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Does Once-Daily Raltegravir Have Any Role in the Antiretroviral Treatment?

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Abstract: Administering raltegravir once daily would make adherence to antiretroviral treatment easier, especially if the concomitant drugs are also administered once daily. We report our experience on the use of raltegravir, both once- and twice-daily.

Retrospective review of HIV-infected patients on treatment with raltegravir 800 mg once or 400 mg twice a day plus 2 analogs. Patients were classified as group A (subjects switched to raltegravir due to adverse events on a previous regimen or drug–drug interactions) and group B (subjects who restarted antiretroviral treatment after a previous drop-out). The primary clinical endpoint was the percentage of subjects with virological suppression after 96 weeks. Treatment's effectiveness (noncomplete/missing equals failure) was also evaluated. Pharmacokinetic study was performed in unselected patients. Plasma raltegravir concentrations were determined by high-performance liquid chromatography coupled with mass spectrometry.

A total of 133 patients were included in the study (74 and 59 on raltegravir once- and twice-daily). There were only 4 virological failures in the entire cohort during the follow-up. Thus, the Kaplan–Meier estimation of efficacy by on-treatment analysis was 96.3% (CI₉₅, 92.8–99.8) at week 96, independently of the dosing regimen and of the raltegravir concentrations. Similar exposures to raltegravir based on AUC_{0–τ}, but higher C_{max} and significantly lower C_{trough} were observed when raltegravir was given once daily compared with 400 mg twice daily. In fact, 14 out of 56 C_{trough} concentrations (25%) from patients taking raltegravir once daily were below the IC₉₅ of wild-type HIV-1 clinical isolates while only 2 samples from patients receiving 400 mg

twice a day were below this value, although no relationship between C_{trough} and efficacy was found. The main limitations of the study are that the raltegravir dosing regimen was not randomized and more than 50% of the patients were virologically suppressed at baseline.

Regimens comprising raltegravir 800 mg once daily plus 2 nucleos(-)ide reverse transcriptase inhibitors can be an efficacious and safe option, particularly in virologically suppressed patients and those with a viral load <100,000 copies/mL.

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Abbreviations: CI = confidence interval, CV = coefficient of variation, GM = geometric mean, GMR = geometric mean ratio, NRTIs = nucleos(t)ide reverse transcriptase inhibitors, RAL = raltegravir, VF = virological failure.

INTRODUCTION

Raltegravir (RAL) was the first approved integrase inhibitor for the treatment of the human immunodeficiency virus (HIV-1) and quickly incorporated into the antiretroviral arsenal both for salvage therapy in experienced patients and for the treatment of naive patients dosed as 400 mg twice daily based on the results of several clinical trials.^{1–4}

Data on its long binding to the HIV integration complex and the absence of apparent plasma concentration–response relationship, both as monotherapy in naive HIV-infected patients and with an optimized background therapy in treatment-experienced patients, suggested that it might be effective in a once-daily dosing.^{1,2,5–7} Afterward, the phase III QDMRK trial in which RAL was given once- or twice daily in combination with coformulated tenofovir plus emtricitabine demonstrated that the efficacy rate, based on the observed failures analysis, was lower for the once-daily dosing in patients with baseline viral loads >100,000 copies/mL (Δ , –9.0%; CI₉₅, –18.0 to –0.2) but not in those patients with ≤100,000 copies/mL (93.2% vs. 94.3%, Δ , –1.1; CI₉₅, –5.9 to 3.5).⁸ However, the conclusions of the investigators were that once-daily RAL cannot be recommended in place of twice-daily dosing. Here upon, most guidelines on antiretroviral treatment recommend giving RAL twice daily.^{9–14}

Given that adherence to antiretroviral treatment is one of the main factors determining its efficacy, with an inverse relationship between adherence and the number of daily doses prescribed,¹⁵ administering RAL once daily would make adequate adherence easier, especially if the concomitant drugs are also administered once daily.

Herein, we report our experience and pharmacokinetic data on the use of RAL, both once- and twice daily, plus 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) in the daily clinical practice.

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METHODS

Study Population

This was a retrospective review of all treatment-experienced HIV-infected patients who used RAL (400 mg twice daily or 800 mg once daily) for the first time plus 2 NRTIs at our center from January 2010 to December 2012. The RAL dosing regimen and the NRTIs backbones were at the discretion of the responsible physicians wherever the genotypic resistance tests showed susceptibility to both NRTIs used;¹⁶ HLA-B*5701 testing was routine before use of abacavir. Patients were classified as group A (subjects switched to RAL because of AEs of the previous regimen or drug–drug interactions) and group B (subjects who restarted antiretroviral treatment after a previous drop-out). Pregnancy and concomitant use of drugs or nonprescription traditional or herbal medications with potential interactions with RAL pharmacokinetics⁶ were the only exclusion criteria. The study was approved by the Committee on Ethics in Biomedical Research of the Hospital Universitario Virgen del Rocío. All patients provided informed consent.

Assessments and Endpoints

A standard checklist was used for recording information extracted from electronic medical records, including demographic variables, clinical, and laboratory data at baseline and every 3 months thereafter. CD4⁺ T cell counts and plasma HIV-RNA were measured by flow cytometry and the Cobas AmpliPrep-Cobas TaqMan HIV-1 test (v 2.0. Roche Diagnostics, Basel, Switzerland) with a lower detection limit of 15 copies/mL, respectively.

The primary clinical endpoint was the percentage of subjects with virological suppression after 48 and 96 weeks according to on-treatment (OT) analysis. Virological failure (VF) was defined as: inability to suppress plasma HIV-RNA to <50 copies/mL after 24 weeks on treatment, a confirmed plasma HIV-RNA of >200 copies/mL, considering the time of the first assessment meeting the failure criteria as the time of failure, or a single HIV-RNA concentrations >200 copies/mL if followed by loss to follow-up. A cutoff concentration of 200 copies/mL was chosen because it is a more accurate measurement of VF than a lower cutoff value.^{9,17} The secondary outcome included treatment's effectiveness (noncomplete/missing equals failure), considering as treatment failure both VF episodes and either treatment interruption or change whatever the reason. AEs were categorized via the standardized toxicity-grade scale used by the AIDS Clinical Trials Group. Patients missing 2 consecutive scheduled visits were considered lost to follow-up.

Pharmacokinetic Data

Data derive from samples taken for routine therapeutic drug monitoring purposes, C_{trough} (concentration at the end of interval dosing) in unselected patients for whom blood samples were drawn at 12 or 24 ± 0.5 h postdose according to the dosing regimen; otherwise, samples were discarded. Additionally, full pharmacokinetic profiles proceed from a previously unreported, open-label, sequential study (ClinicalTrials.gov identifier: NCT01121809) in which patients taking RAL 400 mg twice daily for at least 1 month were admitted to hospital in the morning on day 1 and blood samples were obtained just before and at 1, 2, 3, 4, 6, 8, 10, and 12 hours after supervised drug intake. On day 2 onward, the patients received RAL 800 once daily and a full 24-hour pharmacokinetic profile was performed

a week later with samples taken before and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after the supervised RAL intake. RAL concentrations were determined using high-performance liquid chromatography by tandem mass spectrometry (LC/MS) according to an adapted method previously reported.^{18,19} The assay was validated according to FDA Guidelines with accuracies and precisions of 100 ± 15% and <10%, respectively. The pharmacokinetic parameters of RAL were calculated by noncompartmental analysis (WinNonlin software, Pharsight, Mountain View, CA).

Statistical Analysis

Categorical and quantitative variables were compared using the χ^2 test, the Student *t* test or the Mann–Whitney nonparametric test, according to their distribution. Time-to-event analyses were performed by using Kaplan–Meier survival curves and the log rank test. RAL pharmacokinetic parameters were summarized as geometric means (GM), and compared between days 0 and 7 by geometric mean ratios (GMR) and its 90% confidence interval (90% CI) using RAL 400 mg twice daily as the reference group. The differences in pharmacokinetic parameters between the regimens were considered significant when the interval between low and high 90% CI did not include the value 1.0. Intrasubject variability in drug concentrations was assessed by the coefficient of variation (CV) of all the available values from each patient throughout the follow-up period. Intersubject variability was calculated by using the CV for the geometric mean (GM) of the available values from each patient. Statistical calculations were performed with Statistical Product and Service Solutions software (v. 19.0; SPSS Inc, Chicago, IL).

RESULTS

A total of 133 patients were included in the study (74 and 59 on RAL once- and twice daily, respectively) whose baseline characteristics are summarized in Table 1. Before starting RAL plus 2 NRTIs, 40 patients (once daily, 20; twice daily, 20) had previous VF on NRTIs but resistance mutations to the current regimens were not present in the genotypic tests performed immediately after the VF. The median follow-up was 78 (range, 1–133) and 73 weeks (range, 6–161) for the once and twice-daily regimen ($P = 0.47$), respectively.

Efficacy and Safety

There was only 4 VF in the entire cohort during the first year of follow-up and no one during the second year: 1 patient from group A taking RAL once daily and 3 patients from group B receiving RAL twice daily. Thus, all subjects were analyzed together for virological efficacy. The Kaplan–Meier estimations of efficacy by on-treatment analysis were 96.3% (CI₉₅, 92.8–99.8) both at weeks 48 and 96. Likewise, there were no differences in the Kaplan–Meier estimations of treatment's effectiveness between groups (Figure 1) which dropped to 70.5% (CI₉₅, 62.7–78.3) and 54.5% (CI₉₅, 46.1–62.9) at weeks 48 and 96, respectively. Although there were only 18 patients with baseline HIV-RNA >100,000 copies/mL, we did not find differences in the efficacy after stratifying according to viral load concentrations. Plasma HIV RNA amplification was achieved in 3 out of the 4 patients with VF, neither of them had any RAL-NRTI-associated resistance mutations.

The reasons for treatment failures were similar in the once- and twice-daily dosing regimens: AEs ($n = 1$ in each group;

TABLE 1. Patients' Baseline Characteristics

	Raltegravir qd (n = 74)	Raltegravir bid (n = 59)	P
Male, no. (%)	55 (73.3)	43 (72.9)	0.90
Age, yr, M (range)	47 (39–53)	46.5 (39–53)	0.20
Weight, kg, M (range)	72 (60–81)	71 (65.75–79.25)	0.12
Risk factor for HIV, no. (%)			
Previous iv drug use	17 (22.7)	18 (30.0)	
Homo–heterosexual	52 (69.3)	37 (52.8)	0.60
Other	6 (8.0)	5 (8.3)	
Nadir CD4/ μ L	232 (4–733)	147 (2–706)	0.02
CD4/ μ L, M (range)	423 (282–686)	385 (271–706)	0.22
HIV-RNA copies/mL, M (range)	<20 (<20–783,000)	<20 (<20–89,000)	0.39
<20 copies/mL, no. (%)	40 (53.3)	35 (59.3)	0.59
>100,000 copies/mL, no. (%)	8 (10.7)	10 (16.9)	0.31
Chronic hepatitis, no. (%)	25 (33.3)	26 (43.3)	0.21
Cirrhosis, no. (%)	11 (14.7)	12 (20.3)	0.87
Associated ART, no. (%)			
ABV + 3TC	23 (30.7)	16 (27.1)	0.48
TDF + FTC	52 (69.3)	42 (71.2)	
Patient type, no. (%)			
Group A	46 (61.3)	40 (67.8)	0.47
Group B	29 (38.7)	19 (32.2)	

Group A patients switched to RAL due to adverse effects or drug–drug interactions. Group B patients restarted antiretroviral treatment after a previous drop-out. bid = twice-daily dosing regimen, qd = once-daily dosing.

hypertransaminemia and long-lasting lipodystrophy, respectively), loss to follow-up or treatment dropout (n = 12 vs. 7), switching to other regimens with less pill burden (n = 10 vs. 12), and death not related to treatment (n = 8 vs. 6).

The median increase in CD4 cell counts from baseline at week 48 was 84 cells/ μ L (IQR, –28–215) and 59 cells/ μ L (IQR, –88–176) in the once- and twice-daily dosing group (P = 0.50). At week 96 this increase was 149 cells/ μ L (IQR, –13–364) and 98 cells/ μ L (IQR, –28–244) in the once- and twice-daily dosing group (P = 0.25). Significant changes in the lipid profiles were not found in either dosing group. Overall, the median changes in fasting total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides in the subjects who completed 96 weeks on treatment were –24 mg/dL [IQR, –61–18; range, –304–88], –10 mg/dL [IQR, –45–19; range, –276–

125], –1 mg/dL [IQR, –6–10; range, –28–41], and –24 mg/dL [IQR, –90–11; range, –1995–248]. Fourteen patients (10.5%), 7 of them with chronic hepatitis C, had an increase in aminotransferase concentrations at any time-point throughout the follow-up (grade 1, 2 patients; grade 2, 11 patients; and grade 3, 1 patient). Only in 1 of them it motivated a treatment change; none of these cases was symptomatic, and in everyone else these alterations were transient and improved without treatment discontinuation.

Pharmacokinetics of RAL

RAL C_{trough} concentrations were determined in 86 samples from 58 unselected patients according to the dosing regimen (once daily, 57; twice daily, 29). The RAL C_{trough} was higher for the 400 mg bid dosing (GM: 86.6 ng/mL; IQR, 31.6–222.5; range, 10.8–472) than for the 800 mg qd regimen (GM: 37.0 ng/mL; IQR, 14.9–94.6; range, 1.4–365.0) (P < 0.01) with a GMR of 0.042 (Fig. 2). There was a wide intersubject (172.1% and 98.0%) both for the once- and twice-daily dosing, respectively.

Twelve and 24 hours pharmacokinetic profiles were performed in 8 patients (Fig. 3). Although the GMR of plasma $AUC_{0-\tau}$ was similar with both dosing regimens (0.87; CI_{95} , 0.52–1.44), the actual exposure over 24 hours was lower with the 800 mg once-daily dose than with the 400 mg twice-daily regimen in 5 out of 8 patients. As expected, C_{max} concentrations were higher with the 800 mg once daily regimen (GM: 3413 ng/mL; IQR, 1365–7930) than with the 400 mg twice daily regimen (GM: 1901 ng/mL; IQR, 634–5860) (P < 0.01). However, the plasma C_{trough} was 4-fold lower with the 800 mg once daily dose than with 400 mg twice daily dose (GM: 24 ng/mL; IQR, 10–70) and (GM: 101 ng/mL; IQR, 65–235) respectively (P = 0.02) (Table 2). RAL C_{max} and $AUC_{0-\tau}$ were closely correlated (r = 0.947; P < 0.001) in both regimens but

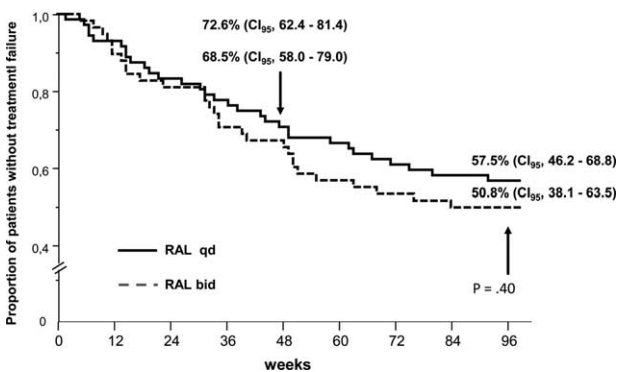


FIGURE 1. The Kaplan–Meier estimations of efficacy by on-treatment analysis by group.

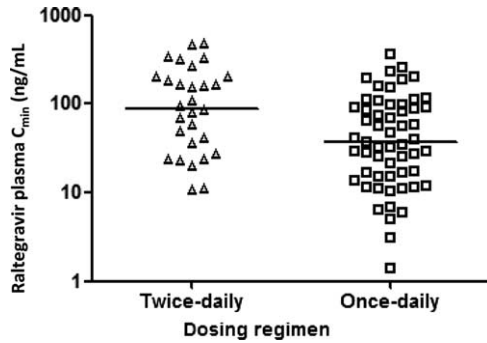


FIGURE 2. Raltegravir plasma C_{trough} (ng/mL) when given as 400 mg twice a day and 800 mg once daily ($P < 0.001$).

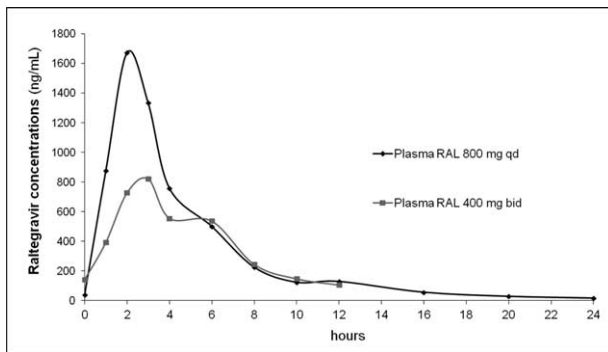


FIGURE 3. Geometric mean of plasma concentrations of raltegravir (RAL) administered as 400 mg twice a day (bid) and 800 mg once daily (qd).

no correlations were observed between these parameters and C_{trough} .

DISCUSSION

Like in other pharmacokinetic studies on RAL,^{20–23} we have observed similar exposure to RAL based on $AUC_{0–\tau}$, but higher C_{max} and significantly lower C_{trough} when RAL was given at 800 mg once daily compared with 400 mg twice daily. In fact, 14 out of 56 C_{trough} concentrations (25%) from patients taking RAL 800 mg once daily were below the IC_{95} of wild-type HIV-1 clinical isolates (13.7 ± 8.9 ng/mL)⁵ while only 2 samples from patients receiving 400 mg twice a day were below this value.

In treatment-naive patients, an exposure–response relationship between RAL C_{min} concentrations and the viral response was suggested initially in a 10-day monotherapy study,⁴ and a consistent trend between C_{trough} concentrations and the probability of achieving an HIV-RNA level of <50 copies/mL at week 48 was observed in the pharmacokinetic/pharmacodynamic analysis of the data in the once daily arm from the QDMRK trial.^{8,20} However, a threshold for RAL concentration associated with reduced efficacy was not found in the phase III BENCHMRK 1 and 2 trials in treatment-experienced patients and its clinical efficacy was much the same irrespective of the dose (200, 400, or 600 mg twice a day) when RAL was administered in combination with optimized background therapy in HIV-infected patients as rescue therapy. Thus, in contrast to naive patients, pharmacokinetics appeared to have less influence on treatment outcome than other covariates such as the use of other active agents in the optimized background therapy in a rescue setting.^{1,2}

In our study, the virological efficacy of RAL plus 2 NRTIs in the on-treatment analysis at 48 and 96 weeks was similar irrespective of the dosing regimen and C_{trough} concentrations, albeit more than 50% of the patients had an undetectable plasma HIV-RNA at the time of switching. The virological suppression rate in our study was similar to the 99% (CI₉₅, 91–100%) at week 48 reported by Caby et al²⁵ in patients who switched to RAL once-daily suppressed viraemia. In this study, the only 3 patients with VF received RAL together with 2 NRTIs and had previously experienced VF failure on NRTI regimens responsible for prior drug resistance mutations on the reverse transcriptase gene. On the other hand, the treatment’s effectiveness dropped to 70.5% and 54.5% at weeks 48 and 96, respectively, due in large part to the high rates of loss to follow-up, treatment simplification, and the excessive mortality rate; the last one attributable to the high rate of subjects with neoplasias included in the study and who started on a RAL-based regimen to avoid drug–drug interactions during chemotherapy (n = 18). Besides the virological efficacy, we have observed an excellent tolerance and lipid profiles.

The main limitations of the study are that the raltegravir dosing regimen was not randomized and the high rate of loss to follow-up due to reasons no related to the treatment per se. Additionally, more than 50% of the patients were virologically suppressed at baseline reflecting properly scenarios in which RAL is used in a real-life setting. Other limitation is that we have estimated the 24-hour RAL exposure ($AUC_{0–24}$) for the 400-mg bid regimen by doubling the $AUC_{0–12}$ obtained from the 12 hours pharmacokinetic profile determined during the day, which might not be fully accurate since there is an apparent

TABLE 2. Plasma Pharmacokinetic Parameters of Raltegravir Given as 400 mg Twice a Day and 800 mg Once Daily (n = 8)

	400 mg/12 h (bid)	CV (%)	800 mg/24 h (qd)	CV (%)	GMR qd/bid (IC ₉₀)
$AUC_{0–\tau}$ (ng h/mL). GM (range)	7060 (1251–24,783)	78	12,283 (1663–48,664)	82	
$\times 2$. GM (range)	14,120 (2502–49,566)				0.87 (0.52–1.44)
C_{max} (ng/mL). GM (range)	1900 (301–7470)	87	3413 (530–16,000)	95	1.79 (0.98–3.28)
C_{min} (ng/mL). GM (range)	100 (18–472)	96	24 (5–151)	116	0.24 (0.08–0.65)
T_{max} (h). GM (range)	2.6 (1–8)		1.8 (1–6)		
$t^{1/2} \beta$ (h). GM (range)	4.3 (2.4–6.6)	30	5.2 (3.0–8.5)	37	1.21 (0.94–1.73)

CV = coefficient of variation, GMR = geometric mean ratio.

circadian rhythm in RAL pharmacokinetics, with differential absorption patterns in the morning versus the evening RAL doses.¹⁸

In this heterogeneous population in which most patients were virologically suppressed, RAL plus 2 active NRTIs maintained virological suppression in most patients regardless of the dosing regimen and of the RAL concentrations. Although RAL 400 mg twice daily is currently recommended for both naive and experienced patients, regimens comprising RAL 800 mg once daily plus 2 NRTIs can be an efficacious and safe option, particularly in virologically suppressed patients and those with a viral load <100,000 copies/mL.

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