Effect of intermittent rifampicin on the pharmacokinetics and safety of raltegravir

Helen E. Reynolds1, Ales Chrđle1, Deirdre Egan2, Mas Chaponda1, Laura Else2, Justin Chiong2, David J. Back2 and Saye H. Khoo1,2*

1Royal Liverpool & Broadgreen University Hospitals NHS Trust, Prescot Street, Liverpool, UK; 2Institute of Translational Medicine, University of Liverpool, Liverpool, UK

*Corresponding author. Department of Pharmacology and Therapeutics, University of Liverpool, 70 Pembroke Place, Liverpool L69 3GF, UK. Tel: +44-151-794-5560; Fax: +44-151-706-4365; E-mail: khoo@liv.ac.uk

Received 19 June 2014; returned 21 July 2014; revised 21 August 2014; accepted 22 August 2014

Objectives: Previous studies of raltegravir and rifampicin have not studied the interaction when rifampicin is dosed intermittently. This study aimed to assess the pharmacokinetics of twice daily raltegravir and intermittently dosed rifampicin.

Methods: This was a prospective, open, single-arm, three-part, controlled study in healthy volunteers. Over a period of 38 days subjects received 5 days of standard-dose raltegravir (400 mg twice daily) followed by 28 days of standard-dose raltegravir plus rifampicin three times a week followed by 5 days of high-dose (800 mg twice daily) raltegravir plus rifampicin three times a week. Pharmacokinetic sampling was performed on days 5, 33 and 38. Raltegravir pharmacokinetic parameters were determined by non-compartmental analysis and reported as geometric means and 90% CIs. ClinicalTrials.gov: NCT01424826.

Results: Sixteen subjects (12 females) completed the study. Raltegravir trough plasma concentration (C12) was significantly lower in the presence of rifampicin when dosed at 400 mg twice daily (40%), which was not observed with 800 mg twice daily dosing. Raltegravir Cmax and AUC0–12 were both significantly higher in the presence of rifampicin when dosed at 800 mg twice daily (76% and 84%, respectively), but this dose was well tolerated.

Conclusions: This study suggests that rifampicin induction of raltegravir is comparable between daily and intermittent rifampicin. In the absence of definitive clinical efficacy data to suggest otherwise, doses of 800 mg of raltegravir twice daily with rifampicin thrice weekly are well tolerated and yield higher AUCs and comparable C12 when compared with raltegravir alone.

Keywords: PK, TB, HIV

Introduction

The overlap between the HIV and TB epidemics makes coinfection with both diseases common, particularly in resource-poor settings where HIV infection in adults commonly presents as newly diagnosed TB. Rifampicin is the mainstay of modern short-course TB regimens. Given its potent induction of hepatic and intestinal cytochrome P450 enzymes, management of HIV and TB coinfection is complex. Studies have confirmed the need to treat both infections concurrently1,2 with ART commenced as early as possible into TB therapy in patients with very low CD4 cell counts.

Drug interactions between rifampicin and first-line efavirenz-containing regimens are complex and may vary according to host genetic polymorphisms in cytochrome P450 CYP2B6 (the main isoform responsible for efavirenz detoxification).3 Given the rising prevalence of drug resistance to NNRTIs4 and the magnitude of drug interactions involving HIV PIs,5 alternative effective antiretroviral regimens are a public health priority in coinfected patients.

The integrase strand-transfer inhibitor raltegravir is an alternative for patients receiving rifampicin who are intolerant of or have resistance to NNRTIs.6 One previous study reported a reduction in raltegravir exposure (AUC) of 40% with daily rifampicin6 in healthy volunteers. The impact of this interaction is modest compared with that observed with HIV PIs, particularly in view of Phase 2 dose-escalation data reporting no apparent diminution in short-term virological efficacy of raltegravir at lower doses than currently licensed for use—thus, this interaction is considered to be manageable with or without dose escalation of raltegravir.
Data from the QDMRK trial suggest that the efficacy of raltegravir is related to $C_{\text{trough}}$, and since trough concentrations of raltegravir were reduced by 61% with daily rifampicin, treatment guidelines recommend that clinicians consider doubling the dose of raltegravir when co-administered with rifampicin in order to prevent the development of drug resistance.

In many parts of the world TB therapy is administered through directly observed treatment (DOTS), with rifampicin given either daily or thrice weekly. Although daily rifampicin fixed-dose regimens are preferred, intermittent thrice weekly rifampicin is frequently deployed within DOTS programmes as a recommended alternative. Previous studies of raltegravir with rifampicin have not characterized the interaction with intermittent dosing of rifampicin three times a week. For intermittent rifampicin regimens, the optimal dosing of raltegravir is unknown. Since the evidence base has largely been absent, an implicit assumption has been applied to directly extrapolate data from daily rifampicin studies. This approach may not be justified for a number of reasons. Rifampicin induction of hepatic metabolism is mediated by the nuclear receptor PXR. Dose-dependent induction of PXR by rifampicin has been observed in vitro. Both the onset and the offset of rifampicin induction may therefore differ between daily and intermittent rifampicin regimens. In intermittent dosing, the relatively short plasma half-life of rifampicin yields significantly different plasma exposures when compared with continuous daily dosing. This differential exposure may be relevant for the induction of certain hepatic enzymes, such as CYP3A4, which has a turnover of around 2 days. Raltegravir is mainly metabolized through glucuronidation, which is also induced by rifampicin (albeit to a lesser extent than CYP3A4). In this study, we sought to characterize the interaction between thrice weekly rifampicin and twice daily raltegravir in healthy volunteers receiving standard-dose (400 mg twice daily) or high-dose (800 mg twice daily) raltegravir.

### Methods

This was a single-centre, open-label, single-arm, three-part, controlled study in 18 healthy volunteers, conducted at the Clinical Research Unit of the Royal Liverpool University Hospital, Liverpool, UK. Healthy male and non-pregnant, non-lactating female subjects >18 years of age were eligible. Exclusion criteria included: any significant acute or chronic medical illness; positive screen for HIV, hepatitis B, hepatitis C or TB; abnormal clinical laboratory determinations; and intake of disallowed concomitant therapies, including proton pump inhibitors. Subjects provided written informed consent prior to study enrolment. The trial was conducted following the good clinical practice guidelines and in accordance with the Declaration of Helsinki. The study was reviewed and gained regulatory (EudraCT 2010-021461-73) and ethics approval from the North West Ethics Committee (II/NW/0461) and was registered in ClinicalTrials.gov (NCT01424826). Based on the wide inter-individual variability (>60%) in raltegravir pharmacokinetic parameters, 18 subjects completing the study would provide at least 80% power at 5% significance to detect a 42% difference in raltegravir pharmacokinetic parameters with the addition of rifampicin.

Each subject received 5 days of standard-dose raltegravir (400 mg twice daily) followed by 28 days of standard-dose raltegravir plus rifampicin three times a week (for maximal enzyme induction to be achieved) followed by 5 days of high-dose (800 mg twice daily) raltegravir plus rifampicin three times a week. Rifaximin was dosed according to the subject’s weight. Subjects weighing <50 kg received 600 mg three times per week and subjects weighing ≥50 kg received 900 mg three times per week. Raltegravir pharmacokinetic sampling was performed over the raltegravir 12 h dosing period on days 5, 33 and 38. Subjects attended having fasted for 8 h and were water restricted for 1 h before and after the ingestion of raltegravir. Subjects remained fasted until after the 4 h sample was obtained. All subjects then received a standardized lunch. Samples for pharmacokinetic analysis were obtained at 0, 1, 2, 4, 6, 8, 10 and 12 h post-dose. Safety analysis was also performed on pharmacokinetic study days.

The primary objective of the study was to evaluate the pharmacokinetics of steady-state raltegravir following intermittent dosing of rifampicin in healthy volunteers. The secondary objectives were to evaluate the safety and tolerability of raltegravir and rifampicin, and adequate plasma concentrations of raltegravir.

The safety and tolerability of the study medication were assessed using clinical evaluation of vital signs and clinical laboratory investigations. Adverse events were graded using the Division of Aids Table for Grading the Severity of Adult and Pediatric Adverse Events (2004) and causality was assigned using an assessment tool. Safety data were reviewed by an Independent Data Safety and Monitoring Group.

Plasma concentrations of raltegravir were determined using extraction via protein precipitation of analyte and internal standard (quinoxaline) followed by reverse-phase HPLC and tandem MS as previously described. The lower limit of quantification was 5 ng/mL and the upper limit of quantification was 5000 ng/mL. The intra and inter-assay coefficients of variation (CVs) did not exceed 10% for each of the low, medium or high controls. The laboratory participates in an external quality assurance programme (KKGT, The Netherlands) and the assay was validated in accordance with FDA Bioanalytical Method Validation Guidelines.

The maximum ($C_{\text{max}}$) and trough ($C_{\text{trough}}$) raltegravir plasma concentrations were determined. The AUC for the raltegravir 12 h dosing period (AUC$_{12}$) was calculated using WinNonLin version 6.3 (Mountain View, CA, USA). Changes in raltegravir drug concentration (standard-dose raltegravir (day 8), standard-dose raltegravir plus intermittent rifampicin (day 33) and standard-dose raltegravir (day 35) versus high-dose raltegravir plus intermittent rifampicin (day 38)) were examined by calculating geometric means (GMs), GM ratios (GMRs) and 90% CIs. The CIs were first determined using logarithms of the individual GMR values and then expressed as linear values. The changes in pharmacokinetic parameters were considered significant when the CI for the GMR did not cross the value of 1.

There is no universal consensus on what constitutes an adequate concentration of raltegravir, and we utilized two widely proposed putative efficacy targets: (i) an in vitro target of 15 ng/mL [minimum effective concentration (MEC) 1, i.e. the in vitro $C_{\text{in vitro}}$, in the presence of 50% human serum]; and (ii) a clinical target of 21 ng/mL (MEC2, i.e. the upper bound of the lowest quartile from QDMRK, associated with blunted therapeutic response).

### Results

#### Demographics

Thirty subjects signed the study informed consent form and were screened. Twelve subjects failed screening due to mild neutropenia (1), raised creatinine kinase (3), raised bilirubin (2), raised ALT (1), raised creatinine kinase and bilirubin (1), concomitant contraindicated medication (1), concurrent medical problem (1) and voluntary withdrawal (2). Sixteen subjects completed the full study protocol with one withdrawal due to a grade 3 adverse event and one was excluded from the pharmacokinetic analysis due to non-compliance with the study drug. The mean (range) age, weight and BMI were 32 (21–54) years, 73 (51–132) kg and 25 (19–37) kg/m$^2$. All subjects were Caucasian and 12 female subjects were included (75%).
Pharmacokinetics

The pharmacokinetic parameters observed for standard-dose raltegravir (day 5), standard-dose raltegravir plus thrice weekly rifampicin (day 33) and high-dose raltegravir plus thrice weekly rifampicin (day 38) are summarized in Table 1. Steady-state raltegravir concentrations are shown in Figure 1 and the wide interindividual variability of raltegravir AUC_{0–12} and C_{12} is shown in Figure 2. There was marked interindividual variability of raltegravir pharmacokinetic parameters, with CV > 35%.

In the presence of thrice weekly rifampicin, raltegravir C_{12} was significantly decreased (by 40%) when dosed at 400 mg twice daily, and four (25%) subjects had C_{12} at or below the MEC2 (Table 1). In contrast, raltegravir dosed at 800 mg twice daily was able to restore C_{12} to concentrations observed when standard doses of raltegravir were used without rifampicin, although C_{max} and AUC_{0–12} were both significantly higher (+76% and +84%, respectively).

Safety and tolerability

In general, the administration of raltegravir and rifampicin was well tolerated, with only one subject not completing the study due to an adverse event. No serious clinical or laboratory adverse events were reported. Eighteen subjects reported a total of 31 non-serious adverse events, 6 of which were determined to be possibly related to the study drug. Headache (33%) was the most common drug-related adverse event. There were 28 nonserious laboratory adverse events, 9 of which were determined to be possibly related to the study drug. All were mild (grade 1) in severity apart from a grade 2 ALT and a grade 3 creatinine kinase. A grade 2 ALT and grade 3 creatinine kinase elevation were reported in one subject following 5 days of 400 mg of raltegravir twice daily, which led to study discontinuation. Both adverse events were thought to be related to raltegravir, on a background of increased exercise. The most common laboratory drug-related adverse events were decreased neutrophils (33%), raised bilirubin (22%) and raised creatinine kinase (22%). Both clinical and laboratory drug-related adverse events resolved upon discontinuation of study medication.

Discussion

In the presence of thrice weekly rifampicin, we observed that raltegravir AUC_{0–12} and C_{max} were not significantly lowered at 400 mg twice daily dosing, but C_{12} was significantly reduced, by 40%. Importantly, a quarter of all subjects taking 400 mg of raltegravir twice daily with rifampicin achieved a C_{12} at or below the MEC2. The effect of rifampicin on raltegravir C_{12} was reversed when the raltegravir dose was increased to 800 mg twice daily, which also yielded a significantly higher AUC_{0–12} and C_{max}.

This is the first study investigating the effect of intermittent rifampicin on raltegravir. We observed a comparable magnitude of effect as previously described for daily rifampicin in healthy volunteers and HIV/TB-coinfected patients, where C_{12} was also disproportionately affected compared with AUC or C_{max}. However, we observed that doubling the dose of raltegravir (800 mg twice daily) with intermittent rifampicin was able to compensate for the significant decrease in C_{12}. In the Reflare study, investigators reported that use of standard-dose...
(400 mg twice daily) raltegravir with daily rifampicin in HIV/TB-coinfected patients yielded AUCs that were broadly similar to those obtained with 400 mg of raltegravir twice daily alone (after TB treatment was completed), although considerable variability was observed, and pre-dose concentrations were significantly lower. Doubling the dose of raltegravir to 800 mg twice daily during rifampicin treatment yielded equivalent raltegravir exposures for both AUC and $C_{\text{trough}}$, and importantly all $C_{\text{trough}}$ concentrations were above MEC1 and MEC2. Of note, in these previous studies participants were not fasted at the time of raltegravir administration. Although the current summary of product characteristics states that there are no food restrictions for raltegravir, food does appear to increase pharmacokinetic variability.

Based on these data, Grinsztejn et al. suggested that standard doses of raltegravir could be used with rifampicin. However, clinical data are not available in sufficient numbers of patients to establish the virological efficacy of raltegravir at this dose. The incremental cost of double-dose raltegravir also has to be considered when weighing up potential risks versus benefits. However, given the observed relationship between raltegravir $C_{\text{trough}}$ and virological success in the QDMRK trial, we have taken the view that, until definitive clinical outcome data are available, raltegravir should be dosed at 800 mg twice daily with daily or intermittent rifampicin co-administration.

There are a number of limitations to our study. Although women were adequately represented, our study population comprised healthy volunteers who were all Caucasian. We did not examine the impact of other components of the TB regimen on raltegravir, although knowledge of their pharmacology suggests that further significant impact on raltegravir pharmacokinetics would be unlikely. We also did not measure the glucuronide metabolite of raltegravir, which would have allowed us to further characterize this drug interaction.

In conclusion, with the absence of definitive clinical efficacy data to suggest otherwise, doses of 800 mg of raltegravir twice daily with thrice weekly rifampicin are well tolerated and yield higher AUCs and comparable $C_{\text{trough}}$ when compared with raltegravir alone.
Acknowledgements
We thank the members of the Independent Data Safety and Monitoring Group, Henry Mwandumba, Edmund Wilkins and Andrew Ustianowski, for providing independent advice and guidance. We also thank the volunteers that took part in the study.

Funding
This study was funded by an investigator-initiated study programme grant from Merck Sharp & Dohme Ltd. MSD also provided the study drug raltegravir. Funding support was also provided by the MRC. The research team acknowledge the support of the National Institute for Health Research, through the Comprehensive Clinical Research Network.

Transparency declarations
H. E. R. and M. C. have received travel grants from GlaxoSmithKline, Bristol-Myers Squibb, Gilead and Abbott. L. E. has received travel grants from Boehringer Ingelheim and Janssen. D. J. B. and S. H. K. have received funding from Gilead, Viiv Healthcare, AbbVie, Janssen and Merck for the Liverpool HIV Drug Interactions Website (www.hiv-druginteractions.org). All other authors: none to declare.

Author contributions
H. E. R. developed the hypothesis, contributed to the study design, provided clinical care and subject identification for the trial and drafted the article. A. C. and M. C. provided clinical care and subject identification for the trial. D. E. analysed the plasma samples. D. E. and L. E. performed statistical analysis. J. C. provided trial management and bioanalytical support. D. J. B. developed the hypothesis and contributed to the study design. S. H. K. developed the hypothesis, contributed to the study design, provided clinical care and drafted the article. All authors approved the final version of the article.

References
11 Li T, Chiang YJ. Rifampicin induction of CYP3A4 requires pregnane X receptor cross talk with hepatocyte nuclear factor 4α and coactivators, and suppression of small heterodimer partner gene expression. Drug Metab Dispos 2006; 34: 756–64.