Abstract P100

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Prevalence of Multiple Protease Mutations at Positions 33, 82, 84 and 90 Among PI-Experienced Patients and the Effect on Virologic Response to Lopinavir/ritonavir-Based Regimens

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BACKGROUND

A recent study demonstrated better 2-week virologic response to a tipranavir/ritonavir-based regimen vs. other boosted protease inhibitor regimens among patients with prior 3-class virologic failure and 3-4 PI mutations at positions 33, 82, 84, and 90.[1] However, the prevalence of such individuals among PI-experienced pts has not been adequately assessed, and in the prior study, other factors such as treatment history or the accumulation of multiple additional protease mutations beyond those present at the four positions of interest may have influenced poorer response to treatment with other protease inhibitors.

Thus, the impact of these mutations on response to other protease inhibitors, such as lopinavir/ritonavir (LPV/r), in other cohorts is of interest. In this analysis of a large observational cohort and multiple clinical trials evaluating LPV/r-based therapy in PI-experienced patients, we assessed the prevalence of these mutation patterns and compared response in patients with 3-4 such mutations to those with fewer mutations.

METHODS

Patients

- A group of 792 patients with baseline genotype and follow-up viral load data in the Kaletra ATU ("Authorisation Temporaire d'Utilisation," Provisional Authorization of Use) program conducted in France ("observational cohort").
- A group of 237 PI-experienced patients with baseline genotype and who were treated with LPV/r for a minimum of 8 weeks in 3 Phase II/III clinical trials ("clinical trials group") These trials included study 765 (phase II, single PI-experienced patients), study 957 (phase II, multiple PI-experienced patients), and study 888 (phase III, single PI-experienced patients).

Virologic Response

- For the observational cohort, response was defined as any HIV RNA value <400 copies/mL or an HIV RNA decline from baseline of at least 1.0 $\log_{10}$ copies/mL during follow-up of up to 1 year.
- For the clinical trials group, in which all patients were NNRTI-naive and received either efavirenz or nevirapine, a stricter measure of response was used: HIV RNA <400 copies/mL at Week 48. A dropouts-as-censored analysis was used in which patients discontinuing prior to Week 48 with HIV RNA <400 copies/mL were censored, while patients discontinuing with HIV RNA above 400 copies/mL were considered nonresponders.

Analysis

- The proportions of responders were compared among patients with 3-4 baseline protease mutations at positions 33, 82, 84, and 90 vs. patients with 0-2 such mutations.

RESULTS

Baseline Characteristics

- In the observational cohort, mean baseline HIV RNA was 4.8 $\log_{10}$ copies/mL, mean CD4 count was 178 cells/mm^3, mean number of prior PIs used was 3.1 (range 1-5), and 78% of patients were NNRTI-experienced.
- In the clinical trials group, mean baseline HIV RNA was 4.2 $\log_{10}$ copies/mL, mean CD4 count was 321 cells/mm^3, mean number of prior PIs used was 1.4 (range: 1-4), and all patients were NNRTI-naive.
- A baseline mutation pattern including 3 or more mutations among positions 33, 82, 84, and 90 in protease was uncommon, occurring in only 55 (5%) patients (Table 1).
- Among patients with virus demonstrating 3-4 mutations, a pattern including mutations at positions 33, 82, and 90 was most common (25/55, 45%).
- The number of additional primary mutations (among D30N, G48V, and I50V) and secondary mutations (among L10F/I/R/V, K20M/R, L24I, M36I, M46I/L, I47A/V, I54A/V/L/S, A71V/T, G73S/A, V77I and N88D) in protease is shown in Table 2.

Table 1. Baseline Genotype Data

Substitution	Observational Cohort (n=792)	Clinical Trials (n=237)
L33F	43 (5%)	18 (8%)
V82A/C/F/S/T	334 (42%)	76 (32%)
I84V	165 (21%)	26 (11%)
L90M	471 (59%)	84 (35%)
No. of mutations among positions 33, 82, 94, 90		
0	147 (19%)	98 (41%)
1	322 (41%)	86 (36%)
2	279 (35%)	42 (18%)
3	43 (5%)	10 (4%)
4	1 (<1%)	1 (<1%)

Table 2. Additional Primary and Secondary Mutations in Protease

Substitution	Observational Cohort (n=792)		Clinical Trials (n=237)	
No. of mutations among positions 33, 82, 94, 90	Mean (range) no. of additional primary mutations	Mean (range) no. of additional secondary mutations	Mean (range) no. of additional primary mutations	Mean (range) no. of additional secondary mutations
0-2	0.1 (0-2)	3.1 (0-7)	0.2 (0-1)	2.7 (0-8)
3-4	0.1 (0-1)	4.2 (0-6)	0.0 (0-0)	4.5 (0-6)

Virologic Response

- In the observational cohort, a baseline mutation pattern including 3-4 mutations at positions 33, 82, 84, and 90 in protease did not result in a significant reduction in virologic response compared to 0-2 mutations at these positions (Figure 1).
- Likewise in the clinical trials, 3-4 mutations among positions 33, 82, 84, and 90 did not result in lower virologic response (Figure 2).

Figure 1. Observational Cohort: Virologic Response by Baseline Genotype

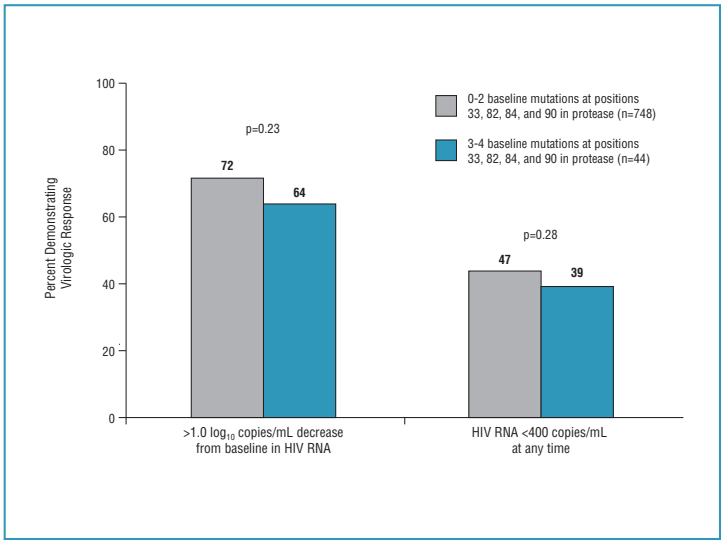
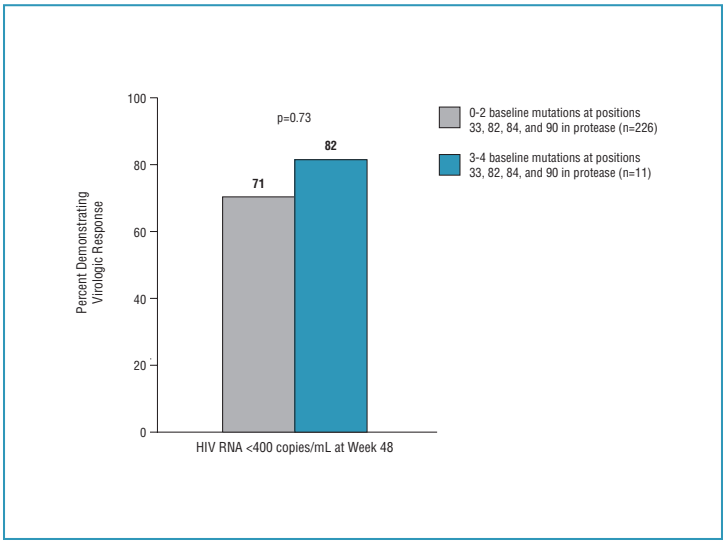


Figure 2. Clinical Trials Group: Virologic Response by Baseline Genotype



- For the most common mutational pattern, which consisted of mutations at positions 33, 82, and 90 and appeared in 25/55 subjects with 3-4 mutations, virologic response compared favorably to overall results
  - In the observational cohort, of 20 patients with mutations at 33, 82, and 90, 14 (70%) demonstrated an HIV RNA decrease >1.0 $\log_{10}$ copies/mL.
  - In the clinical trials, 5/5 patients (100%) with mutations at 33, 82, and 90 demonstrated HIV RNA <400 copies/mL at Week 48.
- Among patients with 3-4 mutations at positions 33, 82, 84, and 90, the V82A mutation did not appear to have a negative impact on virologic response.
  - In the observational cohort, 14/23 (61%) patients with a V82A mutation and 14/21 (67%) patients without the V82A mutation demonstrated an HIV RNA decrease >1.0 $\log_{10}$ copies/mL (p=0.76).
  - In the clinical trials group, 7/8 (88%) patients with a V82A mutation and 2/3 (67%) patients without the V82A mutation demonstrated HIV RNA <400 copies/mL at Week 48 (p=0.49).
- The number of baseline mutations in the "ATU mutation set" (positions 10, 20, 24, 33, 36, 47, 48, 54, 82, 84 in protease) has been shown to be highly associated with response in the patients included in the current analysis.[2,3]
  - However, the number of mutations among positions 33, 82, 84, and 90 (0-2 vs. 3-4) was not associated with response, either by univariate logistic regression analysis or multiple logistic regression analysis after accounting for the impact of the number of mutations from the ATU set (p>0.2 for all analyses).

DISCUSSION

In this analysis of a large observational cohort and multiple clinical trials of lopinavir/ritonavir, virologic response in patients with 3-4 mutations from positions 33, 82, 84, and 90 in protease was not significantly different from virologic response in patients with 0-2 such mutations. This contrasts with the findings in a recent study by Mayers, et al.,[1] in which patients with 3-4 such mutations randomized to a LPV/r-containing regimen experienced only a modest virologic response during the first two weeks.

A number of factors may explain this discrepancy. Patients in the LPV/r observational cohort and clinical trials did not commonly have other primary protease inhibitor mutations and had relatively few additional secondary mutations. If patients in the recently reported study had multiple additional mutations associated with PI resistance, their response may have been correspondingly lower. Patients in the current analysis had not previously received LPV/r. In the recently reported study, if the LPV/r was a recycled drug, a robust virologic response might not be expected. This would be especially true for patients receiving a LPV/r-based regimen at study entry who were randomized to the LPV/r arm (a patient switching from one LPV/r-based regimen to another LPV/r-based regimen does not provide information on the intrinsic antiviral activity of LPV/r).

CONCLUSIONS

- Despite extensive protease inhibitor experience, the presence of multiple PI mutations from positions 33, 82, 84, and 90 was uncommon in a large observational cohort as well as in PI-experienced patients enrolled in clinical trials in the lopinavir/ritonavir development program.
- Virologic response to lopinavir/ritonavir was not significantly reduced among pts with 3-4 such mutations.
- The presence of 3-4 mutations at the positions 33, 82, 84, and 90 does not appear to be a reliable predictor of antiviral activity of a lopinavir/ritonavir-based regimen.

REFERENCES

1. Mayers D, et al. Impact of three or four protease mutations at codons 33, 82, 84, 90 an 2 week virological responses to tipranavir, lopinavir, amprenavir and saquinavir all boosted by ritonavir in Phase 2B trial BI 1182.51. *Antivir Ther* 2004;9:S163.
2. Isaacson JD, et al. Quantitative estimate of the effect of individual baseline mutations in HIV protease on the virologic response to lopinavir/ritonavir therapy in heavily antiretroviral-experienced patients. 9th CROI, Seattle, February 2002, Abstract 559.
3. Norton M, et al. Genotypic algorithms specific to lopinavir/ritonavir outperform nonspecific lists of PI mutations in predicting virologic response to lopinavir/ritonavir in PI-experienced patients. *Antivir Ther* 2004;9:S131.