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Pharmacokinetic and safety profile of raltegravir and ribavirin, when dosed separately and together, in healthy volunteers

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Background: Treatment of chronic hepatitis C virus (HCV) infection in HIV-1-co-infected individuals remains challenging due to numerous factors, including drug–drug interactions. The aim of this study was to assess the safety and pharmacokinetic (PK) profile of raltegravir and ribavirin when dosed separately and together.

Methods: Fourteen healthy volunteers [mean (standard deviation) age 35 (10) years, 71% male] entered this phase 1 PK study and received single-dose ribavirin (800 mg) on day 1 (phase 1). Following a washout period, subjects received raltegravir (400 mg twice daily) on days 15–19 (phase 2) and single-dose ribavirin (800 mg) with raltegravir (400 mg) on day 20 (phase 3). Intensive PK sampling was undertaken on days 1, 19 and 20 and differences in geometric mean ratios (GMRs) for PK parameters between study periods were assessed.

Results: No statistically significant differences in PK parameters were observed for raltegravir between phases 2 and 3. A statistically significant decrease in maximum plasma concentration (C_{max}) and an increase in time to maximum plasma concentration (T_{max}) were observed for ribavirin in phase 3 compared with phase 1 [GMR (95% confidence interval) 0.79 (0.62–1.00) and 1.39 (1.08–1.78), respectively], whereas no significant differences in other ribavirin PK parameters were observed between study phases. No clinically significant safety concerns were reported.

Conclusions: The PK profile of ribavirin is altered when administered with raltegravir (reduced C_{max} and increased T_{max}), with no safety concerns identified. This is unlikely to be of clinical significance or have an impact on the antiviral effects of ribavirin in HIV-1- and HCV-co-infected subjects.

Keywords: PK, antivirals, HCV, HIV

Introduction

The treatment of acute and chronic hepatitis C virus (HCV) infection in HIV-1-co-infected individuals remains a major clinical challenge.[1] In Europe, the prevalence of HCV co-infection in HIV-infected subjects is high, with estimated rates of around 40%, and increasing in recent years.

Challenges include overlapping drug toxicities and drug–drug interactions between antiretroviral agents and those used to treat HCV infection, such as ribavirin.[1] For instance, many of the nucleoside reverse transcriptase inhibitors (NRTIs), the backbone of modern combination antiretroviral regimens,[2] cannot be co-administered with ribavirin, including zidovudine, due to high rates of anaemia,[3,4] and didanosine, due to reports of fatal hepatic failure.[4] Furthermore, recent studies have highlighted suboptimal HCV treatment responses when ribavirin is co-administered with the NRTI abacavir.[5] It has been postulated that poor treatment responses may be due to both of these agents being guanosine analogues, thereby competing for the same intracellular phosphorylation pathway, resulting in an unfavourable pharmacodynamic relationship.

Knowledge regarding the drug–drug interactions between new antiretroviral agents and ribavirin are therefore urgently needed. Raltegravir, a newly licensed HIV-1 integrase inhibitor, is primarily metabolized by glucuronidation and has no known inhibitory or inductive potential against the major cytochrome

P450 (CYP450) iso-enzymes.[6] Since ribavirin undergoes intracellular phosphorylation and does not undergo any hepatic or renal elimination, no drug–drug interaction between raltegravir and ribavirin would be expected. However, frequently in clinical practice, unforeseen and unexpected pharmacokinetic (PK) interactions are observed. For instance, when raltegravir is dosed with rifampicin, a potent inducer of CYP450 and glucuronyl transferase enzymes, a reduction in raltegravir plasma concentration has been reported[7] and, conversely, an increase in raltegravir plasma concentration has been observed when raltegravir is administered with the proton-pump-inhibitor omeprazole.[8]

Ribavirin, a synthetic nucleoside analogue, is rapidly absorbed after oral administration, with a bioavailability of approximately 50%.[9] Responses to antiviral therapy for chronic HCV infection are poorer in HIV-1-co-infected subjects compared with those with HCV mono-infection,[1] and adequate exposure to ribavirin may be crucial to maximize treatment responses.[10] The recommended dose of ribavirin is 1000 mg/day if <75 kg and 1200 mg/day if >75 kg, in divided doses.[1] The primary clinical toxicity of ribavirin is haemolytic anaemia. Furthermore, depression, autoimmune disorders and pancreatitis have been reported to occur with ribavirin, and significant teratogenic effects have been demonstrated in animal species exposed to ribavirin. Ribavirin has a multiple dose half-life of 12 days, and it may persist in the non-plasma compartments for as long as 6 months; therefore, pregnancy should be avoided for 6 months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy.

In view of these effects, the design of PK studies administering ribavirin to healthy volunteers is complex. One option is to administer a single dose of ribavirin, and previous PK studies in the field have utilized single-dose ribavirin 800 mg when assessing interactions with other antiretroviral agents.[11]

The aim of this study was to assess the safety and PK profile of raltegravir 400 mg twice daily when dosed with and without single-dose ribavirin 800 mg in healthy male and female volunteers.

Methods

Subject selection

In healthy male and female volunteers, we assessed the safety and PK profile of raltegravir 400 mg twice daily [Isentress® (Merck Sharp & Dohme Limited) 400 mg tablets] when dosed with and without single-dose ribavirin 800 mg [Copegus® (Roche) 200 mg tablets] in a three-phase, open-label, phase I, prospective PK study.

The study was conducted at St Mary's Hospital, London, UK, between September and November 2009. Healthy male and non-pregnant, non-lactating female adult subjects between 18 and 60 years old inclusive were eligible to participate. All subjects met the study inclusion criteria within 21 days prior to dosing, which included providing written informed consent, having a body mass index (BMI) <32 and having a negative urine pregnancy test for female participants.

Furthermore, all participants were serology negative for HIV infection, active hepatitis B virus infection (hepatitis B surface antigen) and HCV infection (hepatitis C antibody) and had screening laboratory results that fell within the normal range. Exclusion criteria included any clinically relevant alcohol or drug use [positive screening urine drug screen (INSTA-LERT®, Innovacon, San Diego, CA, USA)] or concomitant medication within 21 days of commencing study drug dosing, with the exception of vitamins, paracetamol or oral hormonal contraceptives.

This study was registered on the European Clinical Trials Database (EudraCT number 2009-010005-36), an international clinical trials database (http://clinicaltrials.gov/ct2/show/NCT00982553?term=raltegravir%2C+ribavirin&rank=1), and local ethical approval was obtained prior to recruiting participants.

Study procedures and selection of drug dosage

During phase 1 (days 1–14) a single witnessed dose of ribavirin (800 mg) was administered on day 1, followed by a washout period (days 2–14). This was followed by the administration of raltegravir (400 mg twice daily) for 4 consecutive days during phase 2 (days 15–19). Finally, immediately following this study phase, a single dose of ribavirin (800 mg) was given with raltegravir (400 mg) in phase 3 (day 20) (Figure 1).

Witnessed dosing was undertaken on days 1, 15, 19 and 20 and adherence on other dosing days was assessed at subsequent visits via pill counts. Laboratory safety parameters and direct questioning by trained study staff to determine clinical safety were assessed at screening and days 1, 12–14, 15, 19 and 20. Finally, in view of the teratogenic effects of ribavirin, a final safety follow-up visit was conducted between days 25 and 35 to assess laboratory safety parameters and clinical safety via direct subject questioning, and a urine pregnancy test was administered in female subjects to ensure this remained negative.

PK sampling

Intensive PK sampling was performed on days 1 (single-dose ribavirin), 19 (steady-state raltegravir) and 20 (raltegravir steady-state, plus single-dose ribavirin). Subjects had fasted for >12 h prior to dosing on intensive PK study days. Plasma samples for PK analysis were taken at 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h post-dose. Plasma concentrations of raltegravir were determined using a validated HPLC tandem mass spectrometry method.[12] The lower limit of quantification (LOQ; defined as the lowest concentration of standard used to determine the analyte in this study) was 5 ng/mL. Plasma concentrations of ribavirin were determined by a HPLC-UV method.[13] The LOQ was 78 ng/mL. Intra- and inter-assay variability was <10% for each analyte. Both laboratories participate in an external quality control programme for antiretrovirals (KKGT, The Netherlands), although currently this does not include ribavirin.

Statistical analysis

PK parameters calculated for ribavirin and raltegravir were the maximum observed plasma concentration (C_{max}); the time to maximum observed plasma concentration (T_{max}); the area under the plasma concentration–time curve from 0–12 h (AUC_{0-12}); the trough plasma concentration (C_{min}), defined as the concentration at 12 h after the observed dose; and the elimination half-life ($t_{1/2}$). Where a drug concentration was below the lower limit of quantification (LLQ), the value used for analysis was the LLQ/2. PK parameters were calculated using non-compartmental modelling techniques (WinNolin; Pharsight Corporation, Mountain View, CA, USA).

All statistical calculations were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Geometric mean ratios (GMRs) and 95% confidence intervals (CIs) were calculated to evaluate within-patient changes for PK parameters from phase 1 to phase 3 and phase 2 to phase 3 for ribavirin and raltegravir, respectively. Changes in PK parameters were considered statistically significant when the 95% CIs did not cross 1. Inter-patient variability was expressed as a coefficient of variation [CV; (SD/mean)×100].

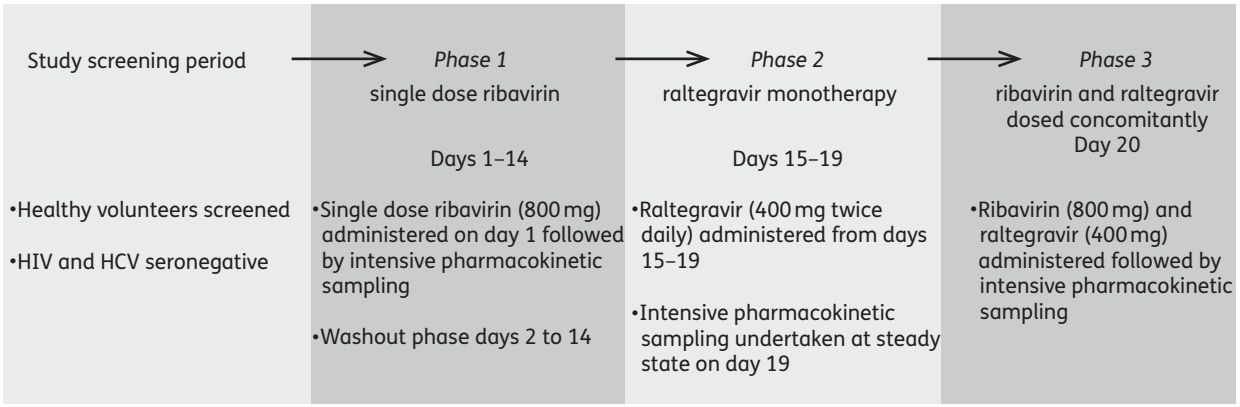

Figure 1. Study flow diagram.

Table 1. Subject baseline characteristics

Characteristic	Value
Number of participants	14
Mean age, years (±SD)	35 (10)
Gender (male), *n* (%)	10 (71)
Mean weight, kg (±SD)	76 (12)
Mean BMI (±SD)	25 (3.7)
Current smoker, *n* (%)	4 (29)
Ethnicity, *n* (%)	
white	11 (79)
black	1 (7)
other	2 (14)

Associations between raltegravir PK parameters and patient characteristics (age, gender, ethnicity, BMI and smoking status) were investigated using linear regression modelling.

Results

Patient characteristics and follow-up

Of 18 subjects screened, 14 completed the study procedures. Three subjects failed the study screening procedures and one subject dropped out after the first PK visit. Patient characteristics are shown in Table 1. Study medication was generally well tolerated and there were no discontinuations due to toxicity. In total, 33 adverse events occurred during the study period, none of which was considered to be of clinical relevance. No clinically significant or grade 3 or 4 laboratory adverse events were observed. All participants reported 100% adherence to the investigational medication during the study period.

PK parameters

PK parameters for all study phases are shown in Tables 2 and 3. No statistically significant changes were observed in raltegravir PK parameters between phase 2 and phase 3 (Table 2). Interestingly, a statistically significant decrease in C_{max} and an increase in T_{max} was observed for ribavirin in phase 3 compared with phase 1 [GMR (95% CI) 0.79 (0.62–1.00) and 1.39 (1.08–1.78), respectively], whereas no significant differences in other ribavirin PK parameters were observed between study phases, including AUC_{0-12} or C_{min} (Table 3 and Figure 2).

The inter-patient variability in plasma exposure to ribavirin was low and unchanged by the addition of raltegravir, as evidenced by the low CV for all the PK parameters measured, whereas the inter-patient variability of raltegravir was high, particularly for T_{max} and C_{min}, and remained so after the addition of ribavirin.

Factors associated with ribavirin/raltegravir plasma exposure

There were no statistically significant associations observed between raltegravir exposure and age, gender, ethnicity, weight or BMI ($P > 0.20$ for all observations).

Discussion

The management of HIV and HCV co-infection remains a major clinical challenge, and novel agents to treat such co-infected patients are urgently needed. In this proof-of-concept trial, no unexpected safety concerns were observed when administering single-dose ribavirin with raltegravir, providing reassuring data on the use of raltegravir, a recently licensed antiretroviral agent, with ribavirin, used as standard antiviral therapy for HCV infection.

We observed a statistically significant increase in ribavirin T_{max} and reduced C_{max} when dosed with raltegravir compared with when dosed alone, while the AUC_{0-12}, $t_{1/2}$ and C_{min} remained unchanged. Although the underlying mechanism for this interaction is unclear, by virtue of the PK changes, a longer absorption phase may be postulated. This effect of raltegravir on ribavirin is unexpected. Ribavirin is absorbed from the proximal small bowel via concentrative N1 sodium-dependent nucleoside transporters. In contrast, while raltegravir is a weak substrate for OAT1 and PEPT1,[14] it is more likely affected by the gastric environment and factors such as food and changes in gastric pH;[15,16] hence an interaction would not be predicted.

Table 2. Pharmacokinetic parameter results for ribavirin ($n=14$)

	Phase 1, ribavirin alone		Phase 3, ribavirin with raltegravir		
	mean (95% CI)	CV (%)	mean (95% CI)	CV (%)	GMR (95% CI)
$t_{1/2}$, h	6.04 (5.29–6.90)	22	6.77 (5.56–8.25)	41	1.12 (0.86–1.46)
T_{max}, h	1.61 (1.12–2.11)	35	2.23 (1.65–3.01)	46	**1.39** (1.08–1.78)
C_{max}, ng/mL	630.09 (490.91–808.54)	40	496.71 (407.38–605.76)	37	**0.79** (0.62–1.00)
C_{min}, ng/mL	184.71 (148.59–229.61)	36	186.98 (157.83–221.56)	35	1.01 (0.87–1.18)
AUC_{0-12}	3325.83 (2703.34–4091.66)	36	2941.03 (2323.27–3722.20)	43	0.88 (0.73–1.07)

CI, confidence interval; CV, coefficient of variation; GMR, geometric mean ratio; AUC_{0-12}, area under the concentration–time curve over 12 h; C_{min}, minimum plasma concentration; C_{max}, maximum observed plasma concentration; $t_{1/2}$, elimination half-life; T_{max}, time to maximum observed concentration.
GMRs shown in bold are those with 95% CIs that do not cross 1.

Table 3. Pharmacokinetic parameter results for raltegravir ($n=14$)

	Phase 2, raltegravir alone		Phase 3, raltegravir with ribavirin		
	mean (95% CI)	CV (%)	mean (95% CI)	CV (%)	GMR (95% CI)
$t_{1/2}$, h	2.99 (2.11–4.23)[a]	64	2.40 (1.58–3.63)[b]	133	0.85 (0.43–1.68)[b]
T_{max}, h	1.51 (0.77–2.96)	117	1.60 (1.02–2.52)	108	1.06 (0.49–2.32)
C_{max}, ng/mL	2227.41 (1489.36–3331.19)	48	2591.19 (1778.28–3774.85)	49	1.16 (0.73–1.86)
C_{min}, ng/mL	83.97 (45.64–154.45)	217	68.91 (40.74–116.55)	149	0.82 (0.36–1.85)
AUC_{0-12}	7737.49 (5619.53–10653.69)	45	8647.69 (6150.35–12159.06)	48	1.12 (0.74–1.70)

CI, confidence interval; CV, coefficient of variation; GMR, geometric mean ratio; AUC_{0-12}, area under the concentration–time curve over 12 h; C_{min}, minimum plasma concentration; C_{max}, maximum observed plasma concentration; $t_{1/2}$, elimination half-life; T_{max}, time to maximum observed concentration.
[a]$n=13$ (subject excluded due to data not fitting non-compartmental modelling techniques).
[b]$n=12$ (subjects excluded due to data not fitting non-compartmental modelling techniques).

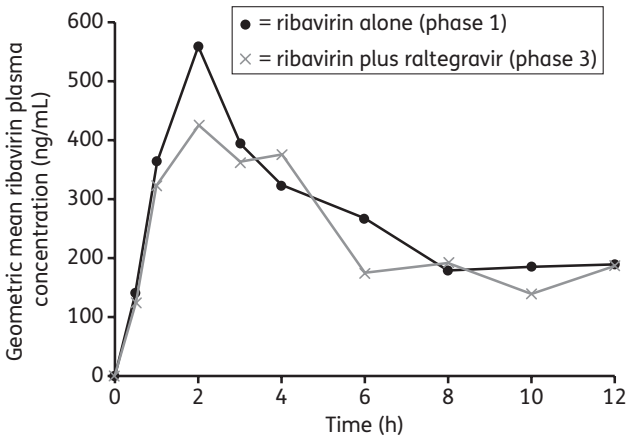

Figure 2. Pharmacokinetic curves of ribavirin in phase 1 (dosed alone) versus phase 3 (dosed with raltegravir) ($n=14$).

In our study, we administered a single dose of ribavirin on two occasions (in phase 1 and in phase 3), which does not mirror clinical practice, where ribavirin would be dosed once or twice daily for several months to years. Due to the known teratogenic effects of ribavirin, we considered this the safest approach to take in a phase 1 study in order to minimize exposure in otherwise healthy adults, and such an approach has been utilized in other PK studies in the field.[11] The extrapolation and relevance of such findings into clinical practice, where steady-state ribavirin PKs are not observed until 4–12 weeks, must be taken with caution. However, in contrast, ribavirin exposure after the first dose has been reported to be predictive of sustained virological response in chronic HCV in one study, supporting the clinical relevance of our findings.[17] Lastly, all investigational agents were administered in a fasted state in our study, which does not mirror clinical practice, where patients may prefer to take medication with food. As the PK profile of raltegravir is highly variable, and variability is increased in the fed state,[18] we chose the fasting approach in order to minimize this variability.

The predominant antiviral mechanism of action of ribavirin against HCV has yet to be elucidated and conflicting opinion exists regarding a correlation between ribavirin plasma concentration and HCV virological response, or the development of toxicity.[19,20] Several mechanisms have been suggested regarding the broad-spectrum antiviral activity of ribavirin, including direct inhibition of viral RNA replication, inhibition of the enzyme inosine monophosphate dehydrogenase (IMPDH),

immunomodulation and increased mutagenesis.[21–24] Therefore, extrapolations regarding the clinical significance of any changes in ribavirin plasma concentrations we have observed when co-administered with raltegravir must be interpreted with caution. Furthermore, the relationship between plasma ribavirin concentrations and biologically active intracellular triphosphorylated concentrations are unclear. One group reported the C_{min} of ribavirin to be significantly greater in subjects with a HCV sustained virological response compared with subjects not responding to therapy at weeks 4 and 12,[25] suggesting that antiviral efficacy is related, at least in part, to the minimum plasma exposure. We would therefore postulate that the HCV antiviral efficacy of ribavirin will not be affected by the reduction in ribavirin maximum plasma exposure we have reported in our study, as no effect on C_{min} was observed. Indeed, the PK interaction we have observed may confer a benefit to patients in terms of reducing the toxicity of ribavirin, such as anaemia, which may be related to maximum plasma exposure.

No statistically significant changes were observed in the PK parameters of raltegravir in our study. Prior work has suggested, based on clinical experience of raltegravir use in HIV-1-infected subjects, that a C_{min} decrease >60% may be considered clinically significant and affect short-term antiviral activity.[15] Our study provides reassuring PK data suggesting that this would not be the case in HIV-1-infected subjects receiving raltegravir and ribavirin. Interestingly, a recent report describing the use of raltegravir and ribavirin with pegylated interferon in a series of five HIV-1- and HCV-co-infected individuals[26] suggested that these agents are both well tolerated and virological efficacy is observed within the target population.

A high inter-patient variability of raltegravir PK parameters was observed, both when dosed alone and in combination with ribavirin, as previously described.[27] As there were no differences in the CV of raltegravir between study phases 2 and 3, ribavirin does not appear to have an effect on the degree of variability.

Our study was undertaken in healthy volunteers, limiting our interpretation due to differences in the handling of drugs that may be observed in HIV-1- or HCV-infected subjects. Additionally, the effects of other concurrent antiretrovirals as well as pegylated interferon, given as standard care in treating HIV-1- and HCV-co-infected patients,[25] may further affect PK parameters of ribavirin and raltegravir in the target population. However, this proof-of-concept study does provide early data to support the use of raltegravir and ribavirin when dosed in combination for the management of HCV and HIV-1 co-infected subjects.

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