Effects of Rifampicin On Pyrotinib Maleate Pharmacokinetics In Healthy Subjects

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Research Article

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Abstract

Purpose: Pyrotinib (PTN) is primarily metabolized by cytochrome P450 (CYP)3A4 isozyme. Rifampicin (RIF) is a strong CYP3A4 inducer. Thus, the effect of oral RIF on PTN pharmacokinetics (PK) was evaluated to provide dose recommendation when co-administered.

Method: This phase I, open-label study investigated the effects of steady-state RIF administration on single-dose PK of PTN, in 18 healthy participants who received PTN 400 mg single doses on days 1 and 13, and were administrated with RIF 600 mg qd on days 6-16. Each dose for RIF was administrated on an empty stomach, PTN were administrated orally in the morning 30 min after the start of the standard meal. Serial PK samples for PTN were collected on day 1 and day 13. Plasma PTN PK parameters were determined with non-compartmental analysis. Geometric least-squares mean ratios (GMRs) and 90% confidence intervals (CIs) were generated by the mixed-effected model for within-subject treatment comparisons. Safety assessments were performed throughout the study.

Results: Eighteen subjects were enrolled and 15 completed the study. RIF significantly reduced PTN exposure: GMRs (90 % CI) for PTN + RIF versus PTN alone were 0.04 (0.034,0.049), 0.04 (0.037,0.054), and 0.11 (0.09,0.124) for area under the curve from time zero to time of last quantifiable concentration (AUC_{0-t}), area under the curve from time zero to infinity ($AUC_{0-\infty}$), and maximum observed plasma concentration(C_{max}), respectively. PTN alone and co-administered with RIF was well tolerated.

Conclusion: Concurrent administration of PTN and RIF was associated with significantly decreased systemic exposure to PTN. The findings suggest that concomitant strong CYP3A4 inducers should be avoided during PTN treatment. Concurrent administration of PTN and RIF was well tolerated.

Introduction

Pyrotinib maleate (PTN, Jiangsu Hengrui Pharmaceuticals Co., Ltd.) is a novel irreversible EGFR/HER2 dual tyrosine kinase inhibitor that is used to treat HER2-positive breast cancer[1], which has been approved by National Medical Products Administration (NMPA) to reach the market because of the remarkable result of the phase II study[2–4]. The mechanism of action of PTN is similar to that of neratinib, but it was found that PTN has better intestinal absorption due to its higher plasma exposure level[5].

PTN is slowly absorbed and widely distributed. The main advantage of PTN is that it irreversibly binds to the site of action with a stable effect. PTN is well tolerated as an oral drug with a small molecular property that enhances the ability to penetrate the blood-brain barrier[5].

Phenotyping experiments demonstrated that CYP3A4 is the most active enzyme responsible for the biotransformation of PTN[6]. Clinically, PTN is likely to be used in combination with other drugs for the treatment of breast cancer or complications[7]. If the drug used in combination is an inducer of CYP3A4 metabolic enzyme, it may reduce the exposure of PTN and affect the anti-tumor effect of PTN.

Rifampicin (RIF), a bactericidal antibiotic drug, is a strong inducer of CYP3A4 isozyme and has been reported to reduce the plasma concentrations of several CYP3A4 substrates, which commonly used as a prototype drugs for evaluating drug interactions involving CYP3A4 induction mechanism[8–11].

The purpose of this study was to evaluate the effect of RIF on the PK profile and safety of oral PTN tablets in healthy Chinese subjects. Furthermore, it provides a reference and basis for dose adjustment of the concurrent administration of PTN and RIF, or other CYP3A4 inducer.

Materials And Methods

Study design

This was a phase I, single-site, open-label, fixed-sequence, crossover study with three treatment periods to evaluate the effect of an oral tablet of PTN on the steady-state PK of orally administrated RIF in 18 healthy subjects. The study was conducted in accordance with the principles of the Declaration of Helsinki. A written informed consent was obtained from every subject. The study protocol was reviewed and approved by an independent Medical Ethics Committee.

All participants received a single 400 mg dose of PTN in the morning on days 1 and 13(Fig. 1). Subjects received RIF 600 mg once daily on days 6-16. PTN 400 mg once daily was co-administrated with RIF 600 mg once daily on day 13. RIF was administrated on an empty stomach, then subjects had a standard meal one hour after RIF administration. PTN were administrated orally in the morning 30 min after the start of the standard meal.

Serial blood samples for determining the plasma concentration of PTN were collected on days 1 and 13 at the following times: pre-dose, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 24 h, 48 h, 72 h, 96 h post-dose.

All blood samples were collected into evacuated heparin lithium anticoagulant tubes. Plasma was separated by centrifugation at around 2500 × g for 10 min at 25±5℃, and the blood sample could be placed at room temperature no longer than one hour. The separated plasma sample should be transferred to -70℃(-60℃~-90℃)freezer, where it was stored until it was shipped for analysis.

Study Subjects

Each subject was evaluated with physical examination, medical history, and laboratory testing at a screening visit conducted within 14 days prior to the first dose of drug. Eligible subjects were 18 to 45 years of age, had a minimum weight requirement of 45 kg for women and 50 kg for men, and a body mass index requirement between 19 and 24 kg/m^2. Key exclusion criteria included history or presence of clinically significant medical, psychiatric disorder; concomitant chronic or acute illness; history or presence of drug addiction or excessive use of alcohol or tobacco; previous drug allergy. Participants whose QT interval longer than 470 msec corrected by Fridericia on 12-lead electrocardiogram were also

excluded from the study. Participants were also excluded from the study if they had taken any drug in the past 14 days or any drugs that alter the activity of liver enzyme in the past 28 days. Subjects were required to have negative screening results for HIV-1, hepatitis B, hepatitis C, and syphilis. Concomitant medication was not permitted during the study except for dealing with adverse events or treating emergencies.

Safety Evaluations

Safety evaluations included the monitoring of adverse events (AEs), physical examinations, clinical chemistry laboratory tests, vital signs, and electrocardiograms. Treatment-emergent adverse events (TEAEs) were recorded throughout the study.

Bioanalytical Methods

Plasma samples were analyzed for PTN by a validated high-performance liquid chromatography tandem mass spectrometry analysis. The LLOQ (lower limit of quantification) for PTN in plasma was 1.00 ng/mL, and the upper limit of quantification was 500 ng/mL. Precision and accuracy were evaluated by replicate analyses of human plasma quality control samples prepared at five concentrations: 1.00, 3.00, 25.0, 400, and 500 ng/mL. Precision, measured as the percent coefficient of variation, the maximum of which is 5.9% across the quality control range. Accuracy, expressed as the percent difference from the mean value, ranged from -2.3 to 5.7%. Both were within acceptance standards of 15%, except that 20% for LLOQ.

Pharmacokinetic Analysis

A non-compartmental PK analysis of the PTN concentration-time data was conducted. PK analyses of plasma PTN concentration-time data were analyzed by Phoenix WinNonlin 8.1. Plasma PK parameters for PTN were calculated using actual elapsed times from dosing. The individual PK parameters that were determined included maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the curve from time zero to the last quantifiable concentration (AUC_{0-t}), area under the curve from time zero to the infinite concentration ($AUC_{0-\infty}$), elimination half-life ($t_{1/2}$), apparent volume of distribution (V_Z/F), apparent clearance(CL/F).

Statistical analysis

This study was designed to estimate the magnitude of drug-interaction effect of RIF on the PK parameters of PTN. PK parameters were log-transformed and analyzed by analysis of variance to determine the point estimate and associated 90% confidence intervals for the difference between test treatment (PTN + RIF) and reference treatment (RIF alone). These values were then back-transformed to calculate the point and interval estimates for test-to-reference treatment ratios on the original scale.

Geometric least-squares mean ratios and 90% confidence intervals were generated by the mixed-effect model for within-subject treatment comparisons.

Results

Demographics

Eighteen subjects, 6 females and 12 males, were enrolled and included in the safety and PK populations. Two male subjects were prematurely discontinued from the study. The two subjects withdrew due to drug induced liver damage on period 3, days 13 (PTN + RIF), with increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level, whose severity both were level 1.

The mean (±standard deviation (SD)) age was 29.1 (±6.7) years and ranged between 19 and 43 years. The mean (±SD) body mass index was 21.94 (±1.35) kg/m^2, height was 165.61 (±8.42) cm, and weight was 60.37 (±7.67) kg. One subjects (5.6%) was minority, and other seventeen subjects (94.4%) were Han.

Safety

A total of 96 treatment emergent adverse events (TEAE) were reported in 18 (100%) of the 18 treated subjects (Table 1). Of these, Three subjects (16.7%) experienced 5 adverse events (AEs) during period 1 (PTN alone). Eighteen subjects (100%) experienced 41 AEs during period 2 (RIF alone). Eighteen subjects (100%) experienced 50 AEs during period 3 (PTN + RIF).

Seven subjects (38.89%) experienced adverse reactions to PTN and 18 (100%) subjects experienced adverse reactions to RIF. All the severity of adverse events is level 1, No serious adverse events or non-fatal serious AEs occurred through the study. Two subjects (11.1%) experienced AEs leading to withdrawal from the trial, which may not be related to PTN, but may be related to RIF.

AEs with an incidence of ≥10% included chromaturia (100%), discoloration stool (100%), leukocyte count decreased (22.22%), ALT increased (22.22%), neukocyte count decreased (22.22%), increased AST level (16.67%), blood triglycerides increased (11.11%) and headache (11.11%). All adverse events are attributed to recovery/resolution.

Table 1
Summary of drug-related adverse events by treatment

	PTN alone (N=18)		RIF alone (N=18)		PTN + RIF (N=18)	
	No.of Subjects	No.of Events	No.of Subjects	No.of Events	No.of Subjects	No.of Events
Any TEAE	3(16.7%)	5	18(100%)	41	18(100%)	50
Kidney and urinary system disorders	0	0	18(100%)	21	18(100%)	27
Urine discoloration	0	0	18(100%)	21	18(100%)	27
Gastrointestinal disorders	0	0	18(100%)	18	1(5.6%)	2
Stool discoloration	0	0	18(100%)	18	0	0
Nausea	0	0	0	0	1(5.6%)	1
Vomiting	0	0	0	0	1(5.6%)	1
Various investigations	3(16.7%)	5	1(5.6%)	2	7(38.9%)	18
white blood cell decreased	0	0	0	0	4(22.2%)	4
ALT increased	1(5.6%)	1	0	0	3(16.7%)	3
Neutrophil count decreased	0	0	0	0	4(22.2%)	4
AST increased	0	0	0	0	3(16.7%)	3
Blood triglycerides increased	2(11.1%)	2	0	0	0	0
Urine leucocyte positive	1(5.6%)	1	0	0	0	0
Bilirubin urine present	0	0	1(5.6%)	1	0	0
Protein urine present	0	0	0	0	1(5.6%)	1
Urobilinogen urine increased	0	0	1(5.6%)	1	0	0
Basophil leukocyte increased	0	0	0	0	1(5.6%)	1
Systolic pressure increased	1(5.6%)	1	0	0	0	0
Diastolic pressure decreased	0	0	0	0	1(5.6%)	1
Blood cholesterol increased	0	0	0	0	1(5.6%)	1

	PTN alone (N=18)		RIF alone (N=18)		PTN + RIF (N=18)	
Various nervous system disorders	0	0	0	0	3(16.7%)	3
Headache	0	0	0	0	2(11.1%)	2
Dizziness	0	0	0	0	1(5.6%)	1

Pharmacokinetics

PK parameters of PTN with and without RIF and treatment comparisons are shown in Table 2, and the mean (SD) concentration time profiles are shown in Fig. 2. The geometric mean AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, of PTN were reduced by 96%, 96%, and 89%, respectively, when PTN was co-administered with RIF. PTN clearance was apparently increased, and its half-life shortened from 15.725 h to 6.261 h when co-administered with RIF.

Table 2
Summary and statistical comparison of plasma PTN with and without RIF

PK parameter	Geometric mean		Ratio of GLS means (90% CI)
	PTN alone (N=18)	PTN+RIF (N=18)	PTN+RIF vs PTN alone
AUC_{0-t} (h*ng/mL)	2616.69	106.74	0.04(0.034,0.069)
$AUC_{0-\infty}$ (h*ng/mL)	2792.03	125.19	0.04(0.037,0.054)
C_{max} (ng/mL)	159.69	16.85	0.11(0.09,0.124)

Discussion

RIF is a strong inducer of CYP3A4 and has been shown to decrease plasma concentrations of a number of drugs. This study demonstrated that repeated dosing of RIF for 11 days resulted in significant reductions of 96, 96 and 89% in AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, respectively, of PTN.

PTN is primarily metabolized to produce O-despicoline (M1), carbonylation M1 (M2), dehydro-pyrrolidine (M5-1), carbonyl-N-methyl Pyrrolidine (M7) and hydroxymethylpyrrolidine (M8-1) and double oxidation and dehydrogenation metabolites (M9) by CYP3A4[6]. Therefore, the increased PTN clearance observed in this study is likely a result of CYP3A4 induction by RIF. It has been reported that full induction is reached 1 week after starting RIF, so the drug-drug interaction was evaluated after 11 days of RIF administration to ensure full inhibition. The dose of RIF is set as 600 mg qd according to regulatory guidance generally recommends in the evaluation of a drug as a perpetrator of drug interaction[8–11].

Compared with lapatinib, PTN has a more comprehensive target, and its inhibitory effect on the target is irreversible, thereby inhibiting tumor growth more effectively; compared with neratinib, PTN has a higher bioavailability[3–5]. Therefore, PTN occupies a higher position in the molecular targeted therapy of breast cancer. The current phase I and phase II clinical studies have confirmed its good pharmacokinetics and safety. For the moment, phase III clinical studies are being actively carried out to extend indications of PTN as well as combination regimens.

The study has several limitations. First, it was conducted in a small number of healthy volunteers. Therefore, the results might not directly apply to a larger population or to special population groups. Second, the effect of CYP3A genetic polymorphisms in the subjects was not considered in the study. Genetic polymorphisms of CYP3A may contribute to the disposition of PTN. Further research is need to investigate the contribution of such CYP3A genetic polymorphisms to drug-drug interaction with PTN.

Conclusions

This study evaluated the magnitude of a drug-drug interaction between RIF, a known strong inducer of CYP3A4, and PTN, a known substrate of CYP3A4. As expected, co-administration of RIF and PTN in healthy subjects resulted in a potentially clinically significant decrease in PTN AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} compared with PTN administered alone. Based on PK data regarding strong CYP3A4 inducer should be avoided during PTN treatment.

Declarations

Ethics approval and consent to participate All procedures performed in the study involving human participants were conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Consent for publication Consent of publication was obtained from all authors.

Availability of data and materials All data generated or analysed during this study are included in this published article.

Competing interests The author reports no conflicts of interest in this work.

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Analyzed Data: Ming-min Cai, Zi-hong Zhai.

Wrote Manuscript: Ming-min Cai, Wei Qian.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest The author reports no conflicts of interest in this work.

Research involving Human Participants and/or Animals The phase I clinical trial was approved by Ethics Committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Figures

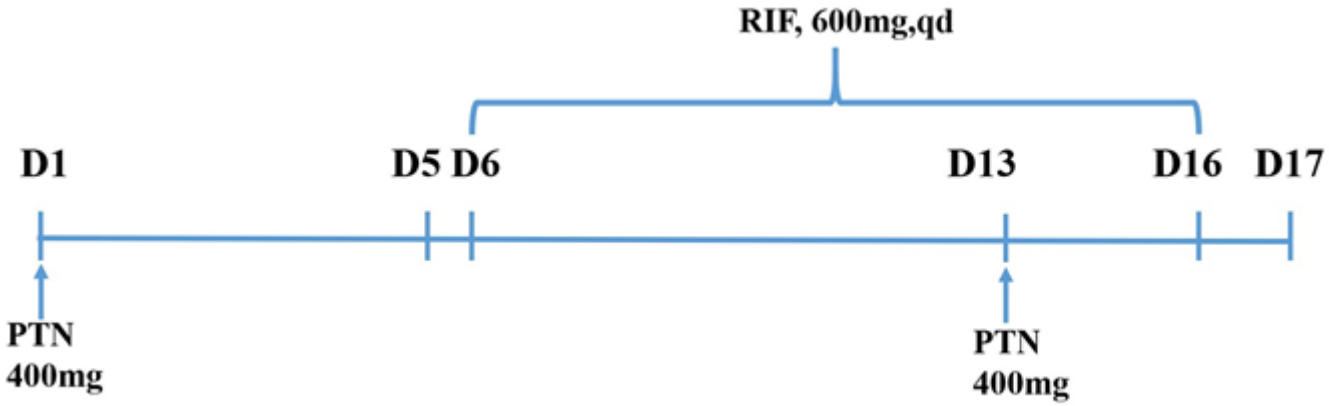

Figure 1

Study design

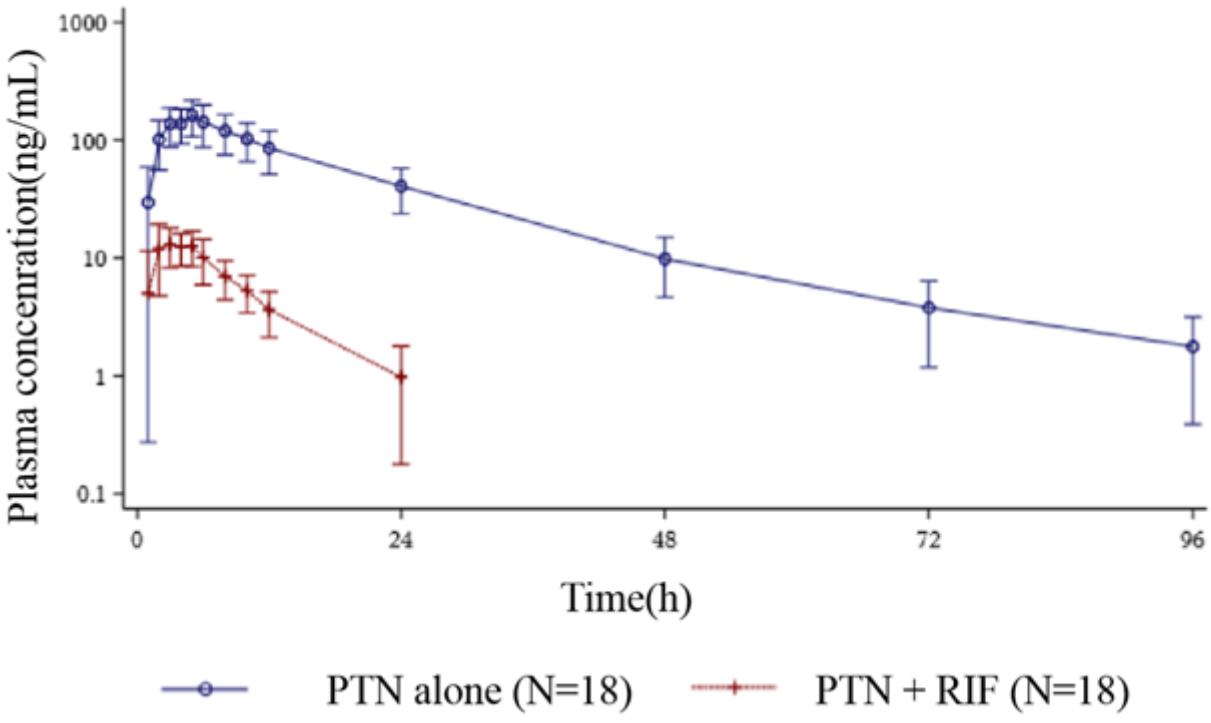

Figure 2

Mean±SD concentration-time profile for PTN with and without concomitant administration of RIF