

Short communication

Dual raltegravir/etravirine combination in virologically suppressed HIV-1-infected patients on antiretroviral therapy

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Background: The combination of raltegravir (RAL) and etravirine (ETR) represents a novel antiretroviral treatment option in patients with toxicity or long-term exposure to standard therapies including protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTI). The objective of this study was to evaluate the capacity of dual RAL/ETR therapy to maintain virological suppression in HIV-1 patients under effective antiretroviral therapy (ART).

Methods: Using the Nadis database we retrospectively identified all patients in our centre who were switched from different ART regimens to ETR 200 mg twice daily plus RAL 400 mg twice daily prior to February 2010, having a suppressed HIV-1 plasma viral load (pVL < 200 copies/ml) at the moment of switch. Patients already on RAL or ETR at baseline were not excluded from the study. Treatment failure was defined as two consecutive

pVL > 50 copies/ml or discontinuation of RAL/ETR for any reason.

Results: A total of 18 patients were included. Median baseline characteristics were: age 48 years (IQR 45–56), duration of ART 14 years (IQR 13–16), duration of viral suppression 6 years (IQR 5–9), duration of NRTI exposure 11 years (IQR 8–14) and PI exposure 6 years (IQR 3–9). In intent-to-treat analysis, the efficacy at 6 months of follow-up was 94.4% ($n=17/18$, 95% CI 74.2, 99%) and 83.3% ($n=15/18$, 95% CI 60.7, 94.1%) at 12 months. In per-protocol analysis, the efficacy at 12 months was 100% ($n=15/15$, 95% CI 80.6, 100%). No tolerability-related treatment discontinuation was recorded.

Conclusions: This study, although on a limited number of patients, suggests that raltegravir plus etravirine represents a potential option of NRTI/PI-sparing strategy, deserving further investigation in randomized studies.

Introduction

Raltegravir (RAL), the first licensed integrase inhibitor, and etravirine (ETR), a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), have been shown to be highly effective at inducing viral suppression both in treatment-naïve and treatment-experienced HIV patients [1–4]. As a new class, the integrase inhibitor RAL is active on viral strains with resistance to nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs and protease inhibitors (PIs). Furthermore, RAL has shown good tolerability and a safe metabolic profile [5,6]. Similarly, ETR has the ability to overcome

class resistance [4] and has a safe metabolic profile [4,7]. Therapies including NRTIs, NNRTIs or PIs have been shown, over years, to be progressively associated with long-term complications, renal dysfunction, bone disorders and cardiovascular events [8–10]. Whether virological suppression can be maintained by using new combinations with a different toxicity profile is a key question in the long-term management of HIV-treated patients.

In order to evaluate whether a dual combination of RAL plus ETR could safely be used in patients with long-term exposure to standard antiretroviral

Table 1. Evolution of patients under RAL/ETR therapy during the first year of follow-up

Patient	Previous NNRTI exposure	Antiretroviral prior to switch	HIV-1 plasma viral load, copies/ml				
			Baseline	M3	M6	M9	M12
1	+VF	PI	<20	<20	<20	<20	<20
2	+VF	2 NRTI/PI	<40	<20	<20	<20	- ^b
3	-	2 NRTI/PI	<40	<20	<20	- ^a	- ^a
4	+	II/NNRTI	<40	<20	<20	100	<20
5	+	2 NRTI/NNRTI	<20	<20	<20	<20	<20
6	+VF	PI	<40	<40	<20	<20	<20
7	-	1 NRTI/PI	<20	<20	<20	<20	<20
8	+VF	2 NRTI/NNRTI	<20	<40	<20	<20	29
9	+	2 NRTI/NNRTI	119	<40	<40	<20	<20
10	-	PI	<20	<20	<20	<20	<20
11	-	II/2 NRTI	<20	<20	153	<20	<20
12	+	II/NNRTI/PI	<20	<20	<20	<20	<20
13	+VF	PI	<20	<20	<20	<20	<20
14	-	2 NRTI/PI	118	153	-	-	-
15	-	1 NRTI/PI	<40	<40	<20	<20	<20
16	-	2 NRTI/PI	<20	<20	<20	<20	<20
17	+	II/2 NRTI	<20	<20	<20	<20	<20
18	-	2 NRTI/PI	<20	<20	<20	<20	<20

M3, M6, M9 or M12 are 3, 6, 9 or 12 months of stable raltegravir/etravirine (RAL/ETR) therapy, respectively. Bold values represent detectable plasma viral loads. ^aMoved to another city, lost to follow-up. ^bETR discontinuation due to interactions with lymphoma treatment. II, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VF, virological failure under a previous non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen.

combinations, we conducted a retrospective study in patients with a suppressed HIV plasma viral load (pVL<200 copies/ml), switching from a standard regimen to an RAL/ETR combination.

Methods

Using the Nadis clinical database of our centre, we retrospectively identified all HIV-infected patients with a pVL<200 copies/ml who were switched from different multiple antiretroviral therapy (ART) regimens to a dual RAL/ETR combination up to February 2010. Patients already on a RAL/ETR-containing treatment at baseline were not excluded from the study. Data was collected regarding ART history, HIV RNA values, reasons for switch, routine haematology, liver and renal tests, lipid profile and drug concentrations. Follow-up data was analysed at 3-month intervals. The primary end point was the proportion of patients who maintained a pVL<50 copies/ml at week 24. Treatment failure was defined as two consecutive pVL>50 copies/ml or discontinuation of RAL/ETR therapy for any reason. Monitoring of drug concentrations was performed either during follow-up or retrospectively on stored samples. Statistics were performed using SAS 9.2 (SAS Institute, Cary, NC, USA) and results analysed in intention-to-treat (ITT) and per-protocol (PP) analyses. ITT analysis included all identified patients under dual RAL/ETR switch therapy with a suppressed pVL (<200 copies/ml) at baseline, while PP analysis included all

ITT patients except those that discontinued this regimen for reasons other than virological failure. Missing data was considered as failure.

Results

In total, 18 patients fulfilling inclusion criteria were identified; 15 patients completed 48 weeks of follow-up. A total of three patients discontinued the study for either virological failure (1), interaction with specific lymphoma treatment (1) or loss to follow-up (1). Median follow-up was 22 months (IQR 18–26).

Table 1 outlines the evolution of patients under RAL/ETR therapy. At baseline, patient characteristics expressed as median values were: age 48 years (IQR 45–56), duration of ARV therapy 14 years (IQR 13–16; *n*=18), duration of viral suppression 6 years (IQR 5–9; *n*=18), duration of NRTI exposure 11 years (IQR 8–14; *n*=16) and PI exposure 6 years (IQR 3–9; *n*=14). All patients except two (119 and 118 copies/ml) had a VL of <50 copies at inclusion.

A total of ten (10/18) patients had received NNR-TIs prior to starting RAL/ETR, for a median duration of 1 year (IQR 0.05–4) including nevirapine (NVP) in 6/10 or efavirenz (EFV) in 3/10 and 2/10 patients (numbers 4 and 9; Table 1) were under EFV at study entry. Five out of the 10 patients had experienced episodes of viral replication (HIV RNA>400 copies/ml; Table 1) and only two of these patients had RNA genotype testing performed at the respective moment, showing

no pre-existing resistance to ETR. Of the total of 18 patients, 15 were ETR-naive and 13 were RAL-naive. Three patients (numbers 5, 8 and 12; Table 1) received an ETR-containing regimen at entry and four were already on RAL at baseline. One patient had an ETR/RAL/PI combination at inclusion. Overall, switched drugs included: NRTI (5/18), PI (5/18) and PI/NRTI (7/18). Reasons for switching to RAL/ETR were mostly toxicity-related: metabolic disorders and/or lipodystrophy (7/18), digestive disorders (2/18), arthralgias (2/18), renal impairment and neurological toxicity (2/18). Other reasons were: drug–drug interactions (3/18 patients) and treatment simplification (2/18). Seven patients (47%) received a lipid-lowering agent concomitantly at entry. Therapeutic drug levels were available in 11/18 patients.

Overall, virological success at 6 months of a RAL/ETR regimen was 94.4% ($n=17/18$; 95% CI 74.2, 99%), both in ITT and PP analyses. At 12 months, the rate of virological success was 83.3% ($n=15/18$; 95% CI 60.7, 94.1%) in ITT analysis and 100% ($n=15/15$; 95% CI 80.6, 100%) in PP analysis. One patient (number 14) with self-admitted poor compliance experienced a single viral load of 153 copies/ml at 3 months and had maraviroc added to his treatment. At the time of failure, no drug levels or genotype analyses were available. There was no known prior resistance associated either to NNRTI or to integrase inhibitors. Two other patients (numbers 11 and 4) had one single viral load above 50 copies/ml at 6 months and 9 months respectively, but this was not considered virological failure as HIV RNA was confirmed below 20 copies/ml at next visits.

No tolerability-related treatment discontinuation has been recorded and clinical tolerance was good. In 15 patients, the lipid profile was available before and after switch and showed a median decrease in cholesterol of -0.2 mmol/l (IQR -0.86 – -0.05) and of -0.4 mmol/l (IQR -0.9 – 0.2) in triglyceride levels, which was not statistically significant. No patients discontinued their lipid-lowering agent; however two had their doses lowered due to improved lipid profile. One patient normalized the lipid profile after switch to RAL/ETR, in the absence of any specific treatment.

Therapeutic drug levels were available in 11 patients and in only 5 cases both at M3 and M6. Concentrations for RAL and ETR were mostly in the therapeutic range, except for low minimal plasma concentration (C_{\min}) of RAL (optimal range 29–118 ng/ml) on three occasions, in different patients: one at M3 (6 ng/ml) and two at M6 (24 ng/ml and 21 ng/ml, respectively). However these patients were undetectable at M12.

Discussion

This pilot study on 18 patients with prior exposure to NNRTI and a long history of ART shows that the dual

combination RAL/ETR was effective in maintaining virological suppression, with a 94.4% and 83.3% rate of success in ITT analysis at 6 and 12 months, respectively.

There was only one case of virological failure with a low viral rebound and self-admitted poor compliance. The patient had no resistance mutations to either ETR or RAL, and no previous exposure to NNRTIs or RAL. This patient had maraviroc added to his therapy at 3 months, but was later put on a tenofovir/emtricitabine/EFV regimen.

Even though a significant proportion of patients were already receiving RAL (4/18) or ETR (3/18) at baseline, one of these patients receiving both drugs in combination with a PI at study entry, previous exposure to RAL/ETR in these suppressed patients was not associated with viral rebound.

Although RAL and ETR are metabolized through different pathways [11], some concerns have been raised regarding interactions between these two drugs [12–14]. In the 11 patients with available drug levels, median RAL and ETR drug concentrations were mostly in the therapeutic range, except for low C_{\min} for RAL in three of them at M3 and M6, not followed by virological rebound by M12. Menard *et al.* [13] suggest a possible induction of UGT1A1 by ETR based on a report of four cases of heavily pre-treated patients in which RAL trough plasma concentration (measured at the end of a dosing interval; C_{trough}) was in the under-therapeutic range after ETR addition. However, these case reports describe patients with different, sometimes complex, backbone regimens and virological control at the time of initiation of this combination was not a parameter included in the analysis. Moreover, in the recent TRIO study, not only were no deleterious interactions evidenced but unexpectedly, there was a 50% increase in RAL minimal concentration (C_{\min}) after ETR introduction [14]. Of note, a clear concentration–effect relationship for RAL has not yet been established [11,14].

There have been few data reported on the efficacy of RAL in combination with an NNRTI. A small study investigating the potential use of RAL/NVP in controlled HIV patients reported no virological failure after 48 weeks of dual therapy [15]. Up to now, RAL and ETR have offered the advantage of not being associated with metabolic toxicities, increased cardiovascular risk, central nervous system disorders or any of the reported toxicity associated with NRTIs such as renal or bone toxicity described for the most widely used NRTI, namely tenofovir [4,6,8,16,17]. The majority of patients in this small study were switched from their virologically suppressive therapy for tolerability or toxicity reasons. Even though the numbers are too small to allow for conclusive results, tolerability of RAL/ETR was good, no treatment interruptions were related to tolerance and lipid profile improved,

allowing a reduction of doses of lipid-lowering agent in two patients.

Given the limited number of patients and, the observational, non-randomized nature of the study, the data in this study should be considered cautiously. However, they suggest that RAL plus ETR may represent a potential option for an NRTI/PI-sparing strategy which deserves further investigation in randomized studies.

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