RALTEGRAVIR-BASED ART IS EFFECTIVE AND SAFE IN HIV+ LIVER TRANSPLANT RECIPIENTS

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Abstract #496

Background

Liver transplantation (LT) is safe in selected HIV-infected individuals. However, management of interactions between immunosuppressants (IS) and some antiretroviral families (especially protease inhibitors [PI] and non-nucleoside reverse transcriptase inhibitors [NNRTI]) remains a challenge. Raltegravir (RAL) is a non-boosted integrase inhibitor that did not interact with IS in a small trial with HIV-infected transplant recipients (Tricot, Am J Transplant 2009). Nevertheless, clinical experience in this setting is limited.

Objectives

The aim of this study was to analyze the efficacy and safety of RAL plus 2 nucleos(t)ide analogs (NUCs) vs. other antiretroviral therapy (ART) regimens in a large series of LT HIV-infected recipients.

Methods

We performed a nationwide, multicenter cohort study, including 272 consecutive patients who underwent LT from 2002 to 2012 and who were followed until December 2016.

For the efficacy analysis, the study population comprised 211 patients who had started any of the four (4) post-LT ART regimens and completed at least one year of follow-up. An ITT analysis was performed.

For the safety analysis, 35 additional patients who died or underwent liver retransplantation (reLT) during the first year were also included, with a total of 246 patients (Table 1).

Table 1. Demographic and clinical characteristics of safety population (N= 246)

	2 NUCs + RAL (N=51)	2 NUCs + PI-based* (N=71)	2 NUCs + EFV (N=95)	3-4 NUCs ART** (N=29)	P-value
Pre-LT variables					
Age (mean, SD)	47.3 (5.3)	45.2 (5.8)	45.7 (6.1)	43.4 (6.6)	**0.041**
Male n (%)	37 (72.5)	54 (76.1)	76 (80.0)	21 (72.4)	0.714
IDUs n (%)	40 (78.9)	53 (77.9)	66 (71)	19 (67.9)	0.340
Previous AIDS events n(%)	19 (37.3)	25 (35.2)	23 (24.2)	9 (31.0)	0.311
HCV coinfection n (%)	51 (20.7)	71 (28.9)	95 (38.6)	29 (11.8)	0.111
HBV coinfection n (%)	6 (11.8)	7 (9.9)	12 (12.6)	4 (13.8)	0.934
HCC n (%)	16 (31.4)	14 (19.7)	32 (33.7)	5 (17.2)	0.116
MELD score (median, IQR)	16 (11-22)	16 (13-20)	13 (9-18)	18 (14-23)	**0.002**
CD4+count, cells/µL (median, IQR)	285 (194-422)	261 (169-389)	334 (193-465)	221 (115-327)	0.181
Plasma HIV < 200 cp/mL (%)	47 (95.9)	63 (95.5)	85 (95.5)	23 (92)	0.887
Donor variables					
Donor age (mean, SD)	56 (16.1)	57 (23)	52 (19.1)	56 (22.5)	0.483
Donor risk index (mean, SD)	1.7 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.5)	0.441
Post-LT variables, n (%)					
ART changes at 48 wk	3 (5.9)	10 (14.1)	17 (17.7)	11 (37.9)	**0.002**
Acute rejection at 48 wk	11 (21.6)	19 (26.8)	30 (31.6)	9 (31)	0.608
Retransplantation at 48 wk	3 (5.9)	1 (1.4)	2 (2.1)	0 (0.0)	0.305
Deaths at 48 wk	7 (14.0)	11 (15.5)	7 (7.4)	2 (6.9)	0.306

NUCs= nucleos(t)ide analogs; RAL= Raltegravir; PI= Protease Inhibitors; EFV= Efavirenz; ART= Antiretroviral treatment; LT= Liver Transplant; HCC= Hepatocellular carcinoma; IQR= Interquartile Range; SD= Standard Deviation
*Lopinavir/ritonavir and darunavir/ritonavir in 35 and 15 cases, respectively; **3/4 NUCs alone or with T20 in 5 cases (17%).

Table 3: Reasons leading to ART discontinuation (N=246)

	RAL	PI	NNRTI	3-4 NUC	P-values
Toxicity, n (%)					
Overall	3 (5.9%)	5 (7.0%)	8 (8.3%)	5 (17.2%)	0.286
Type of adverse events					
- Gastrointestinal	0 (0.0%)	1 (1.4%)	2 (2.1%)	1 (3.6%)	0.648
- Renal	2 (3.9%)	1 (1.4%)	1 (1.0%)	3 (10.7%)	**0.043**
- Neurological	1 (2.0%)	1 (1.4%)	1 (1.0%)	1 (3.6%)	0.820
- Other*	0 (0.0%)	3 (4.2%)	4 (4.2%)	3 (10.7%)	0.148
Other reasons, n (%)					
Overall	**0 (0.0%)**	**5 (7.0%)**	**9 (9.5%)**	**6 (20.7%)**	**0.012**
- Drug-drug interactions	0 (0.0%)	5 (7.0%)	4 (4.2%)	1 (3.4%)	0.283
- Virological failure	0 (0.0%)	0 (0.0%)	3 (3.2%)	4 (13.8%)	**0.001**
- Other**	0 (0.0%)	0 (0.0%)	2 (2.1%)	1 (3.4%)	0.345

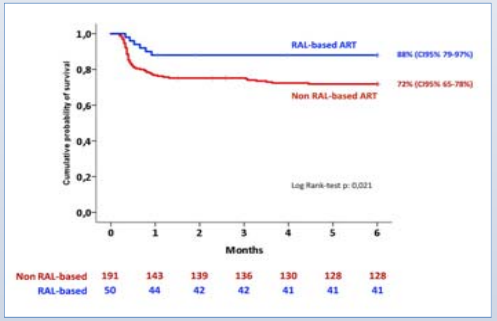
*Liver toxicity in two cases, mitochondrial toxicity, gynecomastia, T20 injection-site reaction, lipodystrophy, pancreatic toxicity and bone marrow toxicity in one case each and unknown in two cases; ** ART simplification in two cases and medical decision in one.

Table 2. Efficacy results through 48 weeks by ART regimen. Only patients with follow-up ≥48 weeks were included (ITT analysis, N=211).

		2 NUCs + RAL (N=40)	PI-based ART (N=59)	2 NUCs+ EFV (N=85)	3-4 NUCs ART (N=27)	P-value
Proportion of patients with plasma Viral load < 200 copies/mL after LT	4 weeks	100.0	80.6	87.1	95.0	0.088
	12 weeks	100.0	93.8	91.8	92.0	0.415
	24 weeks	100.0	98.0	97.3	92.3	0.329
	48 weeks	97.3	96.2	98.7	92.0	0.406
48-week CD4 T cell counts (cells/µL)	Median (IQR)	355 (221;522)	212 (165;303)	292 (200;445)	265 (165;334)	**0.014**
	Median (IQR) Increase from baseline	102 (-42;192)	7.0 (-43;133)	5.0 (-98;141)	86.0 (-43;116)	0.174
	> 200 (%)	76.3	54.9	74.0	61.9	0.076
	> 350 (%)	52.6	19.6	35.1	23.8	**0.009**

ITT= Intent-to-treat analysis; NUCs= nucleos(t)ide analogs; RAL= Raltegravir; PI= Protease Inhibitors; EFV= Efavirenz; ART= Antiretroviral treatment; LT= Liver Transplant; IQR= Interquartile Range.

Figure 1: Time until acute rejection by ART arm



Results

Patients receiving the four ART regimens had comparable baseline donor and recipient characteristics (**Table 1**). Raltegravir-based ART was the least changed regimen during the first 48 weeks post-LT. In terms of virological suppression, no differences were found among the four ART regimens at one year after LT. However, a trend towards better CD4+ T-cell count recovery at 48 weeks was observed in the RAL group (**Table 2**). **Table 3** shows events leading ART discontinuation. As for safety, the survival analysis did not reveal any differences in mortality and/or reLT rates after one year among the four ART regimens (p=.204 at one year for the combined endpoint by the log-rank test). Nevertheless, patients receiving RAL-based ART had a significantly lower cumulative probability of experiencing acute graft rejection during the first six months after LT (**Figure 1**) (p=.021 by the log-rank test).

Conclusions

A post-LT ART regimen based on RAL+2 NUCs was well tolerated and as virologically effective as other ART regimens (PI, NNRTI) at 48 weeks. In addition, the regimen showed a trend towards better immune reconstitution and was associated with significantly lower rates of acute rejection. One-year mortality and reLT were similar among the four ART regimens.

Whenever possible, RAL+2 NUCs should be the preferred ART regimen for HIV-infected individuals undergoing LT.

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