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Full-length article

Effects of cyclosporin A and itraconazole on the pharmacokinetics of atorvastatin in rats[1]

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Key words

pharamcokinetics; P-glycoprotein; cytochrome P450 (CYP) 3A4; cyclosporin A; itraconazole; atorvastatin

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Abstract

Aim: To evaluate the effects of cyclosporin A and itraconazole, which were used as inhibitors of P-glycoprotein (P-gp) and/or cytochrome P450 (CYP) 3A4 on the pharmacokinetics of atorvastatin in rats. **Methods:** The pharmacokinetic parameters of atorvastatin were measured after intravenous (2 mg/kg) and intragastric (10 mg/kg) administration of atorvastatin in rats, which were pretreated with cyclosporin A (5, 10, and 20 mg/kg) or itraconazole (5, 10, and 20 mg/kg). **Results:** Compared with the control rats, cyclosporin A and itraconazole altered the pharmacokinetics of atorvastatin significantly. The $AUC_{0\text{-}t}$ values of atorvastatin after intragastric administration, pretreated with cyclosporin A (5–20 mg/kg), increased by 32.3%, 61.8%, and 187.2%, respectively, but the CL_{bile} values decreased (P<0.01, 5–20 mg/kg). With pretreatment of itraconazole (5–20 mg/kg), the $AUC_{0\text{-}t}$ values of atorvastatin increased by 88.2%, 102%, and 123%, respectively, but the CL_{bile} values decreased (P<0.01, 5–20 mg/kg). **Conclusion:** These data indicated that cyclosporin A could be effective in inhibiting the efflux of atorvastatin, and itraconazole could be effective in inhibiting both the metabolism and biliary excretion of atorvastatin.

Introduction

Antifungal agents or immunosuppressive agents are commonly coadministered with cholesterol-lowering agents in patients. There are growing reports on the risk of development of rhabdomyolysis, induced by concomitant usage of lovastatin, simvastatin, or atorvastatin [competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase] with cyclosporin A or itraconazole. Rhabdomyolysis is the breakdown of muscle fibers with release of muscle fiber contents (myoglobin) into the systemic circulation, and some of these are harmful to the kidney and frequently result in kidney damage[1]. Cyclosporin A is an inhibitor of P-glycoprotein (P-gp) and itraconazole is a selective inhibitor of hepatic microsomal cytochrome P450 (CYP) 3A enzyme[2]. For example, cyclosporin A increases the plasma concentrations of simvastatin in renal transplant recipients[3]. Itraconazole increases the total area under the plasma concentration-time curve from time zero to time infinity (AUC) of atorvastatin[4], simvastatin[5], and lovastatin[6] by about 3-, 19-, and 20-fold, respectively. Lovastatin, simvastatin, and atorvastatin (the first-line agents for hypercholesterolemia), substrates of CYP 3A, have extensive first-pass metabolism[7]. Thus, the dosage of a HMG-CoA reductase is needed to decrease when they are used concomitantly with P-gp or CYP3A inhibitors. It has been reported that coadministration of various HMG-CoA inhibitors and cyclosporin A to rats, cyclosporin A alters the disposition of the inhibitors, resulting in increased AUC of the inhibitors[8]. It has been reported that itraconazole can inhibit the metabolism of simvastatin in female rat liver microsomes[9].

Atorvastatin is a synthetic lipid-lowering agent (the rate-limiting enzyme in cholesterol biosynthesis) and has been demonstrated to be effective in reducing total cholesterol, low-density lipoprotein cholesterol, and plasma triglycerides[10]. It was developed by Pfizer and was approved by FDA in 1996. Atorvastatin is mainly metabolized by CYP3A to a number of active metabolites, which are excreted mainly from bile[11]. As already stated,

atorvastatin is a substrate or an inhibitor of CYP3A and P-gp[12,13].

It has been known that P-gp and CYP3A have notable effects on the absorption and metabolism, respectively, of compounds which are a substrate of P-gp or CYP3A. In order to clarify the drug–drug interactions mediated by P-gp and CYP3A, focusing on the efflux and metabolism, respectively, we investigated the effects of well known inhibitors (cyclosporin A and itraconazole) on P-gp and/or CYP3A4, and evaluated their contributions to the pharmacokinetics of atorvastatin in rats. For this purpose, we assessed the pharmacokinetics and biliary excretion of atorvastatin after intravenous and intragastric administration to rats with cyclosporin A or itraconazole.

Materials and methods

Chemicals Atorvastatin (purity >99%) was supplied by Yang Jiang Medicine Company (Yangjiang, China). Pitavastatin (internal standard, 10 μg/mL) was obtained from the Center of Drug Metabolism and Pharmacokinetics of China Pharmaceutical University (Nanjing, China). Cyclosporin A and itraconazole were products from Hua Dong Medicine Company (Hangzhou, China). Methanol [high-performance liquid chromatographic (HPLC) grade] was purchased from Tedia Company (Fairfield, OH, USA) and water was from ROBUST (Guangzhou, China). Atorvastatin, cyclosporin A, and itraconazole for injection were prepared by dissolving each drug in sterile saline with 2% alcohol. All other chemicals were purchased commercially and were of analytical grade.

Animals Protocols for the animal studies were approved by the Regulations of Experimental Animal Administration, State Committee of Science and Technology of People's Republic of China. Male Sprague-Dawley rats (7–9 weeks old and weighing 250–280 g) were purchased from Shanghai Sciple-Bi-Kai Animal Company Ltd. (Shanghai, China). All rats were maintained in a clean-room at a temperature of 23±2 °C and relative humidity of 50%±10%, and had free access to water and standard animal diet. Rats were fasted overnight with free access to water for 12 h before the experiment.

Rats were randomly divided into three groups (n=5, each); intravenous and intragastric administration of atorvastatin without (control) and with cyclosporine A or itraconazole.

Drug administration The bile duct was cannulated with a polyethylene (PE) tube (0.4 mm, id and 0.8 mm, od; Natsume, Tokyo, Japan) while each rat was under ether anesthesia. Cyclosporin A (approximately 0.25, 0.5 and 1.0 mL for 5, 10, and 20 mg/kg, respectively) or itraconazole (approximately 0.2, 0.4 and 0.8 mL for 5, 10, and 20 mg/kg, respectively) was administered intravenously from tail to rats. After 5 min, atorvastatin was injected via the tail vein at a dose of 2 mg/kg (about 0.6 mL) or intragastricly administered at a dose of 10 mg/kg (about 0.8 mL) using stomach tube to rats. Then, bile samples were collected in 0–1, 1–2, 2–4, 4–8, and 8–12 h into tubes and the volume of each sample was recorded. Simultaneously, blood samples (210 μL) were obtained by orbital bleeding at 0 (control), 4, 8, 12, 30, 60, 90, 120, 240, 360, and 480 min after intravenous administration, and 0 (control), 5, 10, 20, 30, 60, 90, 120, 240, 360, and 480 min after intragastric administration. Blood samples were centrifuged and plasma samples (100 μL) were stored at –20 °C until use for the liquid chromatography-tandem mass spectrometric (LC-MS) analysis of atorvastatin[14,15].

LC-MS analysis of atorvastatin Concentrations of atorvastatin in the samples were determined using an electrospray ionization LC-MS (Shimadzu, Kyoto, Japan). In brief, a 10 μL aliquot of internal standard in methanol (10 ng/mL) and a 20 μL aliquot of 1% hydrochloric acid were added to a 100 μL aliquot of sample. Then, a 500 μL aliquot of acetic ether was added, vortex-mixed for 3 min, and centrifuged (4000×g, 5 min). The upper organic layer (400 μL) was transferred into a clean glass test tube and evaporated to dryness under a gentle stream of nitrogen gas at 40 °C. The residue was reconstituted in a 100 μL aliquot of the mobile phase, and centrifuged (12 000×g, 10 min). Then, a 20 μL aliquot was injected directly onto the LC-MS system using autosampler. Bile samples were diluted with the mobile phase to appropriate concentrations and other procedures were similar to those in plasma samples. The mobile phase, methanol: 5 mol/L ammonium acetate containing 0.1% methanoic acid (70:30, v:v) was run at a flow-rate of 1.0 mL/min at 25 °C. The analytical column, a reversed-phase Hypersil ODS2 column (particle size, 5 μm; 4.6 mm, id×250 mm, l.; Elite Company, Dalian, China), was maintained at 40 °C. Mass spectrometry was carried out in positive ion selected ion monitoring (SIM) mode using target ions at m/z 559.25 for atorvastatin and 422.15 for internal standard. The detector voltage was 1.60 kV. The heat block temperature was 200 °C and the curved desolvation line (CDL) temperature was 250 °C. The nebulizer gas flow rate was 1.5 L/min[16]. The retention times for atorvastatin and internal standard were 4.5 and 4.8 min, respectively.

The calibration curve of atorvastatin was linear within

the ranges from 2 to 1000 ng/mL in both plasma and bile samples (R^2>0.99). The lower limit of quantification was 2 ng/mL. The relative standard deviation (RSD) of inter- and intra-day precisions were both less than 10%. The relative recovery of atorvastatin from plasma and bile samples compared with that in water was more than 60%.

Pharmacokinetic analysis The AUC_{0-t} was calculated using the trapezoidal rule method from time zero to the last measured time, *t*, in plasma. The peak plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were directly read from the experimental data. The extent of absolute oral bioavailability (*F*) was calculated by dividing the mean AUC_{0-t} following intragastric administration by that following intravenous administration after normalization of the dose. The biliary clearance (CL_{bile}) was estimated by dividing the total amount of drug excreted into the 12-h bile by the AUC_{0-t}.

Statistical analysis A *P*-value <0.05 was deemed to be statistically significant using one-way ANOVA with the Statistical Package for the Social Sciences (SPSS) 13.0. All data are expressed as the mean±standard deviation.

Results

The mean plasma concentration-time and biliary excretion-time profiles of atorvastatin after intravenous and intragastric administration at doses of 2 and 10 mg/kg, respectively, with or without cyclosporine A (5, 10, and 20 mg/kg) are shown in Figures 1 and 2, respectively, and the relevant pharmacokinetic parameters of atorvastatin are listed in Table 1. Compared with the control rats, after intravenous administration of atorvastatin, the CL_{bile} was significantly slower (56.5%, 64.5%, and 79.0% decrease for 5, 10, and 20 mg/kg of cyclosporine A, respectively), the 12-h biliary excretion was significantly smaller (32.1%, 57.5%, and 69.0% decrease for 5, 10, and 20 mg/kg of cyclosporine A, respectively), and the AUC_{0-t} was significantly greater (118%, 193%, and 215% increase for 5, 10, and 20 mg/kg of cyclosporine A, respectively) with cyclosporine

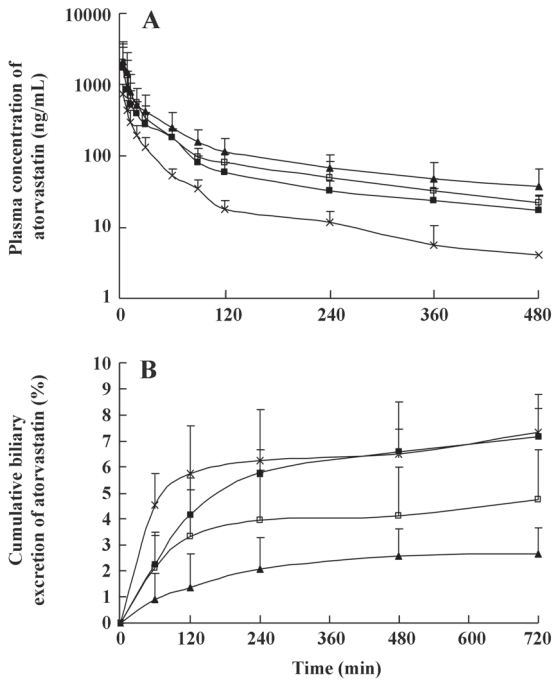

Figure 1. Plasma concentration-time profiles (A) and biliary excretion-time profiles (B) of atorvastatin after intravenous administration at a dose of 2 mg/kg to rats (*n*=5, each). ×, control; ■, Cyclosporin A, 5 mg/kg; □, Cyclosporin A, 10 mg/kg; ▲, cyclosporine A, 20 mg/kg. Bars represent standard deviations.

Table 1. The pharmacokinetic parameters of atorvastatin after intravenous and intragastic administration to rats with or without cyclosporine A (*n*=5, each). All data are expressed as the mean±SD. ^bP<0.05, ^cP<0.01 *vs* control.

Parameter	AUC (min·μg·mL^{-1})	C_{max} (ng/mL)	T_{max} (min)	CL_{bile} (mL·min^{-1}·kg^{-1})	2-h biliary excretion (μg)	*F* (%)
Intravenous						
Control	21.5±3.4			6.2±2.1	26.8±8.2	
5 mg/kg	46.8±18.2^c			2.7±1.6^b	18.2±7.6^b	
10 mg/kg	63.0±14.6^c			2.2±2.1^c	11.4±8.3^c	
20 mg/kg	67.7±41.5^c			1.3±0.3^c	8.3±6.8^c	
Intragastric						
Control	10.2±3.5	121.8±40.3	29.0±9.2	34.9±31.5	55.7±23.1	9.49
5 mg/kg	13.5±6.4	66.1±37.9	72.0±16.4^c	2.8±1.6^c	4.3±0.1^c	5.77
10 mg/kg	16.5±12.3	66.5±35.5	78.0±16.4^c	1.2±0.4^c	2.8±0.2^c	5.24
20 mg/kg	29.3±13.5^c	127.9±55.4	84.0±25.1^c	0.7±0.03^c	1.2±0.04^c	8.66

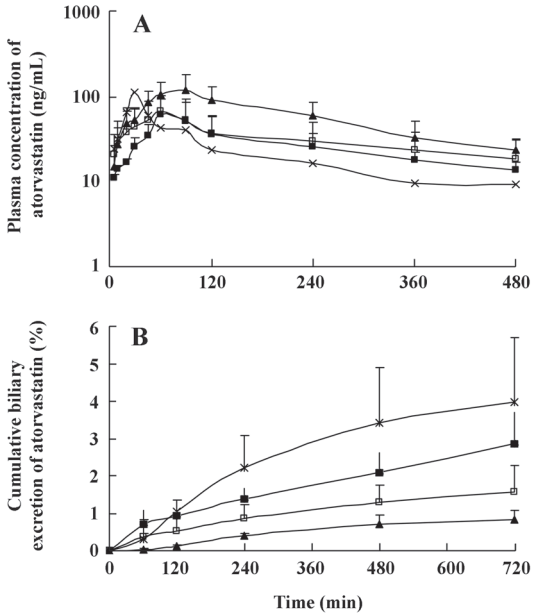

Figure 2. Plasma concentration-time profiles (A) and biliary excretion-time profiles (B) of atorvastatin after intragastric administration at a dose of 10 mg/kg to rats (n=5, each). ×, control; ■, Cyclosporin A, 5 mg/kg; □, Cyclosporin A, 10 mg/kg; ▲, cyclosporine A, 20 mg/kg. Bars represent standard deviations.

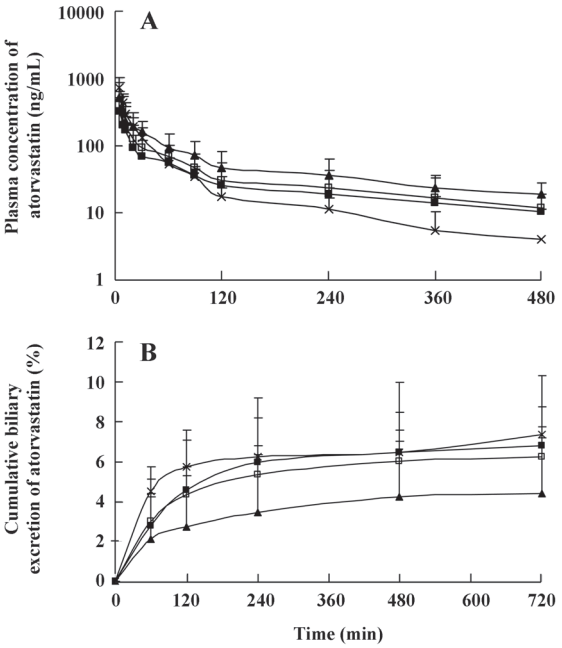

Figure 3. Plasma concentration-time profiles (A) and biliary excretion-time profiles (B) of atorvastatin after intravenous administration at a dose of 2 mg/kg to rats (n=5, each). ×, control; ■, Cyclosporin A, 5 mg/kg; □, Cyclosporin A, 10 mg/kg; ▲, cyclosporine A, 20 mg/kg. Bars represent standard deviations.

A. Compared with the control rats, after intragastric administration of atorvastatin, the CL_{bile} of atorvastatin was significantly slower (92.0%, 96.6%, and 98.0% decrease for 5, 10, and 20 mg/kg of cyclosporin A, respectively), the 12-h biliary excretion was significantly smaller (92.3%, 95.0%, and 97.8% decrease for 5, 10, and 20 mg/kg of cyclosporin A, respectively), and the T_{max} was significantly higher (148%, 169%, and 190% increase, respectively), but the AUC_{0-t} was significantly greater (187% increase at 20 mg/kg of cyclosporine A) with cyclosporine A.

The mean plasma concentration-time and biliary excretion-time profiles of atorvastatin after intravenous and intragastric administration at doses of 2 and 10 mg/kg, respectively, in the presence and absence of itraconazole (5, 10, and 20 mg/kg) are shown in Figures 3 and 4, respectively, and the relevant pharmacokinetic parameters of atorvastatin are listed in Table 2. Compared with the control rats, after intravenous administration of atorvastatin, the CL_{bile} was significantly slower (98.7%, 99.0%, and 99.2% decrease for the 5, 10, and 20 mg/kg of itraconazole, respectively), the 12-h biliary excretion was significantly smaller (91.4%, 92.2%, and 94.4% decrease for the 5, 10, and 20 mg/kg of itraconazole, respectively), and the AUC_{0-t} was significantly greater (24.9% increase at 20 mg/kg of itraconazole) with itraconazole. Compared with the control rats, after intragastric administration of atorvastatin, the CL_{bile} of atorvastatin was significantly slower (99.7%, 99.7%, and 99.8% decrease for 5, 10, and 20 mg/kg of itraconazole, respectively), the 12-h biliary excretion was significantly smaller (98.2%, 96.4%, and 98.0% decrease for 5, 10, and 20 mg/kg of itraconazole, respectively), the C_{max} was significantly lower (77.0%, 61.9%, and 58.1% decrease for 5, 10, and 20 mg/kg of itraconazole, respectively), the T_{max} was significantly longer (65.5%, 79.3%, and 128% increase for 5, 10, and 20 mg/kg of itraconazole, respectively), and the AUC_{0-t} was significantly greater (123% increase for 20 mg/kg of itraconazole) with itraconazole.

Discussion

Our study evaluated the effects of cyclosporine A as well as itraconazole on the pharmacokinetics of atorvastatin in rats to investigate potential drug–drug interactions. P-gp acts as an efflux pump or an absorption barrier by preventing transportation of various compounds from the lumen into intestinal cells[17]. P-gp is expressed in the apical brushborder membrane of the enterocyte and bile-duct, and lateral membrane of the hepatocyte[18]. P-gp is also commonly co-expressed with the CYP3A system in many

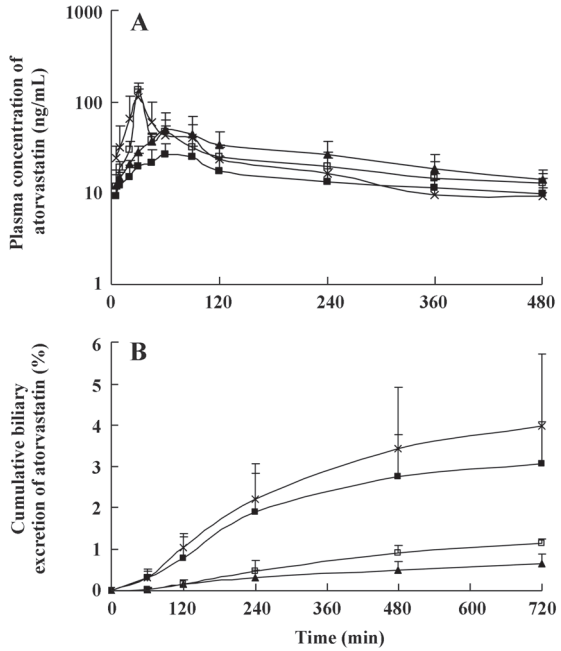

Figure 4. Plasma concentration-time profiles (A) and biliary excretion-time profiles (B) of atorvastatin after intragastric administration at a dose of 10 mg/kg to rats (n=5, each). ×, control; ■, Cyclosporin A, 5 mg/kg; □, Cyclosporin A, 10 mg/kg; ▲, cyclosporine A, 20 mg/kg. Bars represent standard deviations.

normal organs.

The results of this study indicated that both cyclosporin A and itraconazole caused decreases in the 12-h biliary excretion and CL_{bile} of atorvastatin. After pretreatment with cyclosporine A, the 12-h biliary excretion of atorvastatin decreased with increasing doses of cyclosporine A. This could be due to the effect of P-gp by cyclosporine A on the inhibition of biliary excretion of atorvastatin. Thus, the increase in AUC_{0-t} of atorvastatin could be due to the P-gp effect of cyclosporine A, since cyclosporine A does not affect the hepatic metabolism of atorvastatin[19].

The metabolism of atorvastatin was inhibited by itraconazole and the biliary excretion of atorvastatin was inhibited by cyclosporine A. Moreover, itraconazole had dual potency of inhibiting CYP3A and P-gp. But the inhibitory potency of intraconazole for CYP3A was stronger than that for P-gp. P-gp played an important role in the biliary excretion and CYP3A in small intestine. Itraconazole and cyclosporine A increased the bioavailability of atorvastatin in rats.

Adverse effects of statins are mostly associated with drug–drug interactions[20]. The withdrawal of cerivastatin as a result of deaths due to the development of rhabdomyolysis illustrates the clinical importance of drug–drug interactions[21]. Drug interactions with statins may cause pharmacodynamic and/or pharmacokinetic changes. The pharmacodynamic consequences may or may not be closely correlated to pharmacokinetic changes[22].

The CYP enzyme systems play an important role in the metabolism of the statins, leading to clinically relevant interactions with other agents, such as erythromycin, itraconazole, nefazodone, and human immunodeficiency virus (HIV) protease inhibitors, which are also a substrate of this enzyme system[23]. CYP3A isoenzyme is the main metabolic enzyme for simvastatin, lovastatin, and atorvastatin. Interaction studies reveal that simvastatin and lovastatin have the highest potential for clinically relevant interactions, followed by atorvastatin, and coadministered agents alter the activity of CYP3A and lead to increase in toxicity of the statins[24–26].

Table 2. The pharmacokinetic parameters of atorvastatin after intravenous and intragastic administration to rats with or without itraconazole (n=5, each). All data are expressed as the mean±SD. $^bP<0.05$, $^cP<0.01$ *vs* control.

Parameter	AUC ($min \cdot \mu g \cdot mL^{-1}$)	C_{max} (ng/mL)	T_{max} (min)	CL_{bile} ($mL \cdot min^{-1} \cdot kg^{-1}$)	2-h biliary excretion (μg)	F (%)
Intravenous						
Control	21.5±3.4			6.2±2.1	26.8±8.2	
5 mg/kg	21.1±3.4			0.9±0.6^c	2.3±0.12^c	
10 mg/kg	23.3±11.8			0.8±0.1^c	2.1±0.04^c	
20 mg/kg	26.9±15.7^c			0.5±0.3^c	1.5±0.11^c	
Intragastric						
Control	10.2±3.5	121.8±40.3	29.0±9.2	34.9±31.5	55.7±23.1	9.48
5 mg/kg	19.2±2.9	28.1±8.0^c	48.0±6.7^c	1.3±0.3^c	2.4±1.3^c	18.2
10 mg/kg	20.6±4.9	46.5±7.2^c	52.0±17.9^c	1.1±0.9^c	2.0±0.02^c	17.7
20 mg/kg	22.8±4.5^b	51.1±11.1^b	66.0±13.4^c	0.8±0.1^c	1.1±0.04^c	16.7

Some interactions with CYP3A inhibitors may also involve inhibition of P-gp. Thus, rhabdomyolysis may occur following coadministration of cyclosporine A and statins[27, 28]. Thus, attention is needed to the risk of myopathy during treatment of statins with concurrent administration of these agents[29].

Author contribution

Xi-jing CHEN and Jing DONG designed research; Jing DONG, Xue YU, and Lei WANG performed research; Xi-jing CHEN and Jing DONG contributed new analytical tools and reagents; Jing DONG analyzed data; Jing DONG and Ye-bin SUN wrote the paper.

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