Poster 572

Dolutegravir in the French Named Patient Program* in Integrase HIV-2 Resistant Infected Patients

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Introduction

- Dolutegravir (DTG) is a second generation integrase inhibitor (INSTI), active in patients harboring first-generation INSTI resistant virus
- DTG has shown in vitro activity on HIV-2 isolates
- In France, DTG was available before the market authorisation in a named patient program (NPP / ATUn*) in salvage therapy
- We report preliminary safety and efficacy data of DTG containing regimens in HIV-2 infected patients with virological failure.

Methods

- Data from all HIV-2 infected patients with virological failure to raltegravir, receiving DTG 50 mg bid with optimized background antiretroviral (OB ARV) regimens were collected from the NPP.
- Plasma HIV-2 RNA was performed at time of DTG initiation (baseline), Month 3 (M3) and M6.
- Cumulative genotypic resistance tests (current and historical) were interpreted according to the last version of ANRS algorithm (v23).
- DTG plasma concentrations were measured, on the same samples than plasma HIV-2 RNA, using Ultra Performance Liquid Chromatography combined with tandem mass spectrometry (UPLC-MS/MS) (Waters Corporation Milford, MA, USA) (LOQ < 5 ng/ml) [Jung et al, 2007].
- Demographic, biological and therapeutic characteristics were recorded. Medians (IQR) were presented.

*Authorisation for Temporary Use by name

Table 1. Patients characteristics and immuno-virological response to dolutegravir containing regimens at M3 and M6

Pts	Age (Years)	Gender (M/F)	Duration of known HIV-2 infection (Years)	DTG containing ARV Regimens	GSS	Baseline		Month 3		Month 6	
						Plasma RNA (c/ml)	CD4 (/mm3)	Plasma RNA (c/ml)	CD4 (/mm3)	Plasma RNA (c/ml)	CD4 (/mm3)
1	53	M	9	ZDV/3TC/DRV/r/FOSC	3	46760	439	456	324	3170	450
2	43	M	15	TDF/FTC/LPV/SQV/r	2	23120	85	<40	181	<40	NA
3	52	M	9	ZDV/ABC/3TC/DRV/SQV/r/FOSC	3	1280	100	<40	132	<40	140
4	48	M	22	ZDV/3TC/DRV/r/FOSC	1	3096	53	376	76	807	46
5	53	M	13	DRV/r/MVC/FOSC	2	26060	157	<40	157	<40	320
6	54	M	10	3TC/DRV/r/MVC/FOSC	2	138400	62	11440	45	9991	174
7	69	M	20	ZDV/3TC/DRV/r/MVC	2	9544	138	1119	168	6715	118
8	51	F	20	DRV/SQV/r	1	3050	171	<40	157	<40	159
9	50	F	2	DRV/r/MVC	1	18630	355	<40	342	323	616
10	33	M	11	ABC/DRV/r	2	800	77	<40	109	NA	NA
11	58	M	24	TDF/ddI/DRV/r	3	3998	27	5407	NA	4795	NA
12	64	M	15	ABC/3TC/DRV/r	2	21199	97	1450	34	20206	NA
13	51	F	22	TDF/FTC/DRV/r	1	5741	200	6083	207	3995	NA

NA: non available

Table 2. Baseline patterns of protease, RT and integrase associated mutations and tropism

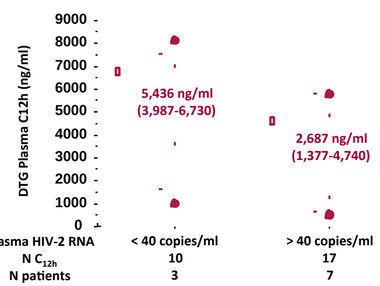
Pts	PR	RT	INI	Tropism
1	10I, 46L, 47A, 71I, 84V, 89V, 90M	65R	155H	X4
2	53L, 54L, 71I	NA	97A, 143C/G	X4
3	10I, 47A, 71I, 84V, 90M	184V	97A, 143H/R, 157Q	X4
4	54M, 71I, 82F, 90M	65R, 70R, 151M	72I, 155H	X4
5	10I, 50V, 71I, 82F, 89V, 90M	67N, 115F, 151M, 184V	97A, 143G	R5
6	54M, 71I, 82F, 89V, 90M	65R, 67M, 151M, 184V	92Q, 155H, 157Q	R5
7	54M, 71I, 84V, 90M	65R, 69S, 184V,	140S, 148R	NA
8	50V, 54L, 71I, 90M	65R, 151M,184V	72I, 97A, 143R	R5
9	10I, 50V, 54M, 71I	65R, 70R, 115F, 184V	92Q, 155H	X4
10	71I	184V	72I, 97A, 143R	X4
11	54M, 71I, 82F, 90M	67N, 184V, 215Y	147G	X4
12	10I, 50V, 89V	184V, 215Y	NA	X4
13	15V, 54M	65R, 151M, 184V	140S, 148K	X4

NA: non available

Results

- Patients baseline characteristics are summarized in **Table 1.**
- A total of 13 HIV-2 infected patients (10 males and 3 females) with a median age of 51 years (50-54) and having received 16 previous ARV prescriptions were in the NPP.
- Median duration of HIV-2 known infection was 15 years (10-20) and median follow up was 9 months (min: 3 - max: 15).
- HIV-2 groups were: A (n=9), B (n=3) and H (n=1) .
- HIV-2 tropism was genotypically predicted as CCR5 in 3 patients.
- Baseline median plasma HIV-2 RNA and CD4 cells count values were 9,544 cp/mL (3,096-23,120) and 100 cells/mm^3 (77-171), respectively.
- Optimized background ARV regimens, included: DRV/r (n=12), SQV/r (n=2), MVC (n=3) associated with NRTIs. Dual boosted PI regimens consisting in DRV/SQV/r and LPV/SQV/r were administered in two patients (pts 2 and 3). Five patients received in addition foscarnet induction treatment (FOSC), 4 of whom with ZDV, and one received in induction FOSC with ZDV just before DTG instauration (patient 8).
- Genotypic Sensitivity Score (GSS) was: GSS =3 (n=3), GSS =2 (=6) and GSS =1 (n=4).
- Baseline patterns of protease, RT and integrase associated mutations and tropism are depicted on **Table 2.**
- Available integrase genotypic resistance patterns were: Y143C/G/H/R (n=5), Q148K/R/S (n=2), N155H (n=4).
- At M3 and M6 plasma HIV-2 RNA was undetectable in 6/10 and 4/11 patients respectively, and median CD4 cells count was 158/mm^3 (101-188) and 166/mm^3 (135-353).
- All patients (4/4) with integrase resistance pattern Y143C/G/H/R (n=5) had an undetectable plasmaHIV-2 RNA at M6 (n=4, one missing data).
- Dolutegravir plasma concentrations (C_{12h}) are presented on **Figure 1.** Despite the small number of samples, DTG C_{12h} in patients with plasma HIV-2 RNA < 40 copies/ml were above than those with detectable plasma HIV-2 viral load at Month 6.
- One patient died from progressive multifocal leukoencephalopathy at M4. No other serious clinical or biological events led to DTG discontinuation.

Figure 1. Dolutegravir Plasma concentrations (ng/ml) according to plasma HIV-2 RNA at Month 6



Conclusions

- These preliminary results demonstrated that DTG-containing regimens provide a substantial efficacy rate for salvage therapy in heavily ARV-experienced HIV-2–infected patients with virus harboring resistance to first-generation INSTIs.
- Larger patient numbers and longer follow-up are needed to confirm these findings.

Reference

Jung BH, Rezk NL, Bridges AS, Corbett AH, Kashuba AD. **Simultaneous determination of 17 antiretroviral drugs in human plasma for quantitative analysis with liquid chromatography-tandem mass spectrometry.** *Biomed Chromatogr* 2007; **21**:1095-1104

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