In other words, the two populations exhibit no difference in the LDL-C-lowing effect of rosuvastatin. The findings of this study imply that for a new compound with a similar mechanism of action as rosuvastatin, its efficacy (LDL-C-lowering effect) in Western populations plus its pharmacokinetics in bridging studies[49, 50] in Asian populations may be used to support a registration of the new compound in Asian countries, or vice versa. This will avoid unnecessary duplication of efficacy trials in different races, reduce the cost of drug development, and minimize the exposure of patients to doses with uncertain safety and

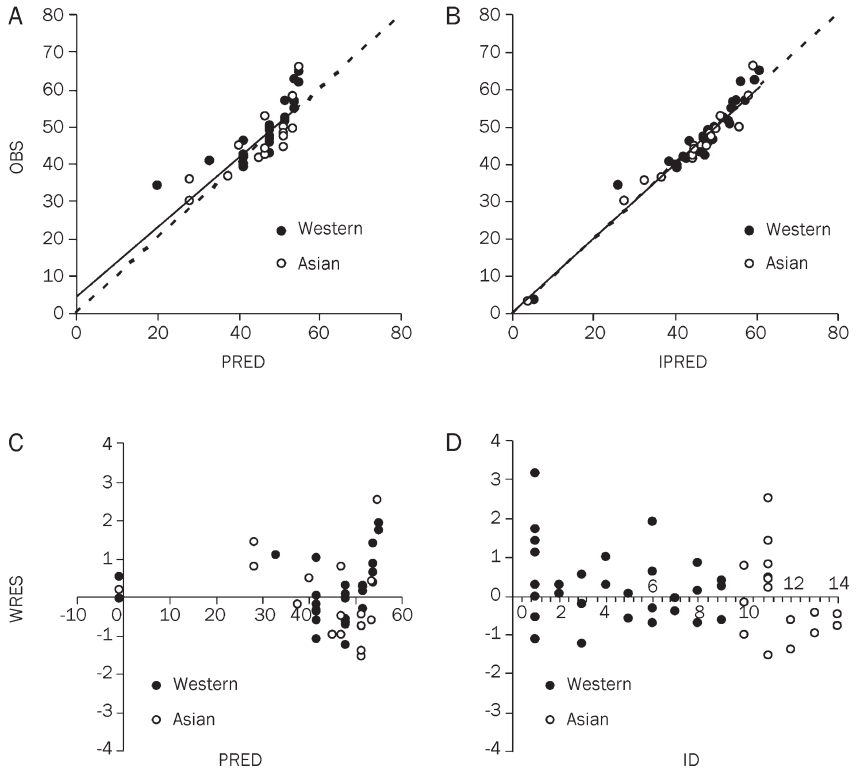

Figure 4. The goodness-of-fit plots for the final PPD model. (A) Scatter plot of population model-predicted effects (PRED) *versus* observed effects (OBS). (B) Scatter plot individual model-predicted effects (IPRED) *versus* OBS. The solid line is a linear regression line and the dashed line is unity. (C) Plot of weighted residuals (WRES) *versus* PRED. (D) Plot of WRES *versus* the trials' identification number (ID).

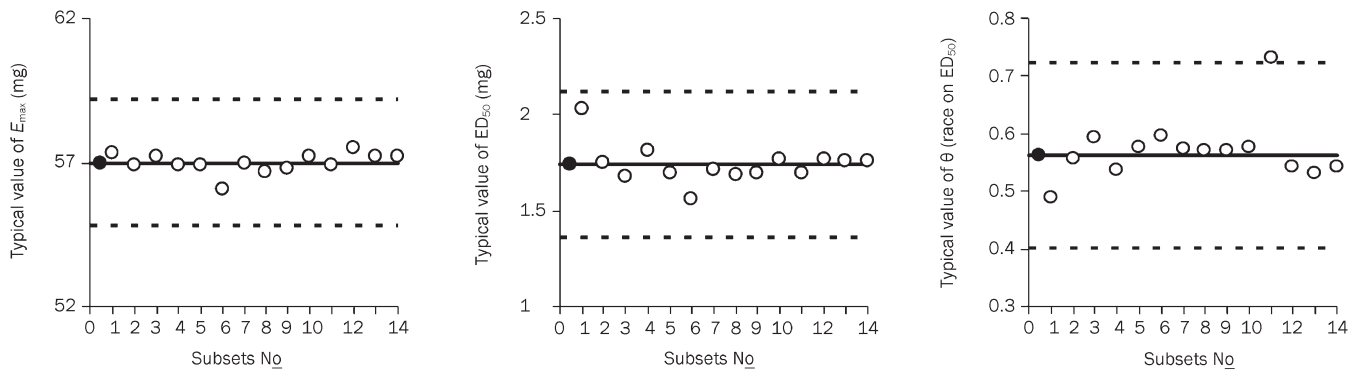

Figure 5. The values of E_{max}, ED_{50}, and θ (race on ED_{50}) in the full data set (●) and for 14 different subsets (○). The solid and dashed lines are the parameter value and ±SE values from the full data set, respectivly.

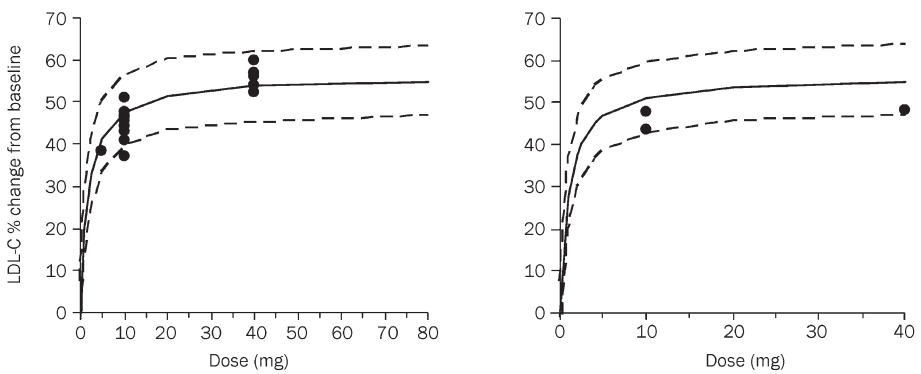

Figure 6. The visual predictive check for the final PPD model in Westerns (left) and Asians (right). The dots are the mean values of LDL-C reduction (%) from the one dose trials. The population-predicted profile (50th percentile) estimated from 1000 Monte Carlo simulations is shown by the solid line, and the 95% prediction intervals are encompassed by the dashed lines in each plot.

efficacy.

Because of the limited amount of data (46 effect samples) available for this study, a previously reported sigmoidal E_{max} model was not suitable for estimating the four required parameters. Therefore, a simple E_{max} model was used and the values of E_{max}, ED_{50}, E_0, and θ were 55.5%, 1.84 mg, 1.21%, and 0.571. In that case, however, the RSE for the estimated E_0 was greater than 900%. To reduce the RSE, E_0 was fixed based on literature values. In fact, the estimated values of E_{max}, ED_{50}, and θ (race on ED_{50}) were not affected by fixing E_0. Consequently, the final model, a simple E_{max} model with a fixed E_0 (-0.812%), was successfully used to describe rosuvastatin pharmacodynamics. Moreover, the robustness of the final model was evaluated by the nonparametric bootstrap and the data-splitting methods[51, 52], which indicated that selected combinations of data yielded results very similar to those obtained using the original full data set. The predictive performance of the final model was confirmed by the visual predictive check using Monte Carlo simulations, which showed that the mean values of LDL-C reduction (%) from the one-dose trials were mostly distributed within the 5th- to 95th-percentile boundaries of the predictive dose-response profiles for both Westerners and Asians.

It has been reported that the maximum response is usually obtained within 2–4 weeks and is maintained during chronic therapy for a fixed dose of rosuvastatin. For this reason, only the mean values of LDL-C reduction (%) that were observed at least 4 weeks after administration were used in the model development. Therefore, it should be noted that the final model in this study was developed to describe the steady state for the LDL-C-lowering effect of rosuvastatin.

In conclusion, the race difference in the pharmacodynamics of rosuvastatin is consistent with that in the pharmacokinetics of the drug, which confirms that there is no significant difference in the exposure-response relationship for LDL-C reduction between Asians and Westerners. This study suggests that for a new compound with a mechanism of action similar to that of rosuvastatin, its efficacy in Western populations plus its pharmacokinetics in bridging studies in Asian populations may be used to support a registration of the new compound in Asian countries.

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Author contribution

Juan YANG and Qing-shan ZHENG conceived and designed the study. Juan YANG, Ying-chun HE, and Yu-cheng SHENG performed the electronic literature retrieval and data extraction. Juan YANG, Lu-jin LI, Kun WANG, and Ling XU analyzed the data. Xiao-hui HUANG and Feng GUO discussed the results. Juan YANG and Qing-shan ZHENG wrote the paper. All authors checked the final manuscript before submission.

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