Original article

Pharmacokinetic parameters of once-daily rilpivirine following administration of efavirenz in healthy subjects

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Background: Rilpivirine and efavirenz share metabolic pathways (CYP3A), potentially leading to drug–drug interactions. We report the pharmacokinetics, ex vivo antiviral activity and safety of rilpivirine, following efavirenz treatment.

Methods: HIV-negative adults received in fixed sequence: treatment A (rilpivirine 25 mg once daily for 14 days, followed by a washout), treatment B (efavirenz 600 mg once daily for 14 days), immediately followed by treatment C (rilpivirine 25 mg once daily for 28 days). Rilpivirine pharmacokinetic profiles were determined on days 1 and 14 of treatment A and days 1, 14, 21 and 28 of treatment C. Ex vivo antiviral activity was measured in treatments A and C using an exploratory assay. Safety was evaluated throughout.

Results: From days 1 to 21, higher mean rilpivirine exposure was observed with treatment A compared with treatment C. The area under the concentration–time curve (AUC24 h) least squares (LS) means ratio (90% CI) for treatment C versus treatment A was 0.54 (0.46, 0.64; Day 1), 0.82 (0.75, 0.89; Day 14) and 0.84 (0.74, 0.94; Day 21). By day 28 of treatment C, the main rilpivirine pharmacokinetic parameters were similar to day 14 of treatment A (AUC24 h LS means ratio [90% CI], 0.91 [0.82, 1.01]), except for the minimum plasma concentration. At each time point in treatment C, samples of >80% of subjects demonstrated similar ex vivo antiviral activity compared with treatment A. All adverse events were grade 1 or 2.

Conclusions: These results provide useful information supporting a clinical study evaluating HIV-1-positive subjects switching from efavirenz to rilpivirine.

Introduction

Initial treatment regimens for HIV-1 infection generally consist of a combination of three antiretrovirals (ARVs) [1]. Drug–drug interactions between ARVs in a subject’s treatment regimen can affect the pharmacokinetic (PK) profiles of the drugs and, ultimately, the safety and efficacy of the treatment. Increased ARV plasma concentrations can lead to safety and tolerability concerns, such as increased risk of adverse events (AEs; see also Liu et al. [2]), whereas subtherapeutic ARV concentrations can lead to virological failure and development of ARV resistance. Additionally, the effects that ARVs and other drugs can have on metabolic enzyme systems can persist for some time after discontinuation of the drug. It is, therefore, important to consider possible drug–drug interactions both when choosing an HIV treatment regimen and when switching ARV regimens.

Rilpivirine (TMC278), recently approved in the US under the brand name Edurant™, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild-type HIV-1 and NNRTI-resistant HIV-1 [3]. A Phase IIb, dose-finding study in ARV-naive, HIV-1-infected subjects demonstrated sustained efficacy of rilpivirine 25 mg once daily over 192 weeks [4]. Furthermore, two large Phase III studies in ARV-naive HIV-1-infected subjects, ECHO (Efficacy Comparison in treatment-naive Of TMC278 and efavirenz) and THRIVE (TMC278 against HIV, in a once daily Regimen Versus Efavirenz), have demonstrated non-inferiority of rilpivirine 25 mg once daily compared with the NNRTI efavirenz (EFV) 600 mg once daily at 48 weeks [5]. Of note, in these trials, more rilpivirine-treated subjects with baseline...
Subjects were healthy HIV-negative adults between 18 and 65 years of age, with body mass indices of 18.0–30.0 kg/m² and normal electrocardiograms at screening. Main exclusion criteria included hepatitis A, B or C infection, any active clinically significant disease, history of clinically relevant heart rhythm disturbances or unusual T-wave morphology at screening, a positive alcohol or drug test at screening, clinically significant allergy to the study medications, previous participation in more than one study with etravirine, dapivirine, rilpivirine or EFV or development of rash during a study with one of these agents, or participation in an investigational drug study within 60 days of first study drug administration. Use of concomitant medication other than ibuprofen or acetaminophen was prohibited; use of over-the-counter or prescription medication had to be discontinued at least 7 or 14 days, respectively, before the first study drug administration. Women of childbearing potential were excluded and sexually active, non-vasectomized, heterosexual men were required to use a highly effective method of birth control for the duration of the study and for 30 days thereafter. The study protocol was approved by an independent ethics committee according to the applicable regulations (for example, the International Conference on Harmonisation and World Health Organization Good Clinical Practice, and the US Code of Federal Regulations). The study was performed in accordance with the ethical standards of the Helsinki Declaration of 1975. All subjects provided written consent prior to the first study procedure.

Study objectives
The primary objective of the study was to assess the PK of rilpivirine 25 mg once daily following a 2-week (steady-state) EFV 600 mg once daily treatment period. The secondary objectives were to evaluate EFV plasma concentrations over time after cessation of EFV intake and to assess the safety of rilpivirine 25 mg once daily alone and after EFV intake. The ex vivo antiviral activity in serum was also measured.

Study evaluations
The 24-h PK profile for rilpivirine was determined on days 1 and 14 (steady-state) of treatment A and on days 1, 14, 21 and 28 of treatment C. EFV plasma concentrations were determined at regular time points during treatments B and C. Plasma concentrations of rilpivirine and EFV were determined using validated liquid chromatography–tandem mass spectrometry methods; the lower limit of quantification for the assay was 1.0 ng/ml for rilpivirine and 100 ng/ml for EFV. Fasting (10-h) blood samples were collected for laboratory assessments on day 13 of treatment A, days 1 and 14 of treatment B, and days 13 and 27 of treatment C. Safety and tolerability were evaluated throughout the study.

Methods
Study design and treatment
This was a Phase I, open-label, single-centre study. All subjects received a fixed sequence of treatments: treatment A, rilpivirine 25 mg once daily for 14 days, followed by a 14-day to 21-day washout period; treatment B, EFV 600 mg once daily for 14 days, which was immediately followed by treatment C, rilpivirine 25 mg once daily for 28 days. There was no washout between treatments B and C. All treatments were administered orally. Rilpivirine was taken within 10 min of completing breakfast and EFV was taken in the evenings, before bed, on an empty stomach.

Subject population
Subjects were healthy HIV-negative adults between 18 and 65 years of age, with body mass indices of
Serum samples for determination of \textit{ex vivo} antiviral activity were collected pre-dose on day 14 of treatment A and on days 2, 4, 7, 14, 21 and 28 of treatment C. \textit{Ex vivo} antiviral activity was determined using a cell culture method with wild-type HIV-1, as previously reported [13,14]. The assay measured the total \textit{ex vivo} antiviral activity resulting from both rilpivirine and EFV present in the serum samples taken during treatment C. The antiviral activity is measured as a median effective concentration (EC\textsubscript{50}) value, which is expressed as the percentage dilution (ranging from 0.02% to 5%) of the serum sample needed to obtain 50% inhibition of viral replication. Based on this highest dilution at 5% and the EC\textsubscript{50} for the wild-type reference virus, the limit of detection for the assay was calculated to be 6 ng/ml. Each subject served as his or her own control by comparing activity levels between treatment A (at day 14) and treatment C (at multiple time points). A twofold variation in the EC\textsubscript{50} value is typically within the limits of this type of assay; thus, when compared with the EC\textsubscript{50} value from treatment A (day 14; set as 100% for each subject individually), the EC\textsubscript{50} value determined during treatment C may, therefore, vary from 50% to 200% without being relevantly different. No pharmacogenomic analyses were performed.

Statistical analysis

With an estimated intrasubject standard deviation for rilpivirine of 0.24 and a sample size of 16 study completers, the point estimate of the ratio of rilpivirine PK parameters with and without a preceding treatment period with EFV was anticipated to fall between 86% and 116% of the true ratio, with 90% confidence. A total of 20 subjects were enrolled in the study to allow for dropouts. Descriptive statistics are reported for the rilpivirine PK parameters of all subjects receiving at least one dose of study drug and with available plasma concentration data (PK population); at certain time points, subjects were excluded from the analysis due to reported non-compliance. As this was a within-subject comparison, each subject served as his or her own control. A linear mixed-effects model, controlling for treatment as fixed effect and subject as a random effect, compared the relevant PK parameters at each time point in treatment C with the respective reference time point in treatment A. Since rilpivirine was at steady-state by day 14 of treatment A, PK parameters from this day were used as the references for comparison to PK parameters from days 14, 21 and 28 of treatment C. The 90% CIs of the least squares (LS) means PK parameter ratios were compared with 0.80–1.25% boundaries to evaluate whether PK parameters were different between treatments. Safety and tolerability are reported for the intent-to-treat population, which included all subjects who received at least one dose of study drug.

### Results

#### Baseline characteristics and subject disposition

In total, 20 subjects were enrolled in the study and received study drug. Most subjects were male (n=18, 90%) and were White (n=14, 70%; Table 1). The median (range) age of the overall study population was 26.0 years (18–51; Table 1). Overall, 17 subjects completed the study. One subject discontinued study medication on day 8 of treatment B due to grade 2 erythematous rash; one subject discontinued study medication on day 22 of treatment C and was subsequently lost to follow-up; and one subject was withdrawn from the study for medication non-compliance on day 2 of treatment C.

#### Pharmacokinetics

Overall, higher mean rilpivirine plasma concentrations were observed with treatment A compared with treatment C (Figure 1A and 1B), particularly during the first weeks after the switch. A within-subject comparison of day 1 of treatment C with day 1 of treatment A showed that rilpivirine PK parameters were lower in treatment C than treatment A, with an area under the concentration–time curve over 24 h (AUC\textsubscript{24 h}) LS means ratio (90% CI) for treatment C versus treatment A of 0.54 (0.46, 0.64; Table 2). Similarly, comparison of PK parameters from days 14 and 21 of treatment C with day 14 of treatment A demonstrated lower PK parameters in treatment C than treatment A (AUC\textsubscript{24 h} LS means ratio [90% CI]: day 14, 0.82 [0.75, 0.89] and day 21, 0.84 [0.74, 0.94]; Table 2). By day 28 of treatment C, however, the main rilpivirine PK parameters were similar to those at day 14 of treatment A (AUC\textsubscript{24 h} LS means ratio [90% CI]: 0.91 [0.82, 1.01]) except for the minimum plasma concentration (C\textsubscript{min}), which was lower on day 28 of treatment C compared with day 14 of treatment A (mean ±SD 56.3 ±23.0 versus 67.3 ±20.7 ng/ml; Table 2). Steady-state of rilpivirine was generally reached after 7–12 days during treatment A and after 19 days during treatment C. Based on the mean EFV plasma concentrations for treatment B, EFV plasma
Figure 1. Mean plasma concentration–time curves of rilpivirine and efavirenz

(A) rilpivirine comparing day 1 of treatments A and C, (B) rilpivirine comparing day 14 of treatment A with days 14, 21 and 28 of treatment C, and (C) efavirenz (EFV) over time during treatments B and C. Please note the different units: ng/ml in (A) and (B) and µg/ml in (C). *During rilpivirine intake.
concentrations were relatively stable over time as of 4 days after start of treatment (Figure 1C). Plasma concentrations of EFV were below the 0.100 µg/ml limit of quantification by 7 days after the end of treatment B for half the subjects. Two subjects had quantifiable EFV plasma concentrations until 22 days after the end of treatment B.

Pharmacodynamics

The total ex vivo antiviral activity resulting from the presence of both rilpivirine and EFV during treatment C was measured and compared with the activity of rilpivirine alone (treatment A, day 14; that is, within-subject reference). At each time point in treatment C, >80% of subjects demonstrated ex vivo antiviral activity that was not relevantly different from that observed in treatment A (Table 3).

Safety

No serious AEs were reported during the course of the study. One subject discontinued the study due to an AE (grade 2 erythematous rash) while on EFV. In total, 19 subjects (95%) reported at least one AE: 10 subjects during treatment A, 15 subjects during treatment B and 8 subjects during treatment C (Table 4). All AEs were grade 1 or 2. The most frequent overall AEs throughout the course of the study were dizziness, abnormal dreams, headache and upper respiratory tract infection (Table 4). Dizziness and abnormal dreams were most frequently reported during treatment B, whereas headache and respiratory tract infection were only reported in treatments A and C. Overall, the incidence of AEs was similar during treatments A and C. AEs considered at least possibly related to rilpivirine were reported in 5 subjects (Table 4). No AEs were considered probably or very likely related to rilpivirine. AEs considered at least possibly related to EFV were reported in 14 subjects. The most frequently reported AEs considered at least possibly related to EFV were dizziness (n=9, 45.0%) and abnormal dreams (n=6, 30.0%).

Most graded laboratory abnormalities were grade 1 or 2. No grade 4 laboratory abnormalities were reported and no subjects discontinued the study due to laboratory abnormalities. Three subjects (15%) experienced treatment-emergent grade 3 laboratory abnormalities: one subject had grade 3 increases in total cholesterol (treatment B, day 14), one subject had grade 3 increases in low-density lipoprotein (treatment C, days 13 and 14), and one subject had grade 3 increases in both total cholesterol and low-density lipoprotein (treatment B, day 14). Of note, all 3 subjects entered the study with at least grade 2 lipid abnormalities. No major differences in graded laboratory abnormalities were noted between treatment phases.

Table 2. Pharmacokinetics of rilpivirine during treatment A and treatment C

| Time point | PK parameter, mean ±SD | Treatment A  
(n=20) | Treatment C  
(n=16) | LS means ratio (90% CI) for treatment C versus A |
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<tbody>
<tr>
<td>Day 1</td>
<td></td>
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<td></td>
<td>C₀, ng/ml</td>
<td>99.8 ±28.3</td>
<td>64.8 ±20.7</td>
<td>0.64 (0.53, 0.77)</td>
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<tr>
<td></td>
<td>AUC₀₋₂₄ₕ, ng•h/ml</td>
<td>1,095 ±327</td>
<td>602 ±204</td>
<td>0.54 (0.46, 0.64)</td>
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<tr>
<td>Day 14</td>
<td></td>
<td>67.3 ±20.7</td>
<td>47.4 ±18.5</td>
<td>0.72 (0.64, 0.81)</td>
</tr>
<tr>
<td></td>
<td>C₀, ng/ml</td>
<td>180.9 ±45.0</td>
<td>140.2 ±33.8</td>
<td>0.81 (0.71, 0.93)</td>
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<td>AUC₀₋₂₄ₕ, ng•h/ml</td>
<td>2,528 ±596</td>
<td>1,940 ±528°</td>
<td>0.82 (0.75, 0.89)</td>
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<td>Day 21</td>
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<td></td>
<td>C₀, ng/ml</td>
<td>–</td>
<td>49.7 ±20.7</td>
<td>0.72 (0.62, 0.84)</td>
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<td></td>
<td>AUC₀₋₂₄ₕ, ng•h/ml</td>
<td>–</td>
<td>153.6 ±30.7</td>
<td>0.87 (0.78, 0.98)</td>
</tr>
<tr>
<td>Day 28</td>
<td></td>
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<tr>
<td></td>
<td>C₀, ng/ml</td>
<td>–</td>
<td>56.3 ±23.0</td>
<td>0.75 (0.56, 1.00)</td>
</tr>
<tr>
<td></td>
<td>AUC₀₋₂₄ₕ, ng•h/ml</td>
<td>–</td>
<td>165.6 ±41.1</td>
<td>0.92 (0.81, 1.05)</td>
</tr>
</tbody>
</table>

Rilpivirine 25 mg once daily. Rilpivirine 25 mg once daily post-efavirenz (EFV) intake. Days 21 and 28 of treatment C are each compared with day 14 of treatment A. *n=18. †n=15. ‡n=14. AUC₀₋₂₄ₕ area under the plasma concentration–time curve over the dosing interval; C₀, maximum plasma concentration; C₀, minimum plasma concentration; LS, least squares; PK, pharmacokinetic.

Table 3. Ex vivo antiviral activity compared with within-subject reference in treatment A

<table>
<thead>
<tr>
<th>Treatment C</th>
<th>Number of subjects with a mean EC₅₀ value that is within the subject's reference range †, n (%)</th>
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<tbody>
<tr>
<td>Day 2</td>
<td>17 (100)</td>
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<tr>
<td>Day 4</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Day 7</td>
<td>17 (100)</td>
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<tr>
<td>Day 14</td>
<td>15 (88.2)</td>
</tr>
<tr>
<td>Day 21</td>
<td>14 (82.4)</td>
</tr>
<tr>
<td>Day 28</td>
<td>15 (88.2)</td>
</tr>
</tbody>
</table>

Ex vivo antiviral activity compared with within-subject reference in treatment A. *Rilpivirine 25 mg once daily post-efavirenz intake. †Reference range defined from treatment A (rilpivirine 25 mg once daily), day 14 50% effective concentration (EC₅₀) value (set at 100%). In comparing EC₅₀ values, a twofold variation (for example, 50% to 200%) of the EC₅₀ values is within the variability limits of the assay.
Discussion

Results from this study demonstrate that although rilpivirine PK were initially lower when rilpivirine was administered after 14 days of EFV treatment (treatment C) than when administered before EFV treatment (treatment A), the AUC$_{24\text{ h}}$ was similar to reference (treatment A) by 28 days post-EFV cessation. Although minimum target trough concentrations have been suggested for some NNRTIs [1,15], there is no consensus regarding which PK parameter is best associated with response [16–18] and, specifically, this has not been established for rilpivirine. In general, rilpivirine PK parameters from this study, across treatments, were in the same range as those observed in treatment-naive, HIV-1-infected adults receiving rilpivirine 25 mg once daily in the ECHO and THRIVE studies [19].

In this study, EFV plasma concentrations became undetectable in all subjects between 7 and 22 days after EFV treatment cessation. EFV plasma concentrations were undetectable in half of the subjects by day 7, but two subjects had detectable EFV plasma concentrations until day 22, demonstrating the intersubject variability of ARV PK parameters. In these two subjects, when comparing treatment C with treatment A, the rilpivirine AUC$_{24\text{ h}}$ ratio was above the mean value and close to 100% as of day 14 after the switch from EFV, and the measured ex vivo antiviral activity was >100% of within-subject reference at all time points. As no pharmacogenetic testing was performed in this study, it is not possible to assess whether genetic factors or other factors contributed to the observed EFV PK variability.

In the exploratory PD analysis, in >80% of subjects at all time points tested, the ex vivo antiviral activity in the samples from treatment C was not different from that in the within-subject reference sample (treatment A, day 14). These results suggest that the PK interaction between EFV and rilpivirine during the first weeks after the switch would not greatly affect the total combined antiviral activity during this period. These data are in agreement with a previous study, which suggested that the in vitro antiviral effects of rilpivirine and EFV are additive [3]. Furthermore, it should be kept in mind that in a clinical setting, subjects who were to switch from EFV to rilpivirine would also continue to have the benefit of an active ARV backbone, which could negate any transient decrease in NNRTI exposure after the treatment switch in patients with undetectable viral loads, who switch for toxicity or simplification reasons. Finally, it should be noted that the ex vivo antiviral activity assay used in this study has not yet been fully validated, and that clinical correlates for efficacy have not been investigated.

The incidence of AEs was low and similar between treatments A and C, suggesting that administration of
rilpivirine after an EFV treatment period is generally safe and well-tolerated. All AEs were grade 1 or 2 and none were considered probably or very likely related to rilpivirine. The most common AEs at least possibly related to EFV, dizziness and abnormal dreams, are common side effects of EFV [10]. Additionally, no clinically relevant changes in mean laboratory parameters were observed. These safety results are in-line with those from the pooled analysis of the ECHO and THRIVE studies, which also reported a low incidence of AEs [4,5,20].

Overall, the results from this study provide useful data that support a clinical study evaluating HIV-1-positive subjects who are switched from EFV to rilpivirine. To this end, primary results from an on-going pilot study of 50 HIV-infected subjects showed that all subjects switching from EFV/emtricitabine ( FTC)/tenofovir disoproxil fumarate ( TDF) to FTC/rilpivirine/ TDF ( single-tablet regimen) remained virologically suppressed at week 12; the FTC/rilpivirine/ TDF single-tablet regimen was well-tolerated (ClinicalTrials.gov identifier: NCT01286740) [21].

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Disclosure statement

HC and JV are employees of Tibotec BVBA, RR is an employee of Tibotec Inc. and JW and DA are employees of Tibotec Therapeutics. All authors involved in this study had full access to the data and take full responsibility for the accuracy of the data analyses.

References


