Immunovirological outcome, genotypic changes and treatment adherence in HIV-1 infected children under lopinavir/ritonavir therapy

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BACKGROUND

Co formulation lopinavir/ritonavir (L/R) simplifies drug administration, which is very useful in HIV-infected paediatric patients. This combination has shown substantial activity against PI-resistant virus. Virological response to therapy with L/R has previously been associated with baseline genotypic pattern although genotypic resistance to L/R has not been completely defined. No single mutation has been found to confer high-level resistance to L/R, but resistance mutations selected by other PIs can contribute to virological failure. Different patterns or scores have been associated to L/R genotypic resistance. The old Kaletra mutation score was based on these 11 mutations: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V, and L90M. The ATU score by ANRS French Group reported a new set of 10 mutations: positions 10, 20, 24, 33, 36, 47, 48, 54, 82 and 84, that better predicted virological response compared to the old score. Although recent studies have suggested that six or more mutations are required to reduce L/R sensitivity, update research reports that 3 or 4 may suffice. Parkin et al report that mutations at positions 46, 54 and 82 were found to have a stronger than average effect on resistance. Mutations associated with greater than ten-fold reductions in L/R susceptibility are 10I, 71V, 90M, 54V, 46I, 84V, 46L, 73S and 20R. According to Abbott^{R}, manufacturer of lopinavir, virological failure in the presence of three of these mutations was very unusual in the absence of a change at codon 82 (Calvez 2001). In addition, the universal Pis associated mutations (UPAMs), including V82A/F/L/S/T, I84L/V, L90M, and L331I/V/F, confer cross-resistance to most PIs.

Consequently, to achieve a consensus pattern more information about genotypic changes in patients treated with L/R and virological failure is need.

OBJETIVES

To analyze the immunovirological outcome, genotypic changes and treatment adherence in 13 HIV-infected children, either antiretroviral-naïve (n = 1) or (PI)-experienced (n = 12) patients.

METHODS

- Plasma viraemia quantification : CA HIV-1 monitor (Roche Molecular system)
- CD4 cell count by cytometric flow
- Sequencing of RT and protease gene by Tru Gene (Bayer laboratories) in patients with detectable load viral (over 1000 copies/ml)
- Plasma concentration measure of L/P by HPLC
- Oral interview with patient and their family about adherence treatment
- Virological Failure was defined as viral load > 50 copies/ml after a minimum of 12 months of treatment with L/R

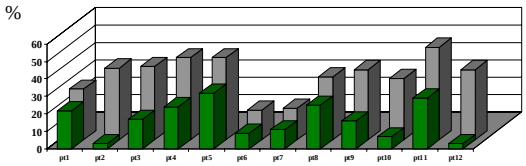
RESULTS

- 12 patients good adherence
- 12 patients good L/R plasmatic concentrations
- 12 patients increase CD4 cell count over 500 cells/ml
- 5 patients viraemia undetectable (42%)

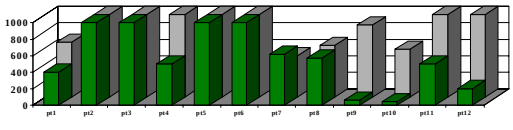
Patients Characteristics at Baseline

	Mean	Range
Age (years)	9	1-13
CD4	566 (28%)	45-1000 (3-32%)
Load Viral HIV Copies/ml	34800 (median)	16100->750000
Time since diagnosis	8 years	0,7-12 years
Previous PI	2	0-3
Number of Mutations at Baseline genotype		
Old LPV Score	2,3	1-5
ATU Score	1,4	0-5
Parkin Score	2,2	0-4
UPAMs	0,7	0-2
Total mutations	4	1-7

Increase CD4 Cell count in 12 patients with good adherence

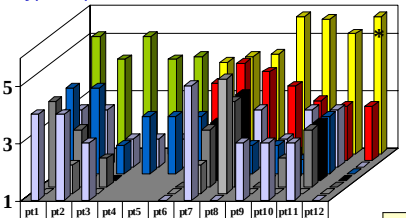


Absolute Cell count



Baseline After > 12 Months of treatment

HIV-1viral load Evolution and Numberof mutations (NM) at Baseline Genotype In patients with Good Adherence



	pt1	pt2	pt3	pt4	pt5	pt6	pt7	pt8	pt9	pt10	pt11	pt12
NM Old Score	4	4	3	NA	NA	1	5	1	3	3	3	1
NM ATU Score	1	2	1	NA	NA	0	2	5	1	1	1	0
NM Parkin Score	4	3	2	NA	NA	0	3	4	1	2	3	0
N° UPAMS Mutations	1	1	0	NA	NA	0	3	4	1	2	3	0
Years of L/R treatment	4	4	2	3	3	3	1,5	2	2	1,5	3	1
Previous IP	3	3	2	2	2	1	2	3	2	3	3	0
Load Viral after Treatment	<50	<50	<50	<50	<50	3,7	4,4	4,1	3,6	3,1	2,9	2,9
Load Viral Baseline	5,1	4,3	5,1	4,3	4,4	4,2	4,4	4,5	5,8	5,7	5,2	5,8

* Patient 12: Naive

RT mutations in Patients with Virological Failure >1000 Copies/ml

	treatment	41	44	67	69	70	74	103	108	118	181	184	190	210	215	219
Pat6	nevirapine +D4T +LdR	41I	WT	WT	WT	WT	WT	WT	WT	WT	181 C	WT	WT	WT	WT	WT
Pat7	abacavir+D4T+L/R	WT	WT	67 N	WT	70 R	WT	103 N	WT	118I	W	WT	WT	WT	215 F	219 Q
pat8	abacavir+D4T+ 3TC+L/R	41I	44D	WT	WT	WT	74V	103 N	WT	118I	W	184V	WT	210 W	215Y	WT
pat9	abacavir+ efavirenz + LR	41L	44D	67 N	69D	WT	WT	103 N	WT	WT	181 C	WT	WT	210 W	215 C	WT
Pat10	tenofovir+ D4T+ LR	41L	44D	WT	WT	WT	74V	WT	108I	118I	181 C	WT	190 A	210 W	WT	WT

PI Genotypic Mutations at Baseline

	CDC *	Nº IP previous	CVBAS	10	20	30	36	46	48	54	63	71	73	77	82	90
pat1	C	3	151000	10I	WT	WT	WT	46I	wt	WT	63P	WT	73s	77I	WT	90M
pat2	C	3	22300	WT	WT	WT	WT	WT	wt	54V	63P	71V	WT	77I	82R	WT
pat3	B	2	127000	10I	WT	MU	WT	WT	WT	WT	63P	71V	WT	WT	WT	WT
pat4	A	2	24200	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
pat5	B	2	31100	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
pat6	B	1	16100	WT	WT	WT	WT	WT	WT	WT	63p	WT	WT	WT	WT	WT
pat7	B	2	28300	10I	WT	WT	WT	46I	WT	55R	63P	71V	WT	WT	82R	WT
pat8	B	3	34800	WT	20R	WT	36I	WT	48V	54V	63P	WT	WT	WT	82R	90M
pat9	C	2	750001	10I	WT	WT	WT	WT	wt	WT	WT	WT	WT	WT	WT	WT
pat10	C	3	601000	WT	WT	WT	WT	WT	wt	WT	63P	WT	WT	WT	82F	90M
pat11	B	3	165000	WT	WT	WT	WT	46L	wt	WT	WT	WT	WT	77I	82R	90M
pat12	C	0	750001	WT	WT	WT	WT	WT	wt	WT	63P	WT	WT	WT	WT	WT
LPV Score																
ATU Score																
Parkin Score																
UPAMS																

PI Genotypic Mutations after Treatment

	postc v	10	20	30	32	36	46	47	48	53	54	63	71	82	84	90	L/R Plasmatic levels
pat1	<50																12,53/0,36
pat2	<50																1,95/0,3
pat3	<50																NA
pat4	<50																4,45/0,20
pat5	<50																6,23/0,33
pat6	6000	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	63P	WT	WT	WT	WT	13,81/0,5
pat7	26300	10I	WT	WT	WT	WT	46I	WT	WT	WT	54V	63P	71V	82A	WT	WT	5,15/0,21
pat8	14800	10V	WT	WT	WT	36I	WT	47V	WT	53L	54V	63P	71V	82A	WT	90M	16,89/1,14
pat9	4730	10I	20R	WT	32I	36I	46I	47V	WT	53L	54V	63P	71V	82A	WT	WT	1,33/0,07
pat10	1310	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	63P	WT	82F	WT	90M	3,41/0,20
pat11	927																8,47/0,54
pat12	962																5,02/0,15
LPV Score																	
ATU Score																	
Parkin Score																	
UPAMS																	

CONCLUSIONS

- **Our Patients showed good adherence to L/P. A good immunological (100%) but milder virological (40%) response were observed.**
- **The patients with virological failure developed these mutations: 10I, 20R, 36I, 46I,47 V (2 patients) 53L, 54V (3 patients) ,63P, 71V (2 patients), and 82A (3 patients)**
- **The most frequent mutations in patients with virological failure and available genotype (5 patients) were 63P (5 Patients) 82A/F (4 patients) 54V and 71V (3 patients)**
- **The absence of PI resistance in one patient with virological failure is remarkable**
- **Further studies are required for a better definition of L/P-associated resistance mutations**

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