



Influence of Genotypic Resistance on the Viral Load Response to Lopinavir/r (LPV/r) in 167 Patients including an Analysis of New Protease Inhibitor Resistant Mutations in 21 Patients who Failed

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ABSTRACT

Background: LPV is a PI that has been found to have a high barrier to resistance. Studies have shown that patients (pts) with > 5 PI mutations (based on a mutational score) have poorer VL response with LPV/r. No specific mutation has been found to confer LPV resistance.

Methods: To determine the influence of resistance patterns on VL response to LPV/r and to analyze the resistance patterns of pts who have failed LPV/r, retrospective cohort study of pts enrolled in the LPV/r EAP in 4 Toronto HIV centres was carried out. To be included, pts must have had a genotype just prior to starting LPV/r and at least 1M F/U. The LPV mutation score was defined as the number of mutations at positions 10, 20, 24, 46, 53, 54, 63, 71, 82, 84 and 90. The proportion of pts who achieved a VL < 50/mL (Chiron, bDNA) at 4-6M was determined for different mutations and for various LPV mutation scores using an on-treatment analysis. Logistic regression was used to determine the effect of each additional PI mutation in the LPV mutation score. Changes in resistance patterns were analyzed in pts who had detectable virus on and who had genotyping after LPV/r.

Results: 167 ARV-experienced pts were analyzed (98.2% were PI-experienced). The mean number PI mutations was 4.8 (SD 3.1). The mean LPV mutation score was 3.3 (SD 2.1). 85.7% had a score of 0-5, 13.1% had a score of 6-7 and 1.2% had a score > 7. 54.8% had the 90M mutation and 1.8% had the D30N mutation. Overall, 37.3% achieved a VL < 50/mL by 4-6M, including 40.5% with a LPV score of 0-5, 25.0% with a score of 6-7 and neither of the 2 pts with a score > 7. Using logistic regression, each additional PI mutation in the LPV score increased the odds of virologic failure by 1.26 (p=0.02), 26.7% of pts with and 52.4% without the 90M mutation achieved a VL < 50/mL at 4-6M (p=0.008).

21 pts who were VL non-responders had a repeat genotype after initiating LPV/r. 4 pts had no new documented PI mutations. New primary PI mutations were noted in 6 pts including 90M in 3 pts, and 82V in 4 pts. Reviewing the drug histories, all of these mutations may have been selected from previous PI use. Mutations that would increase the LPV mutation score by 1, 2 or ≥3 were observed in 5, 5 and 4 pts, respectively. 19 new secondary PI mutations were found in 11 pts including those at sites 33 (5pts), 36 (2 pts) 47 (3 pts), 48 (1pt), 50 (2pts), 73 (3pts) and 77 (3pts) of the protease gene, and may have been selected by previous PI therapy in 15 cases. 33 other PI mutations of uncertain significance were observed in 10 pts and occurred in ≥ 3 pts at sites 37, 55, 58, 52, and 93.

Conclusions: VL failure to LPV/r has a linear relationship with the LPV mutation score. Presence of the L90M mutation is highly predictive of failure. VL failure on LPV/r often selects for mutations that may have developed under previous PI pressure. VL failure on therapy with LPV/r results in an increased LPV mutation score in 2/3 of pts. The significance of new PI mutations observed requires further study.

INTRODUCTION

•LPV/r is a PI combination that has been found to have a high barrier to resistance.

•Studies have shown that patients (pts) with ≥ 5 PI mutations (based on a mutational score) have poorer VL response with LPV/r.

•Calvez et al. found that protease mutations at amino acid sites 10, 46, 54 and 82 are associated with decreased virologic response in patients on LPV/r through the French EAP.

METHODS

•**OBJECTIVES:** To determine the influence of resistance patterns on VL response to LPV/r and to analyze the resistance patterns of pts who have failed LPV/r.

•A retrospective cohort study of pts enrolled in the LPV/r EAP in 4 Toronto HIV centres was carried out.

•To be included, pts must have had a baseline genotype on their failing therapy and at least 1 month of follow-up after the initiation of LPV/r.

•The LPV mutation score = number of mutations at positions 10, 20, 24, 46, 53, 54, 63, 71, 82, 84 and 90.

•The proportion of pts who achieved a VL < 50/mL (Chiron, bDNA) at 4-6M was determined for different mutations and for various LPV mutation scores using an on-treatment analysis.

•Logistic regression was used to determine the effect of each additional PI mutation in the LPV mutation score.

•Changes in resistance patterns were analyzed in pts who failed to respond to or had rebound in VL after initiating LPV/r and who had a repeat genotype.

RESULTS

Table 1 - Characteristics of LPV/r EAP patients with baseline genotype

Number of patients with baseline genotype	167
Proportion of male patients	93%
Mean age (range)	44 years (30-70)
Mean number of previous ARV drugs (range)	8.2 (2 - 14)
Mean number of previous PIs (range)	2.9 (0 - 6)
Proportion of NNRTI-experienced patients	67%
Mean duration of prior ARV therapy (range)	8.2 years (2.2 - 17.8)
Mean months of follow-up (range)	5.8 (1 - 17)

Table 2 - Results of baseline genotype

Mean number of PI mutations (range)	5.0 (0 - 17)
Mean number of RT mutations	6.1 (0 - 41)
Mean LPV mutation score (range)	3.3 (0 - 8)
Score ≤ 5	: 144 (85.7%)
Score 6 - 7	: 22 (13.1%)
Score ≥ 8	: 2 (1.2%)

Table 3 - Mean LPV mutation score in virologic responders* versus non-responders

	Responders	Non-responders	p
N	38	64	
Mean LPV mutation score	2.8	3.8	0.02

* Virologic response defined as VL < 50 copies/mL @ 4-6 months (37.3% overall)

Table 4 - Frequency of specific PI mutations in 167 baseline genotypes

Protease mut location	Frequency
10	65.5%
20	18.4%
24	4.8%
30	1.8%
46	38.7%
53	1.2%
54	26.2%
63	4.2%
71	56.6%
82	64.9%
84	23.2%
90	54.8%

yellow = frequency > 25%

Table 5 - VL response @ 6M on LPV/r-containing salvage regimen a/w specific PI mutations

Virologic response - VL < 50 copies/mL @ 4-6M						
protease mutation	With mutation	%	Without mutation	%	Odds ratio	p
10	22/66	33.3	16/36	44.4	1.6	0.27
46	13/44	29.6	25/58	43.1	1.8	0.16
54	7/30	23.3	31/72	43.1	2.5	0.06
71	20/57	35.1	18/45	40.0	1.2	0.61
82	10/37	27.0	28/65	43.1	2.0	0.11
90	16/60	26.7	22/42	52.4	3.0	0.008

Table 6 - Univariate analysis of the effect of the LPV mutation score on virologic response

LPV mutation score cut-off	Odds Ratio	95% CI	p
≥ 2	2.3	(0.8 - 5.7)	0.09
≥ 3	2.6	(1.1 - 6.2)	0.03
≥ 4	2.7	(1.2 - 6.2)	0.02
Per mutation in LPV mut score*	1.26	(1.04 - 1.54)	0.02

* Using logistic regression

Table 7 - Comparison of different studies' LPV mutation score cut-off predictive of virologic failure

Study	Patient pop'n	LPV mut score cut-off
Calvez et al. (French study)	French ATU patients	≥ 6
Kempf et al. (Abbott study)	Phase II multi-PI-experienced NNRTI-naïve	≥ 5
Loutfy et al. (Present study)	Toronto EAP patients, ARV-experienced, NNRTI-experienced	≥ 3

Table 8 - Multivariate analysis* of the presence of the L90M mutation and the LPV mutation score on virologic response

Variable	Odds Ratio	95% CI	p
L90M	2.5	(1.0 - 6.2)	0.05
per add'n mut in LPV mut score	1.1	(0.9 - 1.4)	0.30

* Using logistic regression

New protease mutations in 21 LPV/r-treated patients

Patient	Previous PIs	Present PI(s)	New protease mutations in 21 LPV/r-treated patients			Number protease mutations before	Number protease mutations after
			White - same mutations	Yellow - new mutations	Blue - disappeared mutations		
1	SQ, IND, RTV, NLF, APV	LPV/r		10, 20, 32, 36, 46, 47, 54, 71, 82, 99	8	9	
2	SQ, IND, RTV, NLF, APV	LPV/r		3, 10, 33, 37, 46, 53, 54, 55, 58, 62, 63, 71, 73, 82, 84, 90, 93, 95	14	10	
3	SQ, IND, RTV, NLF	LPV/r, APV		10, 20, 36, 54, 77, 90	2	6	
4	RTV, NLF	LPV/r, APV		10, 32, 46, 47, 54, 77, 82	6	7	
5	SQ, IND, RTV, NLF	LPV/r, APV		10, 18, 19, 20, 24, 37, 41, 46, 54, 61, 63, 67, 71, 77, 84, 90, 93	5	17	
6	SQ, IND, RTV, NLF	LPV/r		10, 36, 46, 71, 84, 90	6	6	
7	SQ, IND, RTV	LPV/r		10, 24, 46, 54, 77, 82	6	6	
8	SQ, IND, RTV, NLF	LPV/r, APV		10, 20, 33, 35, 36, 43, 46, 50, 54, 55, 61, 62, 63, 71, 72, 73, 82, 90, 93	9	18	
9	NLF	LPV/r		71, 77, 90	3	3	
10	SQ, IND, RTV, NLF, APV	LPV/r, APV		10, 20, 36, 54, 71, 84, 90	6	7	

New protease mutations in 21 LPV/r-treated patients

Patient	Previous PIs	Present PI(s)	New protease mutations in 21 LPV/r-treated patients			Number protease mutations before	Number protease mutations after
			White - same mutations	Yellow - new mutations	Blue - disappeared mutations		
11	SQ, RTV, NLF	LPV/r, APV		10, 20, 33, 35, 36, 37, 46, 54, 55, 62, 63, 71, 73, 84, 85, 90, 93	8	17	
12	SQ, IND, RTV, NLF	LPV/r		10, 20, 36, 46, 54, 71, 73, 82, 90	7	9	
13	SQ, RTV	LPV/r, RTV, APV		10, 20, 36, 48, 54, 58, 74, 82, 90	6	9	
14	SQ, IND, APV	LPV/r		10, 33, 36, 46, 54, 71, 73, 82, 90	5	9	
15	SQ, IND	LPV/r		10, 20, 32, 37, 46, 47, 50, 54, 63, 71, 77, 82, 90	7	12	
16	SQ, IND, RTV, NLF, APV	LPV/r		10, 46, 73, 84, 90	4	5	
17	SQ, IND, RTV, NLF, APV	LPV/r		10, 20, 36, 46, 53, 54, 58, 71, 73, 82, 90	8	11	
18	IND, RTV, NLF, APV	LPV/r		10, 33, 46, 71, 77, 84, 90	5	7	
19	IND, APV	LPV/r		10, 20, 32, 46, 47, 54, 71, 77, 82	1	9	
20	SQ, IND, RTV	LPV/r		10, 46, 54, 58, 71, 77, 82, 90	0	8	
21	IND, RTV, NLF	LPV/r		10, 36, 71, 73, 90	5	5	

Summary of new protease mutations in 21 LPV/r-treated patients

• New primary protease mutations in 6 pts including					
Mutation	No. of pts	Archival			
90M	3	X (3/3)			
82V	4	X (4/4)			
• 33 other protease mutations of uncertain significance were observed in 10 patients					
Mutations in ≥ 3 pts					
	37				
	46				
	55				
	58				
	93				
• No new mutations in 4 patients					
• New secondary protease mutations in 19 cases (14 pts) including					
Mutation	No. of pts	Archival			
33	5	X (4/5)			
36	2	X (2/2)			
47	3	X (2/3)			
48	1	X (1/1)			
50	2	X (0/2)			
73	3	X (3/3)			
77	3	X (3/3)			

CONCLUSIONS

•The overall virologic response (VL < 50 copies/mL) in this heavily ARV-experienced was 37.3% at 4-6 months.

•In this study which included patients that were heavily ARV-experienced and often NNRTI-experienced, a LPV mutation score ≥ 3 was associated with poorer virologic response with LPV/r.

•VL failure to LPV/r has a linear relationship with the LPV mutation score.

•The presence of the L90M mutation is predictive of virologic failure using univariate analysis and multivariate analysis adjusting for total number of mutations in the LPV mutation score.

•VL failure on LPV/r often selects for mutations that may have developed under previous PI pressure.

•VL failure on therapy with LPV/r results in an increased LPV mutation score in 2/3 of pts.

•The significance of new PI mutations observed requires further study.