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The Role of Rilpivirine in Clinical Practice: Strengths and Weaknesses of the New Nonnucleoside Reverse Transcriptase Inhibitor for HIV Therapy

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Abstract

Rilpivirine is a novel second-generation nonnucleoside reverse transcriptase inhibitor that has been recently approved for the treatment of HIV-1-infected patients. Rilpivirine combined with two nucleoside/nucleotide reverse transcriptase inhibitors has been evaluated as first-line therapy in two phase III clinical trials and has demonstrated non-inferior efficacy versus efavirenz, as well as a more favorable toxicity profile. Furthermore, rilpivirine has also been marketed in co-formulation with tenofovir and emtricitabine in a fixed-dose single-tablet regimen, improving the convenience of this combination and making it an attractive first-line option for treatment-naive patients. It could also be a convenient, effective option for treatment switch strategies.

The efficacy of rilpivirine is lower, however, in patients with viral loads greater than 100,000 copies/ml at baseline because of a higher virologic failure rate. In addition, the percentage of new resistance-associated mutations (for both nucleoside/nonnucleoside reverse transcriptase inhibitors) emerging at virologic failure is higher in patients receiving rilpivirine than in those failing efavirenz, mainly in patients with baseline viral load greater than 100,000 copies/ml. Furthermore, when resistance to rilpivirine is selected after virologic failure, cross-resistance to all nonnucleoside reverse transcriptase inhibitors is commonly observed. In addition to these aspects, certain pharmacokinetic issues must be taken into account when rilpivirine is used.

The aim of this review is to highlight the strengths and limitations of rilpivirine that should be taken into account in clinical practice in order to optimize its use within the extensive panel of therapeutic options for HIV-1-infected patients. **(AIDS Rev. 2012;14:268-78)**

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Key words

Rilpivirine. Antiretroviral therapy. HIV-1 infection.

Introduction

The use of potent combined antiretroviral therapy (cART) has led to an increase in the life expectancy of HIV-infected patients through a significant decline in the morbidity and mortality associated with HIV infection[1]. However, as currently available antiretroviral (ARV) drug combinations are unable to eradicate HIV from infected patients[2], cART must be maintained indefinitely to achieve sustained viral suppression and optimal disease control. The main limitations of cART for maintaining optimal long-term viral suppression are the emergence of resistance and drug toxicity[3,4]. Furthermore, a high level of adherence to therapy is essential to guarantee the efficacy of cART and avoid resistance[5,6]. Adherence is often related with the convenience and tolerability of ARV drugs, and poor adherence increases the risk of resistance selection. Hence, in the development of ARV, there is an ongoing search for new compounds with a more favorable safety profile, more convenient dosage, and an improved resistance profile.

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The first-generation nonnucleoside reverse transcriptase inhibitors (NNRTI), efavirenz and nevirapine, remain common components of first-line cART[7-10]. Both have showed long-term efficacy and good long-term tolerability in general, and NNRTI-based regimens usually involve a low number of pills[11-16]. In addition, efavirenz is available co-formulated with tenofovir and emtricitabine as a single-tablet regimen, which has been shown to improve adherence[17]. However, the long-term efficacy of first-generation NNRTI can be limited by toxicity and the low barrier to resistance, with broad cross-resistance between these agents.

Second-generation NNRTI were designed to improve the resistance profile and overcome the safety and tolerability limitations of the original NNRTI, efavirenz and nevirapine. Etravirine was the first second-generation NNRTI to be licensed and marketed. Etravirine is diarylpyrimidine derivative with a higher genetic barrier to resistance and a differentiated resistance profile. Thus, it remains active against multiple HIV-1 variants resistant to efavirenz and nevirapine[18,19]. Etravirine showed high efficacy as a component of salvage regimens for heavily pretreated patients with triple-class resistant HIV-1 infection[20-22]. In addition, the toxicity profile of etravirine is better than that of previous NNRTI[20,23,24]. However, since there is scarce information on the efficacy of etravirine in treatment-naive patients[25], it is not currently recommended for use as initial therapy for HIV-1-infected subjects[7-10].

Rilpivirine (TMC-278) is a recently approved, novel diarylpyrimidine derivative NNRTI, with a molecular structure very similar to that of etravirine. Rilpivirine (25 mg once daily) in association with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) has demonstrated non-inferior efficacy to efavirenz as first-line therapy in phase III clinical trials, and it is currently approved in the USA, Canada, Europe, and Australia for use in treatment-naive HIV-1-infected patients. In addition, rilpivirine has also been marketed in co-formulation with tenofovir disoproxil fumarate and emtricitabine in a fixed-dose, single-tablet regimen. Due to its excellent safety profile and simple dosage, including co-formulation with tenofovir and emtricitabine, rilpivirine could also be an attractive option for HIV therapy in scenarios other than naive patients, such as the need for switching therapy. Nevertheless, there are some limitations and areas of uncertainty related with the efficacy of rilpivirine in patients with a high plasma viral load, resistance considerations, pharmacokinetic aspects, and drug-drug interactions that must be taken into account when rilpivirine is used. In this review, we aim to highlight the main strengths and limitations of rilpivirine for use in clinical practice, based on the current published data.

Efficacy of rilpivirine

Strengths

Efficacy as first-line therapy in HIV-1-infected patients: non-inferior versus efavirenz and very high efficacy in patients with plasma viral load ≤ 100,000 copies/ml

The efficacy of rilpivirine as a component of initial therapy for HIV-1-infected patients was evaluated in two parallel randomized (1:1), double-blind, double-dummy, phase III multinational clinical trials with identical design, the TMC-278-209 (ECHO) and TMC-278-215 (THRIVE) trials. In these studies, rilpivirine (25 mg once daily) was compared with efavirenz (600 mg once daily), both administered with two N(t)RTI in a fixed-dose combination as background regimen (tenofovir/emtricitabine in the ECHO trial and tenofovir/emtricitabine, zidovudine/lamivudine or abacavir/lamivudine in the THRIVE trial). Randomization was stratified by background regimen (THRIVE) and screening viral load (≤ 100,000, > 100,000 to ≤ 500,000, and > 500,000 copies/ml)[26,27]. The primary objective of these trials was to demonstrate non-inferiority of rilpivirine 25 mg once daily compared with efavirenz in terms of percentage of patients who had a confirmed virologic response (viral load < 50 copies/ml), defined by the intent-to-treat time-to-loss-of-virologic-response (ITT-TLOVR) algorithm at 48 weeks. This primary efficacy endpoint was assessed with a predicted-response analysis using logistic regression adjusted for the stratification factors (baseline $\log_{10}$ plasma viral load and background N[t]RTI) and a non-inferiority margin of 12% (lower limit of two-sided 95% CI). In addition to analysis of the data from both trials separately, a preplanned pooled week-48 analysis of the data from both studies was conducted[26-28].

The ECHO trial included 690 patients who received at least one dose of the study drug, 346 rilpivirine and 344 efavirenz. In the primary analysis at week 48, 83% of patients in each group achieved treatment response (confirmed viral load < 50 copies/ml). The difference in the percentage of response according to the logistic regression model was –0.4% (95% CI: –5.9 to 5.2%), demonstrating non-inferior efficacy of rilpivirine compared with efavirenz[26]. Similarly in the THRIVE trial (680 patients, 340 in each group), 86% of subjects who received rilpivirine had a confirmed viral load < 50 copies/ml at week 48 compared with 82% in the efavirenz group. Hence, non-inferiority of rilpivirine was also demonstrated (difference 3.5%; 95% CI: –1.7 to 8.8%)[27]. In the pooled analysis of both trials, 84% of patients assigned to

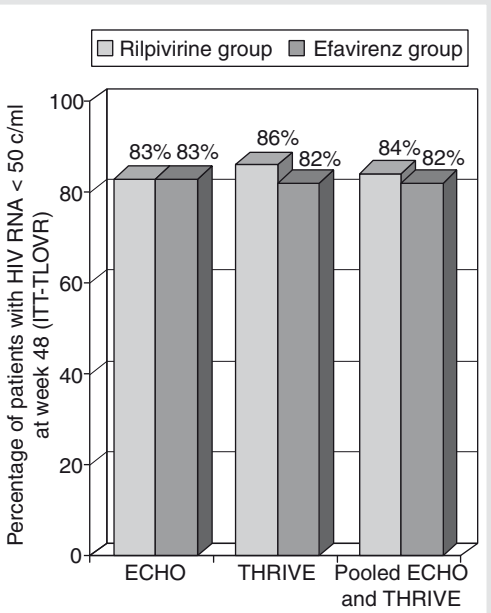

Figure 1. *Efficacy outcomes at week 48 in phase III ECHO and THRIVE trials.*

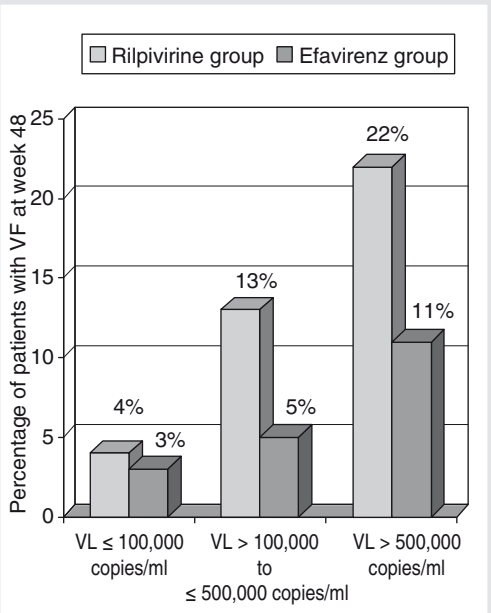

Figure 2. *Efficacy outcomes at week 48 in phase III ECHO and THRIVE trials.*

receive rilpivirine (578 of 686) achieved confirmed treatment response at week 48 compared with 82% of patients (561 of 682) assigned to efavirenz, again demonstrating non-inferiority of rilpivirine (difference 1.6%; 95% CI: –2.2 to 5.3)[28] (Fig. 1 and Table 1). The results observed in the predicted-response analysis, which adjusted for stratification factors, and the per-protocol TLOVR analysis were similar to those of the main analysis (Table 1). Although the overall rate of virologic failures (never suppressed and rebounders) was higher in the rilpivirine group (11 vs. 5%), it was counterbalanced by lower discontinuation rates due to adverse events[26-28] (Table 1). Response rates were similar between the two treatments by background N[t]RTI regimen (overall, 80% received tenofovir/emtricitabine, 15% zidovudine/lamivudine, and 5% abacavir/lamivudine), sex, race, and HIV-1 subtype[28]. The $CD4^+$ cell count increase was also similar with rilpivirine and efavirenz. In the analysis performed at week 96, the percentages of treatment response were similar in the two groups (78%), and the difference in the logistic regression model was within the limits of non-inferiority of rilpivirine compared with efavirenz (–0.4%; 95% CI: –4.6% to 3.8%)[29].

The efficacy of rilpivirine was particularly high in the subgroup of patients with a baseline plasma viral load ≤ 100,000 copies/ml. In this group, 90% of 368 subjects who received rilpivirine had plasma viral load < 50 copies/ml (ITT TLOVR) at week 48 compared with 84% of 330 subjects who received efavirenz. This higher efficacy (ITT TLOVR) of rilpivirine compared with efavirenz in patients with baseline viral load ≤ 100,000 copies/ml was maintained at week 96 (84 vs. 80%; difference 4%; 95% CI: –1.7 to 9.7%)[29,30]. In addition, although the overall rate of virologic failures was higher in patients receiving rilpivirine (Table 1), in subjects with a baseline viral load ≤ 100,000 copies/ml the virologic failure rate was lower and similar in the two treatment groups (Fig. 2)[28].

Efficacy in treatment switch strategies

Due to its good tolerability profile and convenient dosage, rilpivirine could be also a good option for

Table 1. Efficacy of rilpivirine in treatment-naive HIV-1-infected patients: Phase III clinical trials

	ECHO			THRIVE			Pooled ECHO and THRIVE		
	Rilpivirine group	Efavirenz group	Percentage difference (95% CI)	Rilpivirine group	Efavirenz group	Percentage difference (95% CI)	Rilpivirine group	Efavirenz group	Percentage difference (95% CI)
ITT-TLOVR outcome	n = 346	n = 344		n = 340	n = 338		n = 686	n = 682	
Viral load < 50 copies/ml	83%	83%	0.1% (–5.5 to 5.7)	86%	82%	3.9% (–1.6 to 9.5)	84%	82%	2.0% (–2.0 to 6.0)
Virological Failure*	11%	4%		7%	5%		9%	5%	
Discontinuation due to adverse events/death	2%	7%		3%	7%		2%	7%	
Discontinuation due to reason other than adverse event[#]	4%	6%		5%	6%		5%	6%	
Predicted response[‡]	83%	84%	–0.4% (–5.9 to 5.2)	87%	83%	3.5% (–1.7 to 8.8)	86%	84%	1.6% (–2.2 to 5.3)
Per-protocol–TLOVR outcome[§]	n = 335	n = 330		n = 334	n = 332		n = 669	n = 662	
Viral load < 50 copies/ml	84%	83%	0.8% (–4.8 to 6.5)	86%	82%	3.7% (–1.9 to 9.3)	85%	83%	2.3% (–1.7 to 6.2)

ECHO and THRIVE clinical trials[26-28]. Inclusion criteria: HIV-1-infected patients > 18 years old, naive to antiretroviral drugs, had a plasma viral load at screening of ≥ 5,000 copies/ml and viral sensitivity to the N(t)RTI used as background regimen. Exclusion criteria: Patients with HIV-2 infection; documented evidence of at least one NNRTI resistance-associated mutation from a list of 39 (A98G, L100I, K101E/P/Q,K103H/N/S/T, V106A/M, V108I, E138A/G/K/Q/R,V179D/E, Y181C/I/V, Y188C/H/L, G190A/C/E/Q/S/T,P225H, F227C, M230I/L, P236L, K238N/T, and Y318F); active clinically significant disease, renal impairment (glomerular filtration rate < 50 ml/min); and pregnant or breast feeding.

*Virologic failure for the efficacy endpoint, included rebounders: confirmed response before week 48 with confirmed rebound at or before week 48 or never suppressed: patients with no confirmed response before week 48.

[#]Lost to follow-up, noncompliance, withdrew consent, ineligible to continue, sponsor's decision.

[‡]Logistic regression adjusted for baseline viral load, background N(t)RTI regimen and study.

[§]Excluding major protocol violators.

ITT-TLOVR: intent-to-treat time-to-loss-of-virologic-response algorithm; N(t)RTI: nucleoside/tide reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor.

virologically suppressed patients with toxicity problems or in simplification strategies. Although the related published data are still limited, there is some evidence supporting the efficacy of rilpivirine in switching strategies. In patients switching from efavirenz to rilpivirine, maintenance of CYP3A4 induction during the first weeks after efavirenz withdrawal could reduce rilpivirine exposure. The rilpivirine exposure was initially lower after a switch from EFV, but by 4 weeks after the switch, it was similar to the steady-state exposure of rilpivirine in the absence of efavirenz. In addition, samples of > 80% of subjects showed similar ex vivo antiviral activity compared with those subjects receiving only rilpivirine[31]. After this study, a pilot study was conducted with 49 virologically suppressed patients receiving ART with tenofovir, emtricitabine, and efavirenz, and switching to tenofovir, emtricitabine, and rilpivirine. At week 12, all 49 patients remained virologically suppressed. The pharmacokinetic study showed a brief initial period of low rilpivirine concentrations that was not clinically relevant and had no impact on the efficacy of the drug[32].

The SPIRIT trial has evaluated the efficacy and safety of switching to a tenofovir/emtricitabine/rilpivirine single-tablet regimen in virologically suppressed patients receiving two NRTI plus one boosted protease inhibitor (PI). A total of 476 patients were randomized to tenofovir/emtricitabine/rilpivirine (n = 317) or maintenance of boosted PI-based ART (n = 157). After 24 weeks, 93.7 and 89.9% of patients, respectively, remained virologically suppressed, and patients assigned to tenofovir/emtricitabine/rilpivirine had lower rates of adverse events and more favorable lipid changes[33].

Weaknesses

Loss of efficacy as first-line therapy and increased rates of virologic failure in patients with plasma viral load above 100,000 copies/ml and/or low CD4+ cell count

In the ECHO and THRIVE phase III clinical trials in treatment-naive patients, the high efficacy shown by rilpivirine in patients with a baseline viral load ≤ 100,000 copies/ml was not observed in those with higher viral loads. Treatment response in patients with a viral load > 100,000 copies/ml was seen to decrease in both treatment groups, but this reduction of the efficacy was more pronounced with rilpivirine. In the group with baseline viral load between 100,000 and 500,000 copies/ml, rilpivirine efficacy dropped to 80% compared with 90% in patients with viral load ≤ 100,000, whereas in efavirenz-treated patients, efficacy was similar in both subgroups (84 and 83%, respectively). Furthermore, in patients with viral loads > 500,000 copies/ml (n=151, 69 receiving rilpivirine and 82 efavirenz), the percentage of patients responding to treatment was lower with rilpivirine than with efavirenz (70 vs. 76% respectively)[28]. The loss of efficacy of rilpivirine in subjects with a high viral load at baseline is chiefly explained by a higher rate of virologic failure in this group. Among patients with baseline viral load ≤ 100,000 copies/ml, the percentage with virologic failure at week 48 (nonresponders and rebounders) was similar in the two treatment groups (4% rilpivirine vs. 3% efavirenz). However, in the subset of patients with viral load between 100,000 and 500,000 copies/ml, the rate of virologic failure rose to 13% with rilpivirine while it remained stable (5%) with efavirenz. In patients with the highest viral load values, virologic failure was markedly higher in patients receiving rilpivirine (22 vs. 11%) (Fig. 2). It is noteworthy that higher rates of virologic failure were observed in the subset of patients who reported suboptimal adherence, and that the impact of low adherence on the risk of failure seemed to be stronger in patients assigned to rilpivirine[28]. It has been hypothesized that some patients may find it difficult to follow the indication that rilpivirine should be taken with a meal, and this could result in suboptimal absorption of the drug (discussed further below). This fact might have had a greater impact in subjects with a higher baseline viral load and poor adherence[26-28]. Currently ongoing and future studies will help to clarify this issue. Despite the increase in virologic failures in patients with viral loads > 100,000 copies/ml, the efficacy of rilpivirine remained non-inferior to efavirenz in the subset of patients with viral load values between 100,000 and 500,000 copies/ml, in whom there were fewer discontinuations related with adverse events in patients receiving rilpivirine. However, in the subset of patients with viral load > 500,000, non-inferiority of rilpivirine compared with efavirenz was not demonstrated[28].

Similarly, a loss of efficacy of rilpivirine related with an excess of virologic failures was observed in the subset of patients with baseline $CD4^+$ cell counts < 50 cells/µl. Although this represented a small group in the pooled analysis of the ECHO and THRIVE trials (n = 70, 34 receiving rilpivirine and 36 efavirenz), the percentage of treatment response with rilpivirine was 59% compared to 81% in patients receiving efavirenz, and the virologic failure rates were 18 and 3%, respectively[28].

Resistance profile of rilpivirine

Strengths

In vitro activity against HIV-1 variants resistant to first-generation nonnucleoside reverse transcriptase inhibitors

Due to its molecular characteristics, rilpivirine binds preferentially to amino acids located in highly conserved positions within the hydrophobic pocket, such as the W229 residue. These sites have lower mutation rates than the efavirenz and nevirapine binding sites (Y181 and Y188) and theoretically, this would provide rilpivirine with a higher genetic barrier to resistance compared with first-generation NNRTI[34,35]. The presence of three aromatic rings in the chemical structure of rilpivirine confers inherent flexibility that enables adopting multiple conformations and binding the reverse transcriptase, thereby retaining antiviral activity even in the presence of mutations that confer resistance to first-generation NNRTI, such as K103N[34,36,37].

Rilpivirine activity against NNRTI-resistant HIV-1 variants has been demonstrated in laboratory experiments with site-directed mutant strains of HIV-1. Rilpivirine showed activity against HIV-1 mutants harboring most single NNRTI resistance-associated mutations, including V90I, L100I, K101E/Q, K103N/S, V106A/M, V108I, E138A/G/K/Q/R/S, V179D/E/F/T, Y181C, Y188L, G190A/S, H221Y, M230I/L/V, and M236L. In addition, rilpivirine was active against some HIV-1 mutants with two NNRTI resistance-associated mutations[37].

Furthermore, analysis of rilpivirine sensitivity in a panel of 4,786 HIV-1 recombinant isolates with resistance to at least one first-generation NNRTI showed that 62% of isolates remained sensitive to rilpivirine or etravirine, whereas only 11 and 5% were sensitive to efavirenz and nevirapine, respectively[37]. These data have led to the idea that rilpivirine could also be a feasible option for certain patients with first-generation NNRTI-resistant HIV-1 infection, similar to etravirine. However, clinical data on the efficacy of rilpivirine in this setting are lacking.

Weaknesses

High rates of resistance selection after virologic failure of rilpivirine plus 2 NRTI as first-line therapy, especially in patients with viral load >100,000 copies/ml at baseline

The molecular characteristics of rilpivirine and data from *in vitro* experiments have led to the assumption that rilpivirine presents a high genetic barrier to resistance *in vivo*[37]. Nonetheless, genotypic testing in patients with virologic failure in the ECHO and THRIVE trials showed that resistance selection is common in patients failing rilpivirine plus two NRTI, especially among those with viral load > 100,000 copies/ml at baseline. In addition, the rate of selection of NRTI resistance mutations was higher in patients failing rilpivirine plus two NRTI than in patients failing efavirenz plus two NRTI[38].

Overall, among patients with virologic failure in whom genotypic study was available, 44/62 (71%) patients failing rilpivirine and 16/28 (57%) patients failing efavirenz showed new resistance-associated mutations. In patients failing rilpivirine, 38% of patients with baseline viral load ≤ 100,000 copies/ml and 72% of those with baseline viral load > 100,000 copies/ml demonstrated new NNRTI resistance-associated mutations, compared to 42 and 63%, respectively, in patients failing efavirenz. The percentages of N(t)RTI resistance in patients with low and high baseline viral load were 44 and 76%, respectively, in patients failing rilpivirine plus two N(t)RTI compared with 17 and 44% in patients failing efavirenz plus two N(t)RTI. The most common NNRTI resistance-associated mutants emerging at failure in the rilpivirine group were E138K (45%), a mutation that has not been commonly observed with other NNRTI, followed by K101E (13%), H221Y (10%), and V90I, Y181C and V189I (8% each). Regarding N(t)RTI resistance-associated mutations selected at failure with rilpivirine plus two N(t)RTI, the most common was M184I (47%) followed by M184V (23%). Of note, the E138K plus M184I association was observed in 46% of patients failing rilpivirine[38]. The emergence of E138K/M184I double mutants seems to be related with a higher level of resistance to rilpivirine conferred by E138K/M184I, compared with E138K alone (not observed with E138K/M184V), and with a relative replication advantage as compared to M184I alone or E138K/M184V[39,40].

Since rilpivirine and etravirine share similar resistance-associated mutation profiles, cross-resistance would be expected after failure with rilpivirine. Thus, among patients failing rilpivirine with phenotypic resistance to rilpivirine, cross-resistance to all NNRTI including etravirine was documented (90% to etravirine, 87% to efavirenz, 48% to nevirapine) whereas among patients failing efavirenz, only cross-resistance to nevirapine was observed[38].

Tolerability and safety profile of rilpivirine

Strengths

Excellent tolerability and safety profile: lower percentages of adverse events and of discontinuations due to toxicity than efavirenz

At the approved dose of 25 mg once daily, rilpivirine has shown an excellent safety and tolerability profile in clinical trials, with low rates of grade 2-4 adverse events and toxicity-related discontinuations. In the phase III randomized trials, ECHO and THRIVE, grade 2-4 adverse events (at least possibly related to treatment) were less frequent with rilpivirine than with efavirenz (16 vs. 31%; $p < 0.0001$). The rate of discontinuations due to adverse events was also lower in the rilpivirine groups than in the efavirenz groups (3 vs. 8%) (Tabla 1). The most frequent grade 2-4 adverse events at least possibly related to treatment, observed in ≥ 2% of patients in either group (excluding laboratory test abnormalities), were rash, dizziness, abnormal dreams/nightmares, headache, insomnia, and nausea, but these were less frequent in patients receiving rilpivirine. The most common treatment-related adverse events (all grades) occurring in ≥ 10% of patients in either group were dizziness, abnormal dreams/nightmares, and rash, and all were significantly less frequent in patients treated with rilpivirine in comparison with efavirenz (8 vs. 26%; $p < 0.0001$; 8 vs. 13%; $p < 0.05$; 3 vs. 14%; $p < 0.0001$, respectively)[28]. The incidence of rash was highest in the first four weeks of treatment and was significantly lower in the rilpivirine group than in efavirenz patients (3 vs. 14%; $p < 0.0001$). Most rashes were mild (grade 1 or 2), although severe cases (grade 4) were also reported[28].

A significantly lower incidence of grade 2-4 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations was observed in the rilpivirine group than in the efavirenz group (5.1 vs. 9.9%; $p = 0.0009$ and 4.8 vs. 9.0%; $p = 0.003$, respectively). In contrast, the incidence of grade 2 and 3 total hyperbilirubinemia was significantly higher in patients receiving rilpivirine (3.1 vs. 0.4%; $p = 0.0003$). The incidence of serious hepatic adverse events was low in both treatment arms and lower in patients receiving rilpivirine. No serious treatment-related hepatic adverse events leading to discontinuation were observed in the rilpivirine group, whereas two cases were reported in patients receiving efavirenz. The incidence of hepatic adverse events was higher in HBV/HCV-coinfected patients than in non-coinfected ones, with no differences between rilpivirine and efavirenz (27.8 vs. 3.6% in the rilpivirine group and 25.8 vs. 4.5% in the efavirenz group)[41].

Rilpivirine was associated with significantly smaller mean changes from baseline in total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels than efavirenz. Mean LDL cholesterol and triglyceride levels did not increase from baseline with rilpivirine, whereas an increase was seen with efavirenz. Nonetheless, changes in the total cholesterol/HDL cholesterol ratio at week 48 were similar in the two groups[28]. A small increase in serum creatinine levels from baseline was observed in patients receiving rilpivirine, while no changes were observed with the comparator efavirenz. This effect seems to be related with changes in tubular secretion of creatinine and not to direct effects on glomerular filtration, as was shown using alternate glomerular filtration estimation methods such as cystatin C. In any case, no grade 3 or 4 creatinine abnormalities were observed with rilpivirine[28].

In phase I and II clinical trials, an increase in the corrected QT interval on electrocardiography was observed when supratherapeutic doses of rilpivirine (75, 150, or 300 mg daily) were used[42-44]. However, no clinically significant changes in the corrected QT interval have been reported with the ultimately approved rilpivirine dose of 25 mg once daily, either alone in a phase I clinical trial or combined with NRTI in the phase III clinical trials ECHO and THRIVE[28,45].

Lastly, no differences between rilpivirine and efavirenz in limb fat changes or bone mineral density were observed at week 96[46].

Pharmacokinetics of rilpivirine: implications in dosage, administration and drug-drug interactions

Strengths

Once-daily dosage and co-formulation with tenofovir and emtricitabine in a single-tablet regimen

Good adherence to ART is needed to guarantee treatment efficacy[47-49] and avoid the emergence of resistance[5]. However, maintaining a high level of adherence remains a challenge for many patients, especially in certain settings[50-52]. In the last decade, together with progressive improvements in the tolerability of new drugs, the availability of drugs that allow a once-daily regimen and fixed-dose combinations that reduce the pill burden have contributed to improve adherence and ultimately, the efficacy of ART[53-57].

The greatest step in ART simplification has been the development of fixed-dose co-formulations of three drugs in a single pill which has been denominated single-tablet regimens. The first single-tablet regimen available for HIV-infected patients was tenofovir/emtricitabine/efavirenz, approved in 2006 in the USA and 2007 in Europe. Because of the high efficacy of this combination in clinical trials[58-63] and the advantages of the simplified single-tablet formulation, tenofovir/emtricitabine/efavirenz has become one of the preferred combinations in all clinical guidelines[7-10]. The experience with this combination has shown that single-tablet regimen use is associated with an improvement in adherence and treatment efficacy even in difficult settings[17,64-66].

Rilpivirine has a long half-life (35-50 hours)[67] that allows once-daily dosing. In addition, rilpivirine has also been approved in co-formulation with tenofovir and emtricitabine as a new single-tablet regimen. This regimen offers the advantages of a single-tablet combination, the favorable tolerability of rilpivirine, and high efficacy in patients with viral load < 100,000 copies/ml. The availability of two different single-tablet regimen options that can be chosen according to the patients' characteristics will likely contribute to optimizing therapy and improving the patients' quality of life.

No induction of the cytochrome P450 system is expected with rilpivirine 25 mg once daily

The first-generation NNRTI, efavirenz and nevirapine, interfere with the activity of certain isoenzymes within the cytochrome P450 system by acting as either inducers or inhibitors; hence, they interact with drugs that undergo cytochrome P450-mediated metabolism[68-70]. For this reason, concomitant use of efavirenz and nevirapine with such medications is not recommended, and if it is necessary, dose adjustments are required.

In high doses, rilpivirine can also be a moderate CYP2C19 inducer and slight inducer of CYP3A4, 1A2 and 2B6, but no clinical effect is expected with the approved dose of 25 mg once daily[42,43,71]. In general, this dose of rilpivirine can be co-administered with other drugs metabolized by CYP3A, such as statins, oral contraceptives, acetaminophen, sildenafil, methadone, and others[71-77]. In the case of methadone, a modest decrease in methadone bioavailability was observed during co-administration with rilpivirine in healthy volunteers[72]. Thus, although no clinically relevant interaction is expected in most patients, clinical monitoring is recommended and dose adjustments may be needed in some cases.

Weaknesses

The bioavailability of rilpivirine is dependent on food co-administration

Under fasting conditions, the bioavailability of rilpivirine significantly decreases. The maximum concentration (C_{max}) and the concentration-time curve ($AUC_{24\ hours}$) of the drug decreases by 43 and 46%, respectively, when it is taken following a fast, as compared to ingestion with a normal calorie meal or high-fat, high-calorie meal. When rilpivirine is given with a protein-rich nutritional drink alone, the bioavailability also decreases by 50%[78,79]. Therefore, rilpivirine must be taken with a standard meal to ensure adequate bioavailability.

Rilpivirine absorption is dependent on gastric pH: Incompatibility with proton pump inhibitors

Rilpivirine absorption is highly dependent on the gastric acid environment. Thus, drugs that increase the gastric pH (mainly proton pump inhibitors) may reduce the absorption, bioavailability, and subsequently, the efficacy of rilpivirine. Co-administration with omeprazole reduces the concentration-time curve ($AUC_{24\ hours}$) of rilpivirine by 40% and for this reason, concomitant use of rilpivirine and proton pump inhibitors is contraindicated[80]. Other drugs that increase gastric pH, such as H_2 antagonists and antacids can be used, but must be given with caution, at least four hours before or 12 hours after rilpivirine[81].

Drug-drug interactions associated with hepatic metabolism of rilpivirine

Rilpivirine undergoes hepatic metabolism. Although several metabolic processes are involved (hydroxylation, oxidation, glucuronidation, and conjugation), oxidative metabolism by the cytochrome P450 system is the major pathway, primarily by the 3A4 isoenzyme, but also, to a lesser extent, CYP2C19, 1A2 and 2C8/9/10[42,43,71]. Hence, drug-drug interactions are possible if rilpivirine is co-administrated with inducers or inhibitors of these enzymes. Concomitant use of rilpivirine with potent CYP3A inducers may decrease the plasma concentrations and efficacy of rilpivirine; hence, co-administration with rifampicin or rifabutin, certain antiepileptic drugs (e.g. phenytoin, phenobarbital, carbamazepine and oxcarbazepine), dexamethasone (except

single-dose treatments), and St. John's wort is contraindicated[42,43,71] Regarding the use of CYP3A inhibitors, although they may increase plasma concentrations and the risk of toxicity, rilpivirine at the approved dose of 25 mg once daily can be co-administered, in general, with CYP3A inhibitors. Rilpivirine use with ritonavir-boosted PI (lopinavir and darunavir) has been investigated, and no dose adjustment is needed[82,83].

Rilpivirine inhibits P-glycoprotein *in vitro* and could result in an increase of plasma concentrations of certain drugs transported by P-glycoprotein, such as digoxin and dabigatran. A significant interaction *in vivo* between these drugs with rilpivirine at 25 mg is not likely, but the true clinical significance of this interaction has not been investigated[42,43,71].

Uncertain issues

Potential role of rilpivirine in salvage therapy

Rilpivirine could be a viable option for salvage therapy in patients failing a boosted PI-based ART. Although the genotypic resistance profile of rilpivirine and the specific weight of each resistance-associated mutation have not been completely defined, rilpivirine might be considered active in some patients after failure with efavirenz or nevirapine[84]. However, since rilpivirine and etravirine have comparable resistance mutation profiles, cross-resistance would be expected[84]. In addition, the activity of rilpivirine seems to be limited in the presence of two or three NNRTI resistance-associated mutations[84]. A recent study in Spain evaluated the potential role of rilpivirine after NNRTI failure by analyzing genotypic resistance tests of 1,064 patients failing efavirenz, nevirapine, and etravirine. Overall, genotypic cross-resistance to rilpivirine was observed in 19.3% of patients. Among patients failing efavirenz, 14.5% of genotypes were considered rilpivirine-resistant, but this percentage rose to 25.0 and 27.6% in patients failing nevirapine and etravirine, respectively[84]. Only one small phase II clinical trial has evaluated the efficacy of rilpivirine in 36 patients failing an NNRTI or boosted PI-based regimen with at least one NNRTI resistance-associated mutation. A decrease in viral load was observed, but the study was limited to seven days of treatment[84]. Further clinical studies are needed to assess whether rilpivirine may have a role in salvage therapy after NNRTI or PI failures.

Penetration of rilpivirine in reservoirs

Rilpivirine is 99.7% bound to plasma proteins, primarily to albumin[42-43]. The distribution of rilpivirine into compartments other than plasma (e.g. cerebrospinal fluid and genital tract secretions) has not been evaluated in humans. Studies with animals have shown that rilpivirine distributes throughout the body and crosses the blood-brain barrier, but only to a small extent[42,43]. Studies conducted with etravirine, a very similar molecule that is also highly bound to plasma proteins, have shown concentrations of etravirine higher than the EC_{50} for wild-type virus in both cerebrospinal fluid and semen[85,86]. Similar behavior might be expected for rilpivirine, but further studies in humans are needed to assess penetration into these compartments.

Conclusions

Rilpivirine is a new second-generation NNRTI approved for use in combination with two NRTI as initial therapy in treatment-naive HIV-1-infected patients. Rilpivirine with two NRTI has demonstrated non-inferior efficacy to efavirenz in phase III clinical trials (with especially high efficacy in patients with baseline viral load < 100,000 copies/ml) as well as good tolerability and a more favorable toxicity profile than efavirenz. In Europe, rilpivirine (25 mg once daily) is approved by the EMA but its indication is restricted to patients with viral load <100,000 copies/ml, due to the loss of efficacy and high rates of virologic failure and resistance in patients with higher viral loads in phase 3 clinical trials[43]. However, rilpivirine is among the preferred options for initial ART in HIV-1 infected patients with viral load <100,000 copies/ml in the European AIDS Clinical Society (EACS) Guidelines[9]. In the United States, rilpivirine is approved by the FDA for the treatment of HIV-1 infection in ART naïve adult patients but it is still considered an alternative option in the US Department of Health and Human Services (DHHS) guidelines[7].

Although rilpivirine has some pharmacokinetic advantages, certain drug-drug interactions, as well as the need to take the drug with a meal, must be taken into account when rilpivirine is used.

The role of rilpivirine in other scenarios different from initial ART has to be defined in the future. There are still scarce data available to give recommendations about the role for rilpivirine in salvage therapy. However, the favorable tolerability of rilpivirine together with the convenience of its dosage make it a good potential option, not only for naive patients but also for switching and simplification strategies.

Potential conflict of interest

Arkaitz Imaz has received speakers' fees, consultant fees, or funds for research from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dome and ViiV Healthcare.

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