Background

LPV/r used as part of a 3-drug regimen in antiretroviral-naive patients is highly effective in durably suppressing plasma HIV-1 RNA to <50 copies/mL.14 In antiretroviral-naive patients, combination therapy with LPV/r only rarely selects for protease inhibitor (PI) resistance.

• An analysis of 4 Abbott clinical trials that enrolled 654 antiretroviral-naive patients starting a LPV/r-based 3-drug regimen and followed for 2–7 years showed no selection of protease inhibitor (PI) resistance in patients experiencing virologic failure.1–4

• A single case of development of PI resistance during therapy with a LPV/r-based 3-drug regimen has been reported in the literature (Table 1).15

LPV/r monotherapy has shown promising short-term efficacy in small studies of relatively short duration.16 Little is known about the propensity of LPV/r monotherapy to select drug resistance. However, four cases of PI-naive patients on LPV/r monotherapy developing primary PI resistance mutations with virologic failure have been presented (Table 1).

Table 1. Protease Inhibitor Resistance in Protease Inhibitor-Naive Patients on LPV/r Regimen

<table>
<thead>
<tr>
<th>Three-Drug SMART Including LPV/r</th>
<th>Case Source</th>
<th>Prior ARV</th>
<th>Current ARV</th>
<th>Protease Genotype</th>
<th>LPV Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>EFV/ATZ/3TC</td>
<td>Lopinavir</td>
<td>Ritonavir</td>
<td>A71V</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient 2</td>
<td>EFV/ATZ/3TC</td>
<td>Lopinavir</td>
<td>Ritonavir</td>
<td>A71V</td>
<td>N/R</td>
</tr>
<tr>
<td>Patient 3</td>
<td>EFV/ATZ/3TC</td>
<td>Lopinavir</td>
<td>Ritonavir</td>
<td>A71V</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient 4</td>
<td>EFV/ATZ/3TC</td>
<td>Lopinavir</td>
<td>Ritonavir</td>
<td>A71V</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Conclusions

The relative risk of developing resistance with failure of LPV/r monotherapy versus 3-drug therapy is unknown. We evaluated the frequency of emergence of drug resistance among subjects on LPV/r monotherapy in a controlled, randomized trial of the safety and efficacy of LPV/r monotherapy compared to LPV/r + zidovudine/lamivudine (AZT/3TC) in antiretroviral-naive patients.

Methods

Study Design

MONARCH is an ongoing controlled, randomized, open-label, 96-week trial comparing the safety and efficacy of LPV/r + ATZ/3TC to LPV/r monotherapy in antiretroviral-naive HIV-1-infected adults starting antiretroviral therapy.

Figure 1. MONARCH Study Design

Screening

LPV/r 400/100 mg BID

12 weeks

LPV/r 400/100 mg BID + ATZ/3TC 300/150 mg BID

n=63

Screening

LPV/r 400/100 mg BID

n=53

Inclusion criteria included:

• Antiretroviral-naive

• Plasma HIV-1 RNA ≤100,000 copies/mL

• CD4+ T-cell count ≥100 cells/mm³

No evidence of resistance to study drugs on screening HIV-1 drug resistance genotype. Resistance to study drugs was defined as follows:

• AZT: Presence of any mutation in reverse transcriptase (RT) gene leading to an amino acid substitution at codon 215

• 3TC: Presence of any mutation in RT gene leading to an amino acid substitution at codon 184

• LPV/r: Presence of any mutation in the protease gene leading to an amino acid substitution at the following codons: 32, 47, 50, 82, 84 or 90; or >3 mutations at the following codons: 10, 20, 46, 53, 54, 63 or 71

References


Subjects were randomized to either the LPV/r or LPV/r + AZT/3TC arm according to the following scheme: Randomization was 1:1 for the first 60 subjects, then 2:1 in favor of the monotherapy arm for the remaining subjects. Subjects were monitored with plasma HIV-1 RNA levels at Weeks 1, 2, and 4, then every 4 weeks until Week 24, then every 8 weeks until Week 48, then every 12 weeks until Week 96.

Laboratory Evaluation

 Plasma HIV-1 RNA quantitation (AmpliSensor 1.5, Roche, Indianapolis, Indiana, USA) with a lower level of quantitation of 50 copies/mL was performed at a central laboratory (MDS Central Lab, Biollab—France, France).

 HIV-1 drug resistance genotype testing (PCR by C. Delsauge via ARBS technique in the lab of C. Rouszioux, Centre Hospitalier Universte, Necker, Paris, France) was performed at screening to determine study eligibility, and at time of plasma HIV-1 RNA >500 copies/mL, after achieving <50 copies/mL, rebound of >1 log, from nadir of >400 copies/mL, or study discontinuation.

 Additional HIV-1 drug resistance phenotype and genotype testing (Phensense GT, Monogram Biosciences, South San Francisco, CA) was performed on samples demonstrating changes in protease from baseline.

Results

 136 subjects were randomized, 83 to LPV/r monotherapy and 53 to LPV/r + AZT/3TC.

  Mean follow-up for this analysis is 64 weeks (range 48–96 weeks).

  At the time of the present analysis, 24 subjects qualified for resistance testing: 3 on LPV/r + AZT/3TC and 21 on LPV/r monotherapy. Reasons for resistance testing included:

  - Plasma HIV-1 RNA >500 copies/mL after nadir <400 copies/mL: 18 subjects (15 out of 18 had nadir >50 copies/mL).
  - Plasma HIV-1 RNA >500 copies/mL at time of discontinuation from trial after nadir <400 copies/mL: 5 subjects (4 of 5 had nadir >50 copies/mL).
  - Investigator choice due to persistent low level viremia (below protocol-defined virologic failure): 1 subject.

 Figure 2. Genotype: Resistance Testing Results.

 83 subjects on LPV/r monotherapy

  21 (25%) subjects qualify for GT (rebound VL >500 after <400)

  0 4 8 12 16 20 24 28 32 36 40 44 48

  PRO: L33I L63P A71T

  RT: none

  LPV IC50 1.46-fold

  LPV/r + AZT/3TC

  0 4 8 12 16 20 24 28 32 36 40 44 48

  PRO: L33I A71T

  RT: M184V

  PRO: L33I L63P A71T

  RT: none

  Additional HIV-1 drug resistance phenotype and genotype testing (Phensense GT, Monogram Biosciences, South San Francisco, CA) was performed on samples demonstrating changes in protease from baseline.

 Subject 903 (LPV/r Monotherapy Arm)

 Screening sample from Subject 903 showed wild-type RT, and protease L33I/S and V77I (secondary PI resistance mutations frequently noted as natural polymorphisms in wild-type HIV-1). Plasma HIV-1 RNA was 66,400 copies/mL, at Baseline and dropped to <50 copies/mL by Week 20. However, the subject subsequently was viremic with plasma HIV-1 RNA of 70, 281, 809, 1170 and 789 copies/mL, at Weeks 24, 32, 40, 42 and 44, respectively.

 Drug resistance testing at Week 40 showed the following:

  - Genotype:
    - RT with no resistance mutations
    - Protease M184I/V, with persistence of L63P/V and V77I from Baseline
  - Phenotype:
    - LPV IC50 1.46-fold the reference wild-type HIV-1

 Subject then added AZT/3TC to LPV/r with suppression of plasma HIV-1 RNA to <50 copies/mL, for the subsequent 48 weeks.

 Figure 4. Development of Resistance in Subject 903 (LPV/r Monotherapy Arm).

 Subject 5102 (LPV/r + AZT/3TC Arm)

 Screening sample from Subject 5102 showed wild-type RT, and protease L33I/S, L63P and A71T (secondary PI resistance mutations frequently noted as natural polymorphisms in wild-type HIV-1). Plasma HIV-1 RNA was 177,000 copies/mL at Baseline and dropped to a nadir of 57 copies/mL by Week 18. However, plasma HIV-1 RNA subsequently increased to 364, 482 and 3400 copies/mL, at Weeks 20, 24 and 26, respectively.

 Drug resistance testing at Week 26 showed the following:

  - Genotype:
    - RT with M184V (3TC resistance mutation)
    - Protease with persistence of L33I and A71T from Baseline
  - Phenotype:
    - LPV IC50 1.13-fold the reference wild-type HIV-1

 At Week 32, plasma HIV-1 RNA was 2190 copies/mL, and the subject changed antiretroviral regimen to LPV/r + AZT + didanosine. Subject remained persistently viremic through Week 48 when repeat drug resistance genotype showed RT and protease with no changes from the baseline genotype.

 Figure 5. Development of Resistance in Subject 5102 (LPV/r + AZT/3TC Arm).
Subjects were randomized to either the LPV/r or LPV/r + AZT/3TC arm according to the following scheme: Randomization was 1:1 for the first 60 subjects, then 2:1 in favor of the monotherapy arm for the remaining subjects. Subjects were monitored with plasma HIV-1 RNA levels at Weeks 1, 2, and 4, then every 4 weeks until Week 24, then every 8 weeks until Week 48, then every 12 weeks until Week 96.

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Plasma HIV-1 RNA quantitation (Amplisor 1.5, Roche, Indianapolis, Indiana, USA) with a lower level of quantitation of 50 copies/mL was performed at a central laboratory (MDS Central Lab, Baille-en-France, France).

HIV-1 drug resistance genotype testing (PCR by C. Delaupaye via ANRS technique in the lab of C. Rouxolux, Centre Hospitalier Universitaire, Nécker, Paris, France) was performed at screening to determine study eligibility, and at time of plasma HIV-1 RNA >500 copies/mL after achieving <50 copies/mL, rebound of >1 log10 from nadir of <400 copies/mL, or study discontinuation.

**Additional HIV-1 drug resistance phenotype and genotype testing** (Phenosense GT, Monogram Biosciences, South San Francisco, CA) was performed on samples demonstrating changes in protease from Baseline.

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- Mean follow-up for this analysis is 64 weeks (range 48–96 weeks).

At the time of the present analysis, 24 subjects qualified for resistance testing: 3 on LPV/r + AZT/3TC and 21 on LPV/r monotherapy. Reasons for resistance testing included:

- Plasma HIV-1 RNA >500 copies/mL after nadir <400 copies/mL: 18 subjects (15 out of 18 had nadir <50 copies/mL)
- Plasma HIV-1 RNA >500 copies/mL at time of discontinuation from trial after nadir <400 copies/mL: 5 subjects (4 out of 5 had nadir <50 copies/mL)
- Investigator choice due to persistent low level viremia (below protocol-defined virologic failure): 1 subject

**Screening sample from Subject 311 (LPV/r Monotherapy Arm)**

- RT with no resistance mutations
- Protease L10F/L and V82A/V, with persistence of L63P from Baseline
- Phenotype: LPV IC50 1.13-fold the reference wild-type HIV-1

**Screening sample from Subject 903 (LPV/r Monotherapy Arm)**

- RT with no resistance mutations
- Protease M46I/M, with persistence of L63P and V77I from Baseline
- Phenotype: LPV IC50 1.49-fold the reference wild-type HIV-1

**Subject 311 (LPV/r Monotherapy Arm)**

Screening sample from Subject 311 showed wild-type RT, and protease L63P/S and V77I (secondary PI resistance mutations frequently noted as natural polymorphisms in wild-type HIV-1). Plasma HIV-1 RNA was 25,000 copies/mL at Baseline and dropped to <400 copies/mL by Week 8. However, with the exception of Week 32 when plasma HIV-1 RNA was undetectable (<50 copies/mL), subject remained with low-level viremia (50-400 copies/mL) until Week 72 when plasma HIV-1 RNA was 1,160 copies/mL.

Drug resistance testing at Week 72 showed the following:

- Genotype:
  - RT with no resistance mutations
  - Protease L10F/L and V82A/V, with persistence of L63P from Baseline
- Phenotype:
  - LPV IC50 1.13-fold the reference wild-type HIV-1

**Subject 903 (LPV/r Monotherapy Arm)**

Screening sample from Subject 903 showed wild-type RT, and protease L63P/S and V77I (secondary PI resistance mutations frequently noted as natural polymorphisms in wild-type HIV-1). Plasma HIV-1 RNA was 66,400 copies/mL at Baseline and dropped to <50 copies/mL by Week 20. However, the subject subsequently was viremic with plasma HIV-1 RNA of 70, 281, 809, 1170 and 789 copies/mL at Weeks 24, 32, 40, 42 and 44, respectively.

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**Subject 5102 (LPV/r + AZT/3TC Arm)**

Screening sample from Subject 5102 showed wild-type RT, and protease L33I, L63P and A71T (secondary PI resistance mutations frequently noted as natural polymorphisms in wild-type HIV-1). Plasma HIV-1 RNA was 177,000 copies/mL at Baseline and dropped to a nadir of 57 copies/mL by Week 18. However, plasma HIV-1 RNA subsequently increased to 364, 482 and 3400 copies/mL at Weeks 20, 24 and 26, respectively.

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- Genotype:
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Conclusions

To date, 8 of 83 subjects starting LPV/r monotherapy and none of 53 subjects starting a LPV/r-based 3-drug regimen developed PI resistance mutations. Although the incidence of development of PI resistance mutations with LPV/r monotherapy appears to be low, the barrier for the selection of PI resistance with LPV/r monotherapy may be lower than with LPV/r-based 3-drug regimens.

References


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In cases of virologic failure, treatment regimens as per the guidelines were followed. For virologic failure on LPV/r monotherapy, treatment was switched to LPV/r + AZT/3TC (3TC 300 mg bid, LPV/r 400/100 mg bid) if viremia was ≤100,000 copies/mL or ≥100 copies/mL but ≤1,000,000 copies/mL. If viremia was ≥1,000,000 copies/mL, treatment was switched to LPV/r + ddI (didanosine) 400 mg bid + AZT 300 mg bid. If viremia was ≥1,000,000 copies/mL, treatment was switched to LPV/r + ddI (didanosine) 400 mg bid + AZT 300 mg bid + 3TC 300 mg bid. If viremia was ≥1,000,000 copies/mL, treatment was switched to LPV/r + ddI (didanosine) 400 mg bid + AZT 300 mg bid + 3TC 300 mg bid + TDF 300 mg bid.