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Analysis of major and minor IAS-USA PI mutations in the MONET trial of darunavir/ritonavir monotherapy versus DRV/r + 2NRTIs

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Background

For patients on treatment with HIV RNA <50 copies/mL, it is unknown whether the genetic barrier to evolution of resistance is different for DRV/r monotherapy, compared with standard triple combinations of antiretrovirals. Several minor IAS-USA mutations are detected frequently in samples from PI naïve patients.

Methods

In the MONET trial, 256 patients with no history of virological failure and HIV RNA <50 copies/mL on current HAART (NNRTI based (43%), or PI based (57%) switched to either DRV/r monotherapy (800/100 mg OD) versus DRV/r + 2NRTIs. HIV RNA levels were evaluated at Weeks 2, 12, 24, 36, 48, 60, 72, 84 and 96: all patient samples with HIV RNA above 50 copies/mL were sent for genotypic resistance analysis (VircoTYPE HIV-1, Beerse, Belgium). Virtual phenotype was also assessed when PI mutations were detected. The percentage of patients with major or minor IAS-USA PI mutations was analysed by treatment arm.

Results

Patients were 81% male and 91% Caucasian, with median age 43 years, and median CD4 count of 575 cells/uL. While patients were receiving randomised treatment, HIV RNA was above 50 copies/mL for 47/1051 (4.5%) patient-visits in the DRV/r + 2NRTI arm and 69/1009 (6.8%) patient-visits in the DRV/r monotherapy arm. Of 48 patients with at least one successful genotype (27 in the DRV/r monotherapy arm, 21 in the DRV/r + 2NRTI arm), two showed major IAS-USA PI mutations during short-term elevations in HIV RNA (one per treatment arm). Both patients remained phenotypically sensitive to darunavir, with sustained HIV RNA<50 copies/mL during the trial and no change in antiretroviral treatment. The five most common minor IAS-USA mutations detected in the DRV/r mono and DRV/r + 2NRTI arms were L63P (78%, 62% respectively), I93L (59%, 19%), V77I (33%, 43%), I62V (22%, 33%) and I64V (15%, 24%). These five mutations were also commonly observed in the Stanford HIV database of 7601 samples from PI naive patients. Fourteen patients in the DRV/r monotherapy arm had repeated genotypes during intermittent low-level viraemia — there was no evidence for evolution of minor IAS-USA PI mutations over time in these patients.

Conclusions

After 96 weeks of treatment in the MONET trial, there is no evidence for an increased risk of emergence of major or minor IAS-USA PI mutations with DRV/r monotherapy, compared to DRV/r + 2 NRTIs, and no evidence for evolution of PI mutations after repeated genotyping.

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