A 24-week pilot study of dual maintenance therapy with raltegravir and lamivudine

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Background: There is an increasing interest in two-drug regimens. We hypothesized that maintenance therapy with raltegravir and lamivudine would keep HIV-1 suppressed and be well tolerated.

Methods: Virally suppressed HIV-1-infected adults without previous viral failures or known resistance mutations to integrase inhibitors or 3TC/FTC or chronic hepatitis B were randomized 2 : 1 to switch to fixed-dose combination 150 mg lamivudine/300 mg raltegravir twice daily or to continue therapy. Primary outcome was the proportion of patients free of therapeutic failure (defined as viral failure, change in treatment for any reason, consent withdrawal, loss to follow-up or death) at week 24. Secondary outcomes were changes in laboratory, body composition, sleep quality, adherence, and adverse effects.

Results: There were 75 patients included: men 78%; median age 50 years; median $CD4^+$ 622/μl. At week 24, 7 (9%) patients had therapeutic failure: raltegravir and lamivudine 2 (4%) vs. control 5 (20%). The difference in proportions of therapeutic failures raltegravir and lamivudine minus control was −0.159 (95% confidence interval: −0.353 to −0.012). There was a trend to more weight gain with raltegravir and lamivudine, but no significant changes in other secondary outcomes. Sixty-four percent of patients in each arm had at least one adverse effect. Two (6%) patients in control arm and 4 (7%) patients in raltegravir and lamivudine arm had severe adverse effects.

Conclusion: This pilot study suggests that switching to raltegravir along with lamivudine in patients with viral suppression maintains efficacy and is well tolerated. A larger study of longer duration is required to confirm these findings.

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Introduction

Reducing the number of antiretroviral drugs to avoid its potential negative impact on comorbidities has been long considered as a popular strategy, particularly in virally suppressed patients receiving standard three-drug regimens. Dolutegravir shares both potency and barrier to resistance with boosted protease inhibitors and recent data suggest behaviour roughly similar to that of boosted protease inhibitors in regimens with less than three drugs. Dolutegravir monotherapy has shown a higher risk of virological failure than triple standard therapy but, in contrast with protease inhibitor monotherapy, virological failures with dolutegravir monotherapy usually develop cross-resistance integrase mutations [1]. Dual therapy with dolutegravir and lamivudine has met noninferiority when compared with standard triple therapy in both antiretroviral-naïve and virologically suppressed patients and none of the few patients experiencing virologic failure in randomized clinical trials has developed drug resistance mutations so far [2–4].

Similar to dolutegravir, raltegravir does not interfere with comorbidities, has a low risk for interactions, and is better tolerated than boosted protease inhibitors [5]. Dolutegravir has shown noninferiority when compared with raltegravir as standard triple therapy in antiretroviral-naïve patients [6]. Although raltegravir is considered to have lower genetic barrier to resistance than dolutegravir, indirect evidence suggests than raltegravir may perform well in regimens with less than three fully active drugs. A post-hoc analysis of the BENCHMRK study showed that some patients in the raltegravir arm had no other drugs active as shown by the genotypic sensitivity score and yet did not experience virological failure [7]. A subanalysis of SPIRAL study looking retrospectively at patients with previous resistance failure and genotypic resistance tests available in their history database revealed that a proportion of patients were on functional dual or even monotherapy not only in the boosted protease inhibitor arm but also in the raltegravir arm and did not show virological failure [8].

Lamivudine is probably one of the safest antiretroviral drugs, with no specific toxicity profile known or major adverse effects reported after more than 25 years of use [9]. A fixed-dose combination constituting lamivudine 150 mg and a nonpoloxamer formulation of raltegravir 300 mg was approved for treatment of HIV infection under the branded name of Dutrebis by the European Medicines Agency and the US Food and Drug Administration in 2015 [10]. The objective of this fixed-dose combination was to develop an immediate release oral formulation offering at least similar pharmacokinetic properties to the equivalent individual products. Dual therapy with the fixed-dose combination raltegravir and lamivudine is a convenient regimen sparing the use of both protease inhibitors and commonly used nucleos(t)ide reverse transcriptase inhibitors tenofovir disoproxil fumarate and abacavir, which have been limited by multiple toxicities and clinically meaningful drug–drug interactions. We hypothesized that dual therapy with raltegravir/lamivudine would be feasible, able to maintain viral suppression, and well tolerated in patients with sustained viral suppression on combination antiretroviral therapy.

Methods

Study design and participants

The RALAM Study is an open-label, pilot, unicentre, randomized clinical trial. Consecutive asymptomatic and stable HIV-infected adults (≥18 years) receiving combination antiretroviral therapy for at least the previous 12 months were invited to participate if they had plasma HIV-1 RNA less than 50 copies/ml for at least 12 months prior to inclusion. In addition, participants were required not to have any of the following: prior virological failure to any regimen containing integrase inhibitors or lamivudine/emtricitabine, chronic hepatitis B, or any disease or history of disease which, in the opinion of the investigator, might confound the results of the study or pose additional risk to the patient. For women of childbearing age, a negative pregnancy test at the time of study consideration and use of anticonceptive measures throughout the study period were also required. Patients who met all inclusion criteria, none of exclusion criteria, and agreed to participate were randomized 1 : 2 to maintain their antiretroviral therapy (control arm) or to switch to the fixed-dose combination 150 mg lamivudine/300 mg raltegravir (Dutrebis) twice daily (experimental arm). We used an unequal allocation 1 : 2 that favoured the experimental arm over the control arm to increase clinical experience with the study therapy in HIV-infected patients as Dutrebis has been used only in phase I studies with healthy volunteers. The Institutional Review Board of Hospital Clínic approved the study and all participants signed informed consent prior to inclusion. The study was registered at ClinicalTrials.gov: NCT02284035.

Although the hypothesis of the study was based on consistent data to support its potential feasibility, we planned in advance that development of virological failure in at least 10% of the patients in the study arm would be unacceptable and should lead to stopping the trial. Following the request of the Institutional Review Board that approved the study, if the 24-week trial proved to be successful, an additional 48-week extension phase was planned in which patients in the experimental arm would remain treated with the dual regimen to gather long-term efficacy and safety information.

Procedures

After inclusion, each patient had four medical visits: baseline, 4, 12, and 24 weeks. At baseline, patient's characteristics including age, sex, ethnicity, and suspected route of HIV transmission were collected. At each medical

visit, participants had a complete physical examination done, a simplified adherence questionnaire [11] filled, and blood drawn for $CD4^+$ and $CD8^+$ cell counts and standard plasma HIV-1 RNA (COBAS HIV-1 Assay, limit of detection 50 copies/ml). Women of childbearing age had also a pregnancy test done at each medical visit.

At baseline and at 24 weeks: weight and height were measured; the Spanish-validated version of the Pittsburg Sleep Quality Index (PSQI) [12] was self-assessed; blood was drawn after at least an 8-h fasting period to measure blood cells and chemistry including total and high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, insulin, and 25-0H vitamin D; urine was collected to measure beta-2-microglobulin; and a dual X-absorptiometry (DXA) to measure whole body composition and lumbar and femoral bone mineral density was performed. BMI was calculated from weight and height. Estimated glomerular filtration rate [Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] was calculated from plasma creatinine following a standard formula [13]. In addition, plasma and peripheral blood mononuclear cells samples were collected and stored at $-80\,^{\circ}C$ until deferred measurement of markers of inflammation and immune activation, immunophenotyping, ultrasensitive plasma HIV-1 RNA, and total and integrated HIV-1 DNA in $CD4^+$ cells (not reported here).

Outcomes

Primary end-point was the proportion of patients free of treatment failure (noncompleter = failure) at 24 weeks. Treatment failure was defined as any of the following possibilities occurring within the 24-week study framework: virological failure (defined as plasma HIV-1 RNA $\geq$50 copies/ml in two consecutive tests 2 weeks apart), discontinuation of the antiretroviral therapy schedule irrespective of the reason, consent withdrawal, lost to follow-up, pregnancy, inability to comply with the study or any other reason that could make the doctor in charge consider the cessation of the study. In the event of virological failure, plasma HIV-1 RNA would be tested for HIV reverse transcriptase, protease, and integrase mutations by population sequencing (Trugene HIV Genotyping System; Siemens Medical Solutions Diagnostics, Tarrytown, New York, USA) and ultra-deep sequencing (MiSeq platform; Illumina, San Diego, California, USA) following routine protocols. In patients with treatment failure, the investigator decided the most appropriate therapeutic option in agreement with the patient. Patients were followed for the entire trial period regardless of whether they prematurely discontinued assigned study medication.

Secondary outcomes were 24-week changes in laboratory parametres, PSQI score, body fat composition, lumbar spine and femoral bone mineral densities and *T*-scores, and incidence and intensity of adverse events. Intensity of adverse events was assessed according to the Division of AIDS table for grading the severity of adult and paediatric adverse events.

Statistical analysis

Assuming a -10% noninferiority margin, an alpha error of 0.025, a 12% treatment failure rate in the control arm, and the true difference in the proportions between groups of zero, then 68 patients (23 in the control arm and 45 in the experimental arm) would be required to achieve 80% of power to test the noninferiority with the continuity corrected *Z*-test with unspooled variance. The final sample size was established at 75 patients (25 in the control arm and 50 in the experimental arm). All randomized patients were included in the analysis. Statistical analysis was performed with the use of Stata (release 14) software (StataCorp, College Station, Texas, USA). Chi-squared or Fisher's exact tests were used to compare proportions between treatment groups. Mann–Whitney or ANOVA tests were used for comparisons of continuous variables between groups. Analysis of the primary endpoint was performed on both intent-to-treat and per-protocol populations, presenting the 95% confidence interval for the difference in proportion estimated using the Newcombe method 10 [14]. Change over time in continuous variables in each arm was calculated as a difference-in-differences estimation based on linear regression model with time, group and time-group interaction. The time to first adverse event was estimated with the Kaplan–Meier product-limit method. The incidence rate of adverse events in both arms was compared with a Poisson regression.

Results

Population

Between 27 November 2015 and 27 October 2016, 78 patients were assessed for eligibility. Three patients refused to participate because of lack of interest ($n = 2$) or lack of time ($n = 1$). Out of the 75 patients randomized, 50 were allocated to raltegravir/lamivudine and 25 to continue their baseline therapy. One patient randomized to raltegravir/lamivudine withdrew his consent prior to initiation of study medication and was excluded from the analyses.

Baseline characteristics are shown in Table 1. Twenty-three (31%) patients were on their first-line regimen. HIV-1 RNA had been maintained below detection level for a median of 56 (30–79) months before randomization. Thirty-nine (53%) patients were also taking non-HIV medications (median 2, interquartile range 0–4) being neuropsychiatric ($n = 27$ patients) and cardiovascular ($n = 21$ patients) drugs the two most common ones followed by a miscellanea of drugs.

Efficacy

Patients' disposition is shown in Supplementary Figure 1, http://links.lww.com/QAD/B507. In the intent-to-treat analysis, 47 (96%) patients in the raltegravir/

Table 1. Baseline characteristics.

	Control ($n=25$)	Raltegravir/lamivudine ($n=49$)	Total ($n=74$)
Age (years)	50 (13)	50 (12)	50 (12)
Men (%)	21 (84)	37 (76)	58 (78)
Prior ART backbone			
TDF-containing	17	26	43
ABC-containing	8	22	30
Nuke-sparing	–	1	1
Prior ART third drug			
PI	3	8	11
NNRTI	16	29	45
INSTI	5	13	19
NRTI	1	–	1
PSQI score, median (IQR)	4 (3; 9)	5 (4; 9)	4.5 (3; 9)
Adherence score, median (IQR)	19 (18.5; 20)	19 (18; 20)	19 (18; 20)
$CD4^+$ (cells/mm^3)	564 (240)	655 (295)	622 (277)
$CD8^+$ (cells/mm^3)	798 (340)	767 (342)	777 (339)
Creatinine (mg/dl)	0.84 (0.18)	0.85 (0.20)	0.85 (0.19)
eGFR (<90 ml/min/1.73 m^2), CKD-EPI	10 (40)	16 (33)	36 (35)
Triglycerides (mg/dl)	112 (53)	99 (50)	103 (51)
Total cholesterol (mg/dl)	187 (44)	189 (46)	188 (45)
LDL cholesterol (mg/dl)	115 (29)	120 (39)	118 (36)
HDL cholesterol (mg/dl)	46 (13)	48 (15)	47 (14)
Glucose (mg/dl)	96 (13)	96 (12)	96 (12)
Insulin (U/l)	16 (16)	14 (10)	14 (12)
25OH vitamin D (ng/ml)	17 (10)	17 (9)	17 (9)
Urine beta-2 microglobulin (mg/g)	595 (949)	673 (773)	651 (814)
BMI (kg/m^2) (mean, SD)	26 (4)	25 (4)	25 (4)
Fat (DXA)			
Trunk fat (g)	9891 (8052; 12611)	9232 (6587; 12976)	9738 (7140; 12976)
Trunk fat, %	30 (24; 33)	30 (22; 36)	30 (22; 36)
Upper limbs fat (g)	1950 (1538; 2765)	2420 (1370; 2920)	2290 (1508; 2912)
Upper limbs fat (%)	22 (19; 36)	29 (19; 35)	28 (19; 36)
Lower limbs fat (g)	5375 (3156; 9577)	5736 (4094; 7658)	5649 (3918; 8349)
Lower limbs fat (%)	26 (15; 37)	27 (20; 32)	27 (19; 34)
Total body fat (g)	65121 (25318; 74254)	52389 (21558; 66220)	55347 (21558; 70334)
Total body fat (%)	25 (21; 33)	29 (22; 33)	28 (21; 33)
Bone (DXA)			
Total hip BMD (g/cm^2)	0.97 (0.92; 1.04)	0.93 (0.84–1.01)	0.95 (0.89–1.02)
Femur *T*-score (mean, SD)	−0.63 (0.76)	−1.04 (0.88)	−0.90 (0.86)
L1-L4 BMD (g/cm^2)	1.16 (1.05; 1.28)	1.11 (1.00; 1.24)	1.13 (1.02; 1.23)
Lumbar spine *T*-score (mean, SD)	−0.54 (1.08)	−0.92 (1.16)	−0.79 (1.14)

Data are mean (SD) unless otherwise stated. ABC, abacavir; ART, antiretroviral therapy; BMD, bone mineral density; CKD-EPI, chronic kidney disease epidemiology collaboration; DXA, dual-X-absorptiometry; eGFR, estimated glomerular filtration rate; INSTI, integrase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PSQI, Pittsburg Sleep Quality Index; SD, standard deviation; TDF, tenofovir disoproxyl fumarate.

lamivudine arm and 20 (80%) patients in the control arm completed the study and remained free of therapeutic failure (estimated difference 0.159; 95% confidence interval 0.012–0.353) at 24 weeks. Five (20%) of the control arm patients prematurely discontinued because of virological failure ($n=1$, week 4), discontinuation of antiretroviral therapy ($n=2$, both week 4), and lost to follow-up ($n=2$, weeks 4 and 12). In the raltegravir/lamivudine arm, two patients prematurely discontinued the study because of pregnancy (week 10) and Hodgkin lymphoma (week 20), respectively.

In the on-treatment analysis, 47 (98%) patients in the raltegravir/lamivudine arm and 20 (87%) patients in the control arm completed the study and remained free of therapeutic failure (estimated difference 0.110; 95% confidence interval 0.013–0.301) at 24 weeks.

Safety

Sixteen (64%) patients in the control arm and 32 (65%) in the raltegravir/lamivudine arm had at least one adverse event during the study. The time to first adverse event did not show differences between arms (Supplementary Figure 2, http://links.lww.com/QAD/B507). The incidence rate ratio of all adverse events was 6.9 (95% confidence interval 5.1–8.7) per 100 person-years in the raltegravir/lamivudine arm and 7.9 (95% confidence interval 4.9–11.0 per 100 person-years) in the control arm (incidence rate ratio of raltegravir/lamivudine vs. control 0.87, 95% confidence interval 0.55–1.38, $P=0.5550$). Table 2 shows the profile of adverse events; some patients had more than one adverse event. All adverse events were grade 1 or 2. Most common adverse events were muscular, gastrointestinal, and infections, with no substantial differences between arms.

Table 2. Adverse events profile.

	Control ($n=25$)	Raltegravir/ lamivudine ($n=49$)	Total ($n=74$)
Systemic	2 (8%)	–	2 (2%)
Infection	6 (23%)	12 (21%)	18 (22%)
Dermatologic	2 (8%)	2 (4%)	4 (5%)
Cardiovascular	–	1 (2%)	1 (1%)
Gastrointestinal	2 (8%)	16 (28%)	18 (22%)
Neurologic	4 (15%)	5 (9%)	9 (11%)
Muscular	5 (19%)	14 (25%)	19 (23%)
Genitourinary	–	1 (2)	1 (1%)
Ophtalmologic	–	3 (5%)	3 (4%)
Laboratory	5 (19%)	3 (5%)	8 (10%)
Total	26 (100%)	57 (100%)	83 (100%)

Some patients had more than one adverse event. Adverse events were grade 1 or 2.

There was a trend towards more weight gain and more total body fat in the raltegravir and lamivudine arm. There were no significant differences between arms in other secondary outcomes such as 24-week changes in laboratory parametres, PSQI score, and lumbar spine and femoral bone mineral densities, and *T*-scores (Supplementary Tables 1 http://links.lww.com/QAD/B507 and 2, http://links.lww.com/QAD/B507).

Discussion

This study represents a proof of concept that switching from combination antiretroviral therapy to raltegravir/lamivudine in patients with sustained viral suppression maintains viral suppression at 24 weeks and is well tolerated. The results support that raltegravir may behave similarly to dolutegravir to construct dual maintenance regimens along with lamivudine [4,15]. There were no virological failures or blips in the raltegravir and lamivudine arm through 24 weeks. However, these results should be interpreted with caution because of the short follow-up. Viral rebound in dolutegravir monotherapy studies was most commonly observed at 24 weeks or after [3,16–18].

Adverse events were not severe and did not differ between arms. This is particularly important as switching to new drugs in patients already tolerating their antiretroviral regimens usually results in an attrition effect because of tolerability issues with the new drugs. There were no more central nervous system (CNS) adverse effects in the raltegravir and lamivudine arm. CNS effects have been reported more commonly with dolutegravir than with raltegravir or elvitegravir [19–21]. In a recent meta-analysis of randomized trials [22], dolutegravir (vs. other core agents) was associated with a higher risk of insomnia. In our study, the quality of sleep as measured by the PSQI did not differ between arms. There was a nonsignificant higher weight and body fat increase in the raltegravir and lamivudine, but the size of change was small and of doubtful clinical relevance. There have been recent reports suggesting more weight gain with integrase inhibitors than with other agents [23,24]. In the NEAT022 randomized clinical trial, patients who switched from boosted protease inhibitors to dolutegravir gained approximately 1 kg in 48 weeks [25] and weight increase was associated with a decrease in adiponectin [26], a marker of insulin resistance and obesity. More data are needed to determine whether weight increase is a class effect of integrase inhibitors, and which is its clinical meaning.

Our study had limitations. There were few patients and the follow-up was short. However, this was a convenient way for planning such an intensive pilot study on a new therapeutic strategy. To compensate for these limitations, intensive virological and immunological studies were planned, and an additional 48-week extension phase is currently ongoing. Despite having been approved by FDA and EMA, the fixed-dose formulation used, Dutrebis, has never been commercially available because of a decision of the manufacturing company, Merck, but the individual products raltegravir and lamivudine are available in a once daily dose.

In summary, this pilot study suggests that switching to raltegravir and lamivudine in patients with viral suppression maintains efficacy and is well tolerated. This maintenance regimen might be a cost-effective option for patients at risk of drug–drug interactions or needing to avoid the negative impact on comorbidities or specific toxicities of certain antiretroviral drugs.

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Conflicts of interest

There are no conflicts of interest.

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