PE9/2

Analysis of the effectiveness and safety of Raltegravir plus abacavir/lamivudine as a switching strategy for HIV-1 suppressed patients. KIRAL Study (GESIDA-8715)

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EACS European AIDS Clinical Society

OBJECTIVES

Long-term use of CART often results in toxicity/tolerability problems, being this aspect, one of the main reasons for switching treatment. Consequently, there is a need for regimes with low toxicity and high safety and tolerability profiles. Despite the good profile of raltegravir (RAL), clinical data on its combination with abacavir/lamivudine (ABC/3TC) is scarce. We evaluated this regimen as a switching strategy, based on clinical practice data.

METHODS

Multicenter, non-controlled, retrospective study including all virologically-suppressed HIV-1-infected patients who had switched to RAL+ABC/3TC. We evaluated the effectiveness defined as the target/achievement of HIV-1-RNA < 50 copies/mL at 48 weeks with this regimen, including and excluding non-virological reasons. We also recorded adverse effects (AEs), changes in renal, hepatic or lipid profiles as indicators of safety/tolerability and CD4-count during treatment.

RESULTS

The study population comprised 467 patients. The median age was 49 years (IQR, 9; 44-53 years). Males accounted for 75.4%. AIDS was diagnosed in 48.8% and active hepatitis C co-infection in 33.4%. Median lymphocyte CD4+ count at baseline was 580 cells/µL (IQR, 409.5; 372-781).

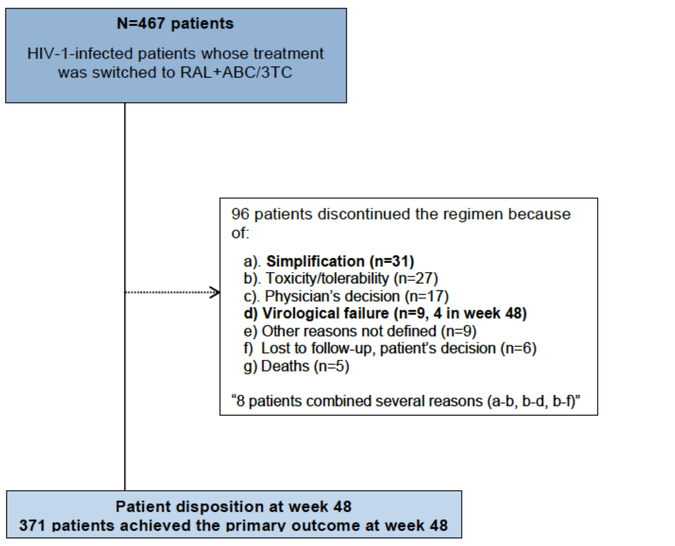
- The main reasons for switching to RAL+ABC/3TC were toxicity/tolerability (197/467; 42.2%) and physician's criteria (133/467; 28.5%).

- The primary outcome was achieved in 371/467 patients (79.4% [95% CI, 71.8-87.0]); in 371/380 patients (97.6% [95% CI, 96.4-99.0]) when excluding non virological reasons.
  There were 96 failures, mainly due to treatment simplification (31 patients, 32.3%), toxicity/poor tolerability (27 patients, 28.1%), physician's decision (17 patients, 17.7%), and virological failure (9 patients, 9.4%). The 9 patients who experienced protocol-defined virological failure compromised 1.7% of the total population. Four of this patients were using RAL once daily and 2 of them presented previous resistance mutations which compromised the switching regimen.

- A total of 73 AEs were detected in 64 patients (13.7%). The events resolved in 43/64 (67.2%) patients. In 40/73 (54.8%) events, clinicians did not find any relationship between the AEs and RAL+ABC/3TC or such a relationship was unlikely. Only in 6/73 (8.2%) events the association with treatment was clear and likely related in 27/73 (37.0%). Grade 3 AEs (8 events in 8 patients) were not related to medication, and Grade 2 AEs (14 events in 12 patients) could have been associated with treatment in only 3 patients. Thus, most treatment-associated AEs were Grade 1 (30/33, 90.9%).

Parameter	n = 467
Demographics	
Age (years); Median (IQR)	49 (45-53)
Gender; n (%)	
Male	352 (75.4)
HIV risk factors; n (%)	
IDU	226 (48.4)
Heterosexual relations	91 (19.5))
MSM	90 (19.3)
Bisexual relations	7 (1.5)
Other/Unknown	51 (10.9)
CD4 and HIV viral load	
Baseline CD4; median (IQR)	
CD4 count (cells/µl)	580 (409; 372-781)
CD4%	28 (13)
Nadir CD4; median (IQR)	169 (209; 65-274)
AIDS diagnosis; n (%)	228 (48.8)
Time since HIV diagnosis (years); median (IQR)	17 (12; 10-22)
Months since undetectable viral load (<50 copies/ml); median (IQR)	62 (7.7; 2.2-9.9)
Co-infections; n (%)	
HBV (HbsAg +)	14 (3.0)
HCV (PCR +)	156 (33.4)
Reasons for switching; n (%)	
Drug toxicity/tolerability	197 (42.2)
Physician's criteria*	133 (28.5)
Unknown reasons	123 (26.3)
Regimen simplification	38 (8.1)
Cost reduction	4 (0.9)
Previous cART; n (%)	
Single-tablet regimen	
DGV/ABC/3TC	3 (0.6)
RPV/FTC/TDF	4 (0.9)
EFV/FTC/TDF	20 (4.3)
Non-nucleoside reverse transcriptase inhibitor	
RPV 25 mg	12 (2.6)
EFV 600 mg	30 (6.4)
NVP 200 (400) mg	18 (3.8)
ETV 200 (400) mg	20 (4.3)
Protease inhibitor	
LPV 200 (800) mg	38 (8.1)
FPV 700 (1400) mg	31 (6.6)
ATV 200 (400) mg	65 (13.9)
ATV 300 mg	25 (5.3)
DRV 400 (800) mg or 800 mg	47 (10.1)
DRV 600 (1200) mg	19 (4.07)
Integrase inhibitor	
RAL 400 (800) mg	118 (25.3)
Nucleoside reverse transcriptase inhibitor	
ABC/3TC	221 (47.3)
FTC/TDF	124 (26.5)
AZT/3TC/ABC	22 (4.7)
3TC	36 (7.7)
ABC	11 (2.3)
FTC	7 (1.5)
TDF	8 (1.7)
AZT	21 (4.5)
Entry Inhibitors	
MVC	5 (1.1)
Monotherapy; n (%)	18 (3.8)
LPV 200 (800) mg	7 (1.5)
DRV 400 (800) mg or 800 mg	11 (2.3)
Dual therapy; n (%)	17 (3.6)
LPV 200 (800) mg (+3TC: 3; +RAL: 1)	4 (0.8)
DRV 400 (800) mg or 800 mg (+3TC: 4, +RAL: 3; +ETV: 2; +NVP: 1)	10 (2.1)
ATV 300 mg	1 (0.2)
RAL 400 mg (+DRV: 3; +LPV: 1; +ETV: 1; +NVP: 1)	6 (1.3)

Baseline characteristics



Study Flowchart

Primary outcome

Including non-virological reasons
79.4% (371/467) [95% CI, 71.8-87]

Excluding non-virological reasons
97.6% 371/(371+9 VF) [95% CI, 96.4-99.0]

Virological failures defined per protocol (n=9)

VF	VL >50 copies/mL before week 48	RAL QD	Pre-existing NRTI resistance mutations
1	+	+	+
2	-	+	-
3	+	+	-
4	+	+	-
5	-	-	+
6	-	-	-
7	-	-	-
8	+	-	-
9	+	-	-

Trait	n AE	% AE	n pts	% pts
Summary of adverse events				
Patients with ≥1 AE			64	13.7
Total number of AE	73			
Discontinuation due to AE	29	39.7	27	5.8
Deaths	5	6.8	5	1.1
Resolved	50	68.5	43	67.2
Types of adverse events				
Systemic (asthenia, myalgia-weakness, anemia, neutropenia, lymphoma, duodenal carcinoma, urothelial carcinoma, liver transplantation)	21	28.8	16	25.0
Digestive (digestive intolerance, reflux, jaundice, abdominal pain, pancreatitis, hepatic encephalopathy)	15	20.5	15	23.4
Neuropsychiatric (insomnia, depression, anxiety, mood changes)	14	19.1	11	17.2
Dermatological (skin lesions, rash, pruritus)	6	8.2	6	9.4
Infectious (pneumonia, pyelonephritis, Shigella ileocolitis, malaria)	5	6.8	5	7.8
Rheumatic (arthralgia)	4	5.5	4	6.2
Metabolic (hypercholesterolemia, onset of diabetes)	3	4.1	3	4.7
Cardiovascular (myocardial infarction, stroke)	2	2.7	2	3.1
Renal (renal insufficiency)	2	2.7	1	1.6
Respiratory (pulmonary thromboembolism)	1	1.4	1	1.6
Severity of adverse events				
Grade 3-4 (fatal or life-threatening)	8	10.9	8	1.7
Grade 2 (requires medical treatment or hospitalization)	14	19.2	12	2.6
Grade 1 (does not require major medical intervention)	51	69.8	44	9.4
Association of adverse events with RAL+ABC/3TC				
Related	6	8.2	4	0.9
Likely	27	37	24	5.1
Unlikely	14	19.2	12	2.6
Not related	26	35.6	24	5.1

Adverse events overview

- Variables related to lipid, hepatic, and renal profiles and lymphocyte CD4+ count were determined at baseline, 12, 24, 36, 44, and 48 weeks. GLM analyses indicated that none of the profile variables changed significantly during the study period (*P*>0.131).

- The availability of a generic co-formulation of ABC/3TC with a more competitive price makes this regimen a cheaper switching strategy than other common antiretroviral regimens including boosted protease inhibitors and other integrase inhibitors.

CONCLUSIONS

The results of the KIRAL study support the use of RAL+ABC/3TC as an effective, safe, well-tolerated and inexpensive switching strategy in virologically stable HIV-1patients.

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