Development of resistance in patients with virologic failure (VF) on darunavir/ritonavir (DRV/r) or lopinavir/ritonavir (LPV/r): results of a randomized, controlled, Phase III trial in treatment-experienced patients (TITAN)

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Introduction

The non-NRTI 1st-pretreatment inhibitor (PI), darunavir (DRV; TMC114), has significant in vitro antiretroviral (ARV) activity against both wild-type virus and modifying resistant HIV-1 strains.2 DRV possesses a high genetic barrier2 defined as the drug’s ability to delay the development of resistance and to retain antiretroviral activity despite the occurrence of mutations within the viral target genes.3 DRV is at a dose of 600/100mg bid but has been approved in the USA and other countries including those in Europe4 for the treatment of HIV-1 infection in treatment-experienced adult patients.5 DRV/r (Darunavir/ritonavir) is an ongoing Phase III trial designed to assess the efficacy and safety of DRV/r versus LPV/r in patients with a broad range of treatment experience, typical of that encountered in a clinical setting.6 The emergence of resistance to highly active antiretroviral therapy (HAART) presents a significant challenge to managing HIV-1 infection.7

This post-hoc study evaluated resistance in TITAN patients experiencing VF with DRV/r or LPV/r.

Methods

Design and patient population

TITAN is a randomized, controlled, 38-week, open-label Phase III trial designed to assess the efficacy and safety of DRV/r versus LPV/r in naïve, treatment-experienced, HIV-1-infected patients.8

The primary objective of the trial was to establish non-inferiority of DRV/r versus LPV/r at Week 48 with VFs ≤100 copies/mL.9

Patients with HIV-1 RNA ≥1000 copies/mL and treated with their current HAART for ≥10 days were randomized to receive an optimized background regimen (OBR) consisting of 2–3 ARVs (NRTIs with or without NNRTIs, enfuvirtide prohibited) plus either DRV/r 600/100mg bid or LPV/r 400/100mg bid (Figure 1) – patients on a structurally treated regimen (STR) of ≥12 weeks were also permitted to enroll.

Patients with previous or current use of LPV, DRV, tipranavir or enfuvirtide and current use of NNRTIs were excluded from the trial.

The development of resistance at endpoint (i.e. the last available timepoint with a genotype/phenotype determination) was performed by Virco BVBA in Europe.

Patients with HIV-1 RNA >1000 copies/mL and treated with their current HAART for ≥10 days were randomized to receive an optimized background regimen (OBR) consisting of ≤2 ARVs (NRTIs with or without NNRTIs, enfuvirtide prohibited) plus either DRV/r 600/100mg bid or LPV/r 400/100mg bid (Figure 1) – patients on a structurally treated regimen (STR) of ≥12 weeks were also permitted to enroll.

Patients with previous or current use of LPV, DRV, tipranavir or enfuvirtide and current use of NNRTIs were excluded from the trial.

Results

Baseline characteristics

A total of 555 patients were randomized and treated, of these, 31% had not used PI’s previously. Eighty-two percent of baseline isolates were susceptible to ≤1 PI.

Virologic baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>DRV/r (n=298)</th>
<th>LPV/r (n=297)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Median FC (range)</td>
<td>0.00 (0–6)</td>
<td>0.00 (0–6)</td>
<td></td>
</tr>
<tr>
<td>LPV FC &gt;10, n (%)</td>
<td>29 (9.9)</td>
<td>29 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Primary PI</td>
<td>0 (0–6)</td>
<td>0 (0–6)</td>
<td></td>
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<tr>
<td>NRTI RAMS</td>
<td>2 (0–7)</td>
<td>2 (0–8)</td>
<td></td>
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<tr>
<td>DRV FC (n=297)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median FC (range)</td>
<td>3.1 (0–25)</td>
<td>3.2 (0–25)</td>
<td></td>
</tr>
<tr>
<td>Median phenotypic sensitivity score of OBR (range)</td>
<td>2.1 (0–4)</td>
<td>2.8 (0–4)</td>
<td></td>
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<tr>
<td>NRTIs – resistant substituted residues</td>
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All patients were PVL naive at study entry; baseline characteristics showed that at baseline, 89.5% of patients were fully susceptible to DRV (FC ≤10) and 90.2% of patients were fully susceptible to LPV (FC ≤10). – baseline demographics and treatment history were similar between treatment groups.

This suggests that DRV has a higher genetic barrier to the development of resistance than LPV.

Overall efficacy results

More DRV/r- than LPV/r- patients achieved VL <400 copies/mL at Week 48 (Figure 2). DRV/r was proven superior to LPV/r in this timepoint compared to those receiving DRV/r.

Virologic failures

Patients receiving DRV/r failed to respond to treatment or rebounded compared to those receiving DRV/r (Figure 4a). VI failure with DRV/r was two-fold higher than with LPV/r – patients with LPV/r FC ≥10 (Figure 4b) or those with previous use of or none of any PI (Figure 4c), fail to have many patients receiving DRV/r failed to respond to rebounded compared to those receiving DRV/r.

Development of mutations in VFs

Fewer VFs on DRV/r than on LPV/r developed primary PI mutations or NRTI RAMS (Figure 4a). – DRV/r patients with PI FC ≥10 had fewer VFs with previous use of or none of any PI (Figure 4b) or those with previous use of or none of any PI (Figure 4c) than those with previous use of or none of any PI (Figure 4d) or those with previous use of or none of any PI (Figure 4e) but those with previous use of or none of any PI (Figure 4f).

Analysis of the 1443 (33%) VFs on DRV/r treatment with PI FC ≤10 and 1311 (32%) VFs on LPV/r treatment with previous use of or none of any PI (Figure 4f) developed a primary PI mutation.

Figure 2. Proportions of DRV/r and LPV/r patients with VL <400 copies/mL, to Week 48 (TLOVR-RT).

Conclusions

In the TITAN study, DRV/r treatment-experienced TITAN patient population, twice as many patients receiving LPV/r had VF compared with those receiving DRV/r – even after excluding patients with LPV FC >10 or those with previous use of two or more PI’s, twice as many patients receiving LPV/r had VF compared with those receiving DRV/r.

Powerful ARR has evolved as a new PI with improved virological characteristics compared with VFs receiving LPV.

This conclusion remains true when patients with LPV FC >10 or patients who previously used two or more PIs were excluded, none of the VFs on DRV/r treatment lost susceptibility to PI while loss of LPV susceptibility was still observed in some of the LPV/r treatment when patients with LPV FC >10 or patients who previously used two or more PI’s were excluded, virological LPV/r still experienced a greater loss of susceptibility to NRTIs in the treatment regimen compared with DRV/r.

These findings suggest that DRV has a higher genetic barrier to the development of resistance and that the earlier use of DRV/r may better preserve future treatment options.

References

2. DRV possesses a high genetic barrier: defined as the drug’s ability to delay the development of resistance and to retain antiretroviral activity despite the occurrence of mutations within the viral target genes.
3. DRV/r (Darunavir/ritonavir) is an ongoing Phase III trial designed to assess the efficacy and safety of DRV/r versus LPV/r in patients with a broad range of treatment experience, typical of that encountered in a clinical setting.
4. DRV/r at a dose of 600/100mg bid has been approved in the USA and other countries including those in Europe for the treatment of HIV-1 infection in treatment-experienced adult patients.
5. DRV/r (Darunavir/ritonavir) is an ongoing Phase III trial designed to assess the efficacy and safety of DRV/r versus LPV/r in patients with a broad range of treatment experience, typical of that encountered in a clinical setting.
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7. DRV/r (Darunavir/ritonavir) is an ongoing Phase III trial designed to assess the efficacy and safety of DRV/r versus LPV/r in patients with a broad range of treatment experience, typical of that encountered in a clinical setting.
8. DRV/r (Darunavir/ritonavir) is an ongoing Phase III trial designed to assess the efficacy and safety of DRV/r versus LPV/r in patients with a broad range of treatment experience, typical of that encountered in a clinical setting.
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