950101

Efficacy and Safety of Lopinavir/r and Atazanavir Without a Nucleoside Backbone in Antiretroviral Therapy Experienced HIV-Infected Subjects

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Abstract

Nucleoside reverse transcriptase inhibitors have traditionally been considered the backbone of highly active antiretroviral therapy (HAART). Reports of mitochondrial toxicity, along with simplifying HAART regimens have tempered the enthusiasm for these agents and led to consideration of nucleoside sparing therapy. The objective of this study was to assess the efficacy and tolerability of LPV/r and ATV without a nucleoside backbone in ART-experienced HIV-infected subjects.

This was a 48-week, prospective, single-center pilot study in HIV-infected, ART-experienced subjects with HIV RNA <50 copies/mL. Subjects (n=11) were eligible for this study upon completion of a pharmacokinetic study of lopinavir/r and atazanavir. Four subjects elected to participate. Subjects had a history of 4 or more weeks on a regimen consisting of LPV/r 400/100 mg BID + ATV 300 mg QD + nucleoside backbone. At baseline, subjects discontinued the nucleoside backbone, remaining on LPV/r 400/100 mg BID and ATV 300 mg QD. Efficacy and safety data were assessed at 7 visits over 48 weeks.

All subjects (n=4) completed the study. At week 48, 100% of subjects remained virologically suppressed (HIV RNA <50 c/mL). Mean subject CD4+ T-cell count rose from 569 cells/mm^3 (344 – 929) at baseline to 663 cells/mm^3 (390 – 911) at week 48. One subject experienced a grade I increase in plasma bilirubin concentration, no other adverse events occurred through 48 weeks.

The combination of LPV/r 400/100 mg BID + ATV 300 mg QD was shown to be efficacious and well-tolerated. There were no virologic failures and the mean CD4+ T-cell count increased. Although the study population was small, these results suggest that this dual PI combination is a safe and effective nucleoside sparing regimen, and further studies are warranted.

Introduction

Nucleoside reverse transcriptase inhibitors have traditionally been considered the backbone of a highly active antiretroviral therapy (HAART) regimen. Increasing reports of mitochondrial toxicity along with the goal of simplifying HAART regimens have tempered the enthusiasm for the use of these agents and has led to the consideration of nucleoside sparing therapy. This study aimed to explore the efficacy and safety of dual boosted lopinavir/r with atazanavir in virologically suppressed HIV+ experienced subjects.

Objective

To assess the efficacy and tolerability of LPV/r and ATV in ART-experienced HIV-infected subjects with undetectable viral loads.

Methods

- A 48-week, prospective, open-label, single-center pilot study in HIV-infected subjects with HIV RNA <50 copies/mL.
- Subjects were eligible for participation following completion of a pharmacokinetic study.
  - During this PK study, subjects spent 4 weeks on a regimen consisting of LPV/r 400/100 mg BID + ATV 300 mg QD + nucleoside backbone, during which a pharmacokinetic analysis of LPV and ATV plasma concentrations was performed.
- At baseline subjects discontinued nucleoside backbone, remaining on LPV/r 400/100 mg BID + ATV 300 mg QD.
- Efficacy and safety parameters were assessed at 7 study visits over the course of 48 weeks.
- Adverse events were graded according to the ACTG toxicity grading scale.

Results

- Pharmacokinetic results from analyses performed prior to baseline suggested no clinically significant interaction between LPV/r and ATV (**Table 1**, **Figures 1** and **2**).
- Four subjects enrolled in follow up study, all completing 48 weeks (**Table 2**).
- At week 48, 100% (n=4) of subjects remained virologically suppressed (HIV RNA <50 copies/mL) (**Table 3**).
- Mean subject CD4+ T-cell count rose from 569 cells/mm^3 (344 – 929) at baseline to 663 cells/mm^3 (390 – 911) at week 48 (**Figure 3** and **Table 3**) .
- One subject experienced a grade I increase in plasma bilirubin concentration. No other adverse events occurred through 48 weeks.
- No clinically significant changes in lipids occurred through 48 weeks.

Results (cont.)

Results Mean (± SD) LPV and ATV PK were available for 11 subjects and are summarized in the table below. In all subjects, baseline HIV RNA was ≤75 copies/mL and the mean (± SD) CD4 count (cells/mm^3) was 517 (± 252).

Table 1. Results Mean (± SD) LPV and ATV PK

Parameter	LPV/r (+ ATV)	LPV/r (Subject Controls)	ATV (+ LPV/r)	ATV + Ritonavir (historical controls)
Dose (mg)	400/100 q12h	400/100 q12h	300 q24h	300 + 100 q24h
N	11	11	11	10
C_{min} (mcg/mL)	4.2 (± 2.4)	3.8 (± 2.1)†	0.8 (± 0.4)	0.9 (± 0.8)
$AUC_{0\text{-}12h}$ (h•mcg/mL)	73.4 (± 25.1)	74.7 (± 17.3)‡	–	–
$AUC_{0\text{-}24h}$ (h•mcg/mL)	–	–	33.1 (± 13.6)#	53.8 (± 35.3)
CL/F (L/h)	6.1 (± 2.3)	5.6 (± 1.2)†	10.2 (± 3.4)	not available

† $p > 0.05$
# Reported mean (± SD) AUC for ATV 400 mg q24h in 13 HIV+ subjects = 22.3 (± 20.2) h•mcg/mL

Figure 1. Mean ± SD LPV Concentrations (n=11)

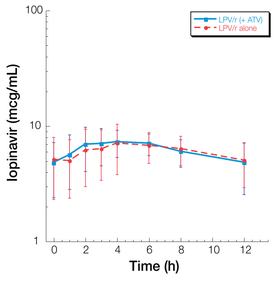


Figure 2. Mean ± SD ATV Concentrations (n=11)

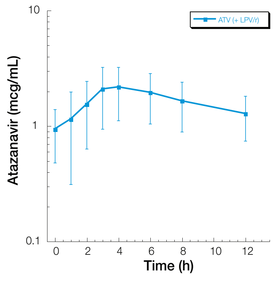


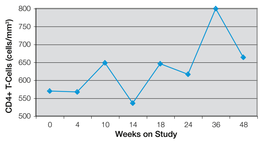
Table 2: Study Subject Demographics and Baseline Viral Load/T-cell Statistics (n=4)

Subject #	001	002	003	004	Mean (range)
Age	43	53	38	38	43 (38 – 53)
Sex	Male	Male	Male	Male	NA
# of previous PIs	1	1	1	1	1
# of years of ARV therapy prior to study start	1.4	3.5	3.7	4.0	3.2 (1.4 – 4.0)
Baseline HIV RNA (copies/mL)	<50	<50	<50	<50	NA
Baseline CD4+ T-cells (cells/mm^3)	344	455	549	929	569 (344 – 929)

Table 3: Dual boosted PI pilot study subject results, viral load and CD4+ T-cells results at 48 Weeks (n=4)

Subject #	001	002	003	004	Mean (range)
HIV RNA (copies/mL)	<50	<50	<50	<50	NA
CD4+ T-cells (cells/mm^3)	390	607	911	745	663 (390 – 911)

Figure 3. Mean Subject CD4+ T-cells/mm^3 at Each Study Visit from Baseline to Week 48 (n=4)



Discussion

- Dual boosted PI therapy of lopinavir/ritonavir and atazanavir in HIV+ subjects has demonstrated favorable pharmacokinetic profiles for both lopinavir and atazanavir in a number of studies[1,2,3].
- In virologically suppressed HIV+ experienced subjects on a lopinavir/r based regimen, the addition of atazanavir to lopinavir/r followed by simplification of the nucleoside backbone lead to sustained virological response and further improvement in CD4 cells.
- Dual boosted lopinavir/r with atazanavir could provide a treatment option to spare long-term toxicities associated with NRTI use, preserve against NRTI resistance, and manage those with NRTI resistance.

Acknowledgements

The study acknowledges the clinical research support of Michael Norton, M.S., P.A.C. from Abbott.

References

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Conclusions

The combination of LPV/r 400/100 mg BID + ATV 300 mg QD was efficacious and well-tolerated by study subjects. There were no virologic failures (HIV RNA >50 copies/mL) and the mean CD4+ T-cell count increased. Although this study population was small, these results suggest that this dual PI combination is a safe and effective nucleoside sparing regimen. Further studies are warranted.