title

Darunavir, promising option in therapy multi-experience HIV-infected patients

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summary

Darunavir was approved in 2006 by the US FDA for patients harboring HIV-1 resistant to more then one protease inhibitor. It belongs to the second generation of protease inhibitors with potent activity against viral strains to all currently available protease inhibitors. Darunavir should always be co-administrated with low-dose ritonavir and with food. Current guidelines suggest that the goal of therapy in all HIV infected patients, including heavily experienced, is full viral suppression. Treatment options for patients infected with multidrug resistant HIV are limited. The results of clinical trials demonstrated that darunavir is effective and well tolerated. The POWER-1, 2, and 3 trials that used DRV/r showed that the compound had a potent effect in heavily pretreated patients. Ongoing studies in treatment-naïve and treatment-experienced will provide more data on the safety and efficacy of darunavir.

key words

protease inhibitor, darunavir, HIV resistance

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Protease inhibitors (PIs) selectively inhibit the cleavage of HIV encoded Gag-Pol protein, thereby preventing the formation of mature virus. The introduction PI-based HAART regimens led to enhanced HIV management and extended patient's life. Since 1996 PI constitute an important component of highly active antiretroviral therapy (HAART). The therapy with the first generation PIs, however, was associated with severe side effects and drug toxicities, higher therapeutic doses due to 'peptide-like' character and the emergence of drug resistance. Current guidelines suggest that the goal of therapy in heavily experienced patients is full viral suppression through the initiation of combination antiretroviral therapy (cART) with multiple active drugs [11, 13] Treatment options for patients infected with multidrug resistant HIV are limited. It has been reported that treatment failure has ultimately occurred in at least half of patients, who initially achieved viral suppression with HAART to undetectable levels. Persistent viral replication has been reported under HAART in 10-40% patients as result of transmission of drug-resistant HIV-1 strains [1, 4, 12, 18, 20,23, 32]. There are at least 26 specific to PI amino acid mutations described by the International AIDS Society (IAS) from the 2006 summary. There are about 15 primary or major mutation that are significant enough to change drug activity, the other so-called minor or secondary mutations that alone are less likely to affect drug activity. Single secondary mutations do not equate with drug resistance, but a combination of mutations result in high level drug resistance. Mutations can also confer resistance to one drug, but enhance the activity of other drug or even drugs [16].

Darunavir (DRV) is one of the second generation PIs and has demonstrated activity in vitro against wild-type HIV-1 and multidrug-resistant strains. It has potent activity against viral isolates that are resistant to all currently available protease inhibitors [8-9]. Darunavir has been a subject of a clinical programme that begun in 2001 [3]. Darunavir was approved in June 2006 by the US Food and Drug Administration (FDA) under its accelerated approval process within six month for the treatment of antiretroviral therapy multiexperienced patients and in those harboring viruses resistant to more then one PI [30]. The recommendation was based on the results of 2 pivotal trials phase 2b studies (POWER-1, and POWER-2) supported by two non randomized trialsTMC114-215 and 208 submitted by Tibotec [17, 21, 24]. Darunavir is administered in combination with low dose (100mg) ritonavir (DRV/r) [30]. DRV/r is now being studied in less treatment-experienced (TITAN) and treatment-naive patients (ARTEMIS).

Darunavir is well absorbed following oral administration. The bioavailability and the effect of different meal types on pharmacokinetics of DRV was evaluated in HIV-negative healthy volunteers. Co-administration with ritonavir in dose 100mg b.i.d. increased systematic exposure to DRV by ~14-fold compared with DRV alone [28, 30]. Administration of drugs in a fasting condition resulted in a decrease in darunavir Cmax and AUClast of approximately 30% compared with administration after a standard meal. Thus DRV should always be coadministrated with ritonavir, and taken with food. [15, 29-30].

Darunavir was studied primarily in two controlled phase IIb clinical trials POWER-1 (TMC114-213) and POWER-2 (TMC114-202) enrolling 605 heavily pretreated multiple PI resistant patients. In the combined analysis of those studies it was shown that patients had received a median of 5 PIs before randomization, only 36% of them in DVR/r group and 39% in comparator group were infected with HIV sensitive to more then 1 PI. A median of 3-8 total protease inhibitor mutations with at least 3 of those being primary mutations were present on baseline. Patients enrolled to POWER-1 and 2 trials were randomized to receive one of 4 doses of DRV/rtv or control PI selected by investigator plus optimized background regimen. Although all doses of DRV/r demonstrated improved efficacy with compared PIs, the best benefit was found in group treated with the 600/100 mg twice-daily dose. The proportion of patients who achieved and maintained HIV RNA below 50 copies/μl was 36% for DRV/r 600/100 b.i.d. vs 7% in the control arm of POWER-2 and 57% vs 16% in POWER-1 [17, 24, 26]. In the combined 48-week analysis a viral load was reduced by a mean value of 1.63 $\log_{10}$ copies/mL in the DRV/r group and 0,36 $\log_{10}$ copies/mL in the comparator group. The best virologic response was connected with the presence of ≤ 1 primary protease inhibitor mutations but even in presence 2 or 3 mutations the response was better then in control group. The studies had shown no dose related toxicities and finally 600/100-mg twice-daily dose was selected for treatment experience patients [25, 27]. The results of 96 week analysis support the findings of POWER-1 and 2 at both 24 and 48 week analysis. The proportion of patients who achieved HIV-RNA < 50 copies/mL at week 96 was 39% of DRV/r patients compared with 9% in the control group. The difference was statistically significant. Enfuvirtide (ENF) use was a strong predictor of antiretroviral response in many previous salvage studies. In POWER-1, and 2 studies the rate of patients using ENF in the optimized background therapy was similar between DRV/r and control groups. ENF was used for the first time by 32% in the DRV/r group and 30% in the comparator groups ad was reused by 14% and 12% respectively. In the analysis the co-administration of ENF in patients naïve to that drug led to strongest replication suppression. The rate of patients who achieved viral load below 50 copies /mL was 58% among patients who started ENF vs 11% among patients without ENF in treatment regimen [31].

POWER-3 study was an analysis of two (TMC114-C215/C208) open label, nonrandomized trials. TMC114-C215 was conducted in 13 sites from different countries all over the world and TMC 114-C208 conducted in the one site in Australia. It was conducted to assess the long-term efficacy and safety of DRV/r in treatment-experienced patients. The POWER-3 trial enrolled 336 adult patients starting treatment with DRV/r 600/100mg b.i.d.; among them 303 were newly recruited patients and 33 patients who had previously participated in the control arm of the POWER-1 or 2 trials. The primary efficacy point was the proportion of patients with ≥ 1 $\log_{10}$ reduction of viral load by week 24. Over a period of six month, reduction of HIV-RNA ≥ 1 $\log_{10}$ was observed in 65% of patients. The reduction of viral load to < 400 copies/mL and < 50 copies/mL was noted in 57% and 40% of patients, respectively [24]. In the 96 week analysis the mean change in HIV RNA from baseline was 1.43 $\log_{10}$ copies/mL, 52% of patients receiving DRV/r had a viral load reduction ≥ 1 $\log_{10}$ and 42% of them had reached HIV-RNA < 50 copies/mL. In the analysis of three POWER studies the presence of 3 or more of mutations as V11I, V32L, L33F, I47V, 150V,154L or M , G73S, L76V, I84V or L 89V was associated with decrease virologic response. When the baseline HIV genotype had 0-2; 3 and more then 4 of those mutations, the proportion of patients receiving DRV/r in the currently recommended dose achieving undetectable viral load, was 50%, 22% and 10% respectively. Co-administration of ENF increased the chance of reaching undetectable viral load [2, 31].

TITAN (Treatment-Experienced Patients Naïve to Lopinavir/Ritonavir) study was conducted to assess non-inferi-