

DRUG-DRUG INTERACTIONS WITH RALTEGRAVIR

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Abstract

Objective: To review all currently published drug-drug interaction studies with the HIV-integrase inhibitor raltegravir.

Methods: A PubMed search was conducted for all published reports up to August 1, 2009 as well as a review of updated European and US Prescriber's Information (EMA & FDA) and abstracts from recent international scientific meetings.

Results: A total of 14 drug-drug interaction studies were found. Due to the relatively broad therapeutic range of raltegravir almost all co-administered agents can safely be combined with raltegravir, with the exception of rifampin in which a doubling of the raltegravir dose to 800mg BD is currently recommended.

Conclusions: Raltegravir is not without drug-drug interactions but due to the lack of an effect on CYP450 or UGT by raltegravir and the broad therapeutic range of raltegravir itself, this agent can safely be combined with almost all tested agents.

INTRODUCTION

Drug-drug interactions remain a major concern in the treatment of HIV-infected patients. This is caused by the treatment and prophylaxis of opportunistic infections, the treatment of malignancies, the high prevalence of use of psycho-active agents in the HIV-infected patient population, the treatment of adverse effects caused by this polypharmacy, etc.. As a result, it is more likely that a drug-drug interaction is present in a particular patient than that it is absent, and any HIV clinician should always be suspecting a drug-drug interaction when prescribing medications to an HIV-infected patient.

With the recent introduction of newer antiretroviral agents such as the HIV-integrase inhibitor raltegravir, there is an urgent need for an updated and complete overview of potential drug-drug interactions with this agent, especially when raltegravir is used in patients being treated with multiple recently-developed antiretroviral agents, or as a substitute of other drugs in otherwise virologically stable patients (switch scenario).

PHARMACOKINETICS OF RALTEGRAVIR

The pharmacokinetics of raltegravir after single and multiple doses have been mainly characterized in healthy subjects [1]. The drug is rapidly absorbed with a median t_{max} in the fasted state of approximately 1 hour. Raltegravir plasma concentration decrease in a

biphasic manner with a rapid initial phase ($t_{1/2}$ of approx. 1 hour) and a slower terminal phase ($t_{1/2}$ of approx. 7-12 hour). During twice-daily dosing, this terminal elimination half-life is difficult to assess, but it is more apparent after single dosing or multiple QD dosing. Steady-state conditions are already reached after 2 days with only minimal accumulation over time. Raltegravir AUC increases almost proportionally in a single dose range of 10 – 1,600mg.

Food has a remarkable effect on raltegravir pharmacokinetics. When compared to intake on an empty stomach, the AUC of raltegravir was decreased by 46%, increased by 13% and almost doubled after intake with a low-fat, a moderate fat, or a high-fat meal, respectively [2]; in all cases, intersubject variability was increased by concomitant food intake. Because in phase III studies raltegravir was allowed to be taken with or without food, and there is a broad therapeutic range of raltegravir exposure (see below), it is recommended that raltegravir can be taken without regard to food.

Raltegravir is not metabolized by cytochrome P450 enzymes but rather by glucuronidation. The enzyme responsible for the formation of phenolic hydroxyl glucuronide metabolite of raltegravir appears to be the UDP-glucuronosyltransferase (UGT) 1A1 subtype, with minimal contributions of UGT1A3 and UGT1A9 [3]. Approximately 7-14% of a raltegravir dose is excreted unchanged in the urine. Moderate hepatic insufficiency (Child-Pugh scores 7-8) or severe renal insufficiency (creatinin clearance 13.0 – 28.8 mL/min/1.73 m²) did not have a clinically important effect on raltegravir pharmacokinetics [4]. There are known genetic polymorphisms in UGT1A1, more precisely the UGT1A1 *28/*28 genotype, which is associated with Gilbert's syndrome. UGT1A1 activity is approximately 30% of that in normal healthy volunteers, and, as expected, leads to average 41% higher plasma concentrations of raltegravir [5]. This increase is not considered clinically significant.

Raltegravir is bound to plasma proteins for approximately 83% at therapeutic concentrations. Animal data demonstrate passage through the placental barrier, but not through the blood-brain barrier. Human data on penetration into sanctuary sites is pending.

PHARMACOKINETIC – PHARMACODYNAMIC RELATIONSHIPS FOR RALTEGRAVIR

In order to be able to make a sound interpretation of the reported drug-drug interactions, one should have a

detailed knowledge of the pharmacokinetic-pharmacodynamic relationships for raltegravir. Initially, it was assumed that, as with most other antiretroviral agents [6], also for raltegravir the C_{\min} (or trough concentration) would be most important pharmacokinetic parameter related to antiviral response. Based on in vitro data that the IC_{95} was 33 nM ($\approx 16 \mu\text{g/L}$) it was assumed that only patients with C_{\min} above this value should have optimal antiviral response. A phase II study of 10 days of monotherapy in treatment-naïve individuals [7], however, showed equal antiviral potency over a dose range of 100 – 600mg BD, despite more patients in the lower dose groups (100 & 200mg BD) having C_{\min} values below 33 nM than in the higher dose groups (400 & 600mg BD). A similar observation was made in a phase II study in treatment-experienced patients with multidrug-resistant virus where there were no differences in response in a dose range of 200 – 400 – 600mg BD [8].

In agreement with these observations, an analysis of patients from phase III studies could not find a relationship between raltegravir C_{\min} and antiviral response [9]. Baseline viral load and the presence of other active antiretroviral agents were the most important factors predicting antiviral response. In a post-hoc analysis, however, it appeared that if from patients in these phase III studies simply all drug level results were averaged (so not only those taken as a trough), and this was called a geometric mean of all samples (GM_{all}), then a weak but significant positive relation with antiviral response was demonstrated. This suggests that apparently not the exposure at the end of the dose interval but more the average exposure during a dose interval may determine the antiviral response to a raltegravir-containing regimen. This was further supported by subsequent analyses from an in vitro hollow fiber infection model that concluded that raltegravir AUC is the most important pharmacokinetic parameter for antiviral response, although a target or threshold value was not given [10].

With respect to the other end of the therapeutic range, there are no data supporting a toxic raltegravir dose or concentration. In phase II studies, multiple dosing of raltegravir at 150% of the licensed dose (i.e. 600mg BD) was not associated with a difference in tolerability when compared to the normal dose of 400mg BD [8, 7].

From the above it can be concluded that in the absence of a target AUC value for raltegravir any change in exposure that is within a 50-150% range of that observed with 400mg BD (based on similar antiviral and tolerability results from 200 - 400 - 600mg BD) should not be of any concern.

DRUG-DRUG INTERACTIONS WITH RALTEGRAVIR (Table 1)

In vitro studies have indicated that raltegravir itself does not influence CYP450 enzymes or UGT [11]. Studies in healthy subjects with midazolam or lamotrigine as typical CYP3A or UGT substrates, respectively, have confirmed raltegravir's lack of inhibiting or inducing properties on these enzymes [12, 13]. Raltegravir did not have an influence on the pharmacoki-

netics of oral hormonal contraceptives [14]. Raltegravir also does not influence the membrane transporter P-glycoprotein [11]. This is important as NNRTIs and PIs do influence various CYP450 and UGT enzymes and are involved in multiple drug-drug interactions, including those with psychoactive agents, statins, cytostatics, immunosuppressants, etc. In all these complicated patient situations, raltegravir may become the drug of choice due to its lack of causing clinically relevant drug-drug interactions.

As a result of the above, most of the drug-drug interaction studies have had a focus on (and were designed to study only) the influence of the co-administered agent on raltegravir pharmacokinetics, with less attention on the potential effect of raltegravir on the co-administered agent. A summary of these studies is given in Table 1.

Table 1. Reported drug-drug interaction studies with raltegravir.

Co-medication	Effect of co-medication on raltegravir AUC	Reference
NRTIs		
• Tenofovir	+49%	[28]
NNRTIs		
• Efavirenz	-36%	[16]
• Etravirine	-34%	[23]
PIs		
• Tipranavir/r	-24%	[18]
• Ritonavir (low-dose)	-16%	[16]
• Atazanavir (400mg QD)	+72%	[15]
• Atazanavir (300mg BD)	+53%	[17]
• Atazanavir/r	+41%	[15]
• Darunavir/r	-29%	[19]
• Lopinavir/r	+3%	[20]
Other agents		
• Rifampin (RAL 400mg BD)	-40%	[26]
• Rifampin (RAL 800mg BD)	+27%	[26]
• Omeprazole	+221%	[27]

ANTIRETROVIRAL AGENTS

A total of 6 different antiretroviral agents (or combinations) have been studied with raltegravir. Most interesting is the effect of atazanavir (with/without ritonavir) on the pharmacokinetics of raltegravir. Atazanavir is known to inhibit UGT1A1, the enzyme responsible of the metabolism of raltegravir (and also bilirubin, hence the asymptomatic hyperbilirubinemia associated with atazanavir use). As a consequence, raltegravir concentrations were increased by 72% when raltegravir was combined with atazanavir 400mg QD in healthy subjects [15]. This effect is somewhat lower when raltegravir is combined with atazanavir/ritonavir, namely a 41% increase, because ritonavir itself is an inducer of UGT1A1 [15]. This was confirmed in a study in which raltegravir was combined with only low-dose ritonavir (100mg BD) and a 16% decrease in raltegravir AUC was observed [16]. The increased

concentrations of raltegravir when combined with atazanavir or atazanavir/ritonavir did not lead to more adverse effects, so this is an interesting combination for future evaluation. A separate study conducted by Bristol-Myers Squibb evaluated a combination of raltegravir (400mg BD) and unboosted atazanavir (300mg BD) [17]. Again, raltegravir plasma concentrations were increased (by 53%), but remarkably, atazanavir plasma concentrations were reduced by on average 19%. This reduction is not considered clinically relevant when atazanavir is administered unboosted in a BD 300mg dose, or boosted with ritonavir in a 300/100mg QD dose. However, when atazanavir is dosed QD unboosted, a dose increase to 600mg may be warranted, and is currently under study.

Not surprisingly, raltegravir plasma concentrations were also reduced when combined with other boosted PIs: tipranavir/ritonavir: -24% [18], darunavir/ritonavir: -29% [19], because the net effect of these combinations is expected to be UGT induction. In contrast, lopinavir/ritonavir did not appear to influence the AUC of raltegravir [20], which is conflicting with other data indicating that lopinavir/ritonavir induces the glucuronidation of other UGT substrates such as lamotrigine [21] and abacavir [22]. NNRTIs are also known to induce UGT1A1, and indeed a reduction in raltegravir exposure by efavirenz (-36% [16]) and etravirine (-34% [23]) could be determined. Although not studied, it is expected that the effect of the other NNRTI nevirapine will be similar.

In all these cases, the reductions in raltegravir plasma concentrations by selected boosted PIs or NNRTIs are not considered clinically relevant as they fall in the 50-150% window as explained above. Recently, some concern was raised about low raltegravir plasma concentrations observed in a Therapeutic Drug Monitoring (TDM) service in France [24]. In 4 out of the 7 patients who were treated with an etravirine – raltegravir combination raltegravir C_{min} was lower than the IC_{95} and it was questioned whether a dose adjustment of raltegravir was indicated, in contrast to the recommendation based on a healthy volunteer study [23]. Based on current information, we do not think a dose adjustment is necessary. First, we have discussed above that not the C_{min} is the primary pharmacokinetic parameter of raltegravir but the AUC; second a TDM service may not be appropriate to accurately assess the magnitude of a drug-drug interaction as often doses and food intake are not observed, there is no inpatient comparison, and other agents may be co-administered. Nevertheless, etravirine was not used during raltegravir's clinical development so one should always be alert on potential suboptimal efficacy in experimental combinations. Another report from France demonstrated that patients with etravirine + raltegravir did not perform worse than patients on raltegravir without etravirine [25].

The only NRTI that has been studied with raltegravir is tenofovir. In a study in healthy subjects, the plasma concentrations of raltegravir were increased by 49% due to a yet unexplained mechanism. Tenofovir may increase the pH of the environment where raltegravir is absorbed leading to higher exposure to ralte-

gravir (see also the effect of omeprazole below); the same mechanism could be responsible for the negative effect of tenofovir on atazanavir, which is better absorbed at a lower pH. Again, this increase is not considered clinically relevant as it falls within the 50-150% window, and tenofovir is also part of the phase III program for use of raltegravir in treatment-naïve patients.

OTHER CO-ADMINISTERED AGENTS

Rifampin is known to be one of the most potent UGT inducers, and hence a major effect of this agent on raltegravir pharmacokinetics was expected. This indeed happened because a 40% reduction in raltegravir AUC occurred when it was dosed as 400mg BD with rifampin 600mg QD [26]. Rifampin was also not allowed as a co-administered agent during raltegravir's clinical development and there are no clinical data to indicate that this major reduction in raltegravir AUC has no clinical consequence. A subsequent study with an increased dose of raltegravir (800mg BD) demonstrated that the negative effect of rifampin on raltegravir exposure could be reversed, and even a 27% higher AUC was reached when compared to raltegravir 400mg BD without rifampin [26]. The definitive answer to the question whether a dose increase of raltegravir is needed for patients with rifampin should come from a clinical trial that is currently ongoing (NCT00822315, see www.clinicaltrials.gov). It is likely that the same dose recommendation will be applicable when raltegravir needs to be combined with other strong UGT inducers such as phenytoin and phenobarbital.

Raltegravir is better absorbed in an environment with a higher pH and hence a drug-drug interaction study with an acid reducing agent was indicated. Combined use of omeprazole and raltegravir in healthy subjects led to a 212% increase in plasma concentrations of raltegravir [27]. Although this is above the upper threshold of 150% as mentioned before, it is not expected that concomitant omeprazole use will lead to a lower tolerability of raltegravir. The first argument for this comes from an analysis of patients in phase III studies (where concomitant use of acid reducing agents was allowed) which did not show a tolerability problem in patients taking these agents [11]. A second argument may be that HIV-infected patients often have achlorhydria or hypochlorhydria, and hence the effect of any acid-reducing agent may be less in an HIV-infected patient vs. a healthy volunteer. This is currently under study.

CONCLUSIONS

Raltegravir is not without drug-drug interactions, but the minor changes in raltegravir AUC are probably not clinically relevant given its broad therapeutic range and the fact that the licensed dose is well at the maximum plateau of the dose-response curve. Dose adjustment is needed only with rifampin, where a dose increase of raltegravir to 800mg BD is advised, and with unboosted atazanavir, where a dose increase of atazanavir to 600mg QD or 300mg BD is recommended.

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