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Darunavir exhibits a potent activity as boosted PI in subjects on a salvage antiretroviral regimen

P Vitiello*, S Ferramosca, M Lo Cicero, PDV Di Vincenzo, M Capasso, M Galli, ME Moroni and SR Rusconi

Address: Dipartimento di Scienze Cliniche "Luigi Sacco", Sezione di Malattie Infettive e Immunopatologia, Università degli Studi, Milan, Italy
* Corresponding author

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Purpose of the study

This study aimed at testing the immuno-virological response in 20 consecutive HIV-1 infected patients treated with darunavir (DRV) within the early access program through 12 months of therapy. Evolution of drug resistance on HIV-RNA, on proviral DNA and proviral DNA quantification at different time points were carried out.

Methods

20 virologically multifailed subjects received a new HAART regimen composed by two NRTI and DRV as boosted PI; 16/20 were under T20 treatment. Immuno-virological response was determined through CD4+ cell counts and viral load (VL) detection. Genotypic analysis on HIV-RNA was performed from plasma samples at the baseline (BL) and on proviral DNA from PBMCs at different time points: BL, week 4, 12, 24, 36 and 48. HIV-RNA was extracted from patients with HIV-RNA >400 copies/mL and processed by RT-PCR. Nested-PCR for all samples was carried out in order to sequence pol and env gene, proviral DNA was quantified by real-time PCR.

Summary of results

Immune-virological status at BL showed a mean value of 248 CD4+ cells/μL and a viral load of 3.9 log10. After 12 months of therapy, we observed an increase in CD4+ count of 164 cells/μL and a decrease in HIV-RNA of 1.9 log10. We analyzed RNA mutations at BL in 13/20 patients and 11/13 showed the presence of at least one DRV mutation. The two most frequent DRV mutations were L33F (54%) and I84V (31%). BL proviral DNA showed changes in 7/20 patients. In 2/7, some mutations detected in RNA at BL mirrored in proviral DNA after one month of therapy. Mutational pattern at BL was more represented on HIV-RNA than on proviral DNA since the mean DRV mutational score was 4.4 for the former and 2.7 for the latter. During follow-up, 4/20 patients showed a progressive decrease of the DRV mutation number in the pro gene. After 12 months of treatment, all these subjects reverted to wild-type. On the contrary, restoration to a wild-type status did not occur in RT. No new mutation appeared on the env gene. Patients with high HIV-RNA at BL showed high levels in proviral DNA at the end of observation, whereas responders behaved in the opposite way.

Conclusion

We demonstrated that the immune-virological response during a DRV-including therapy was optimal in the majority of enrolled subjects. The decrease in the number of mutations during therapy is likely due to a reduced capacity in the DNA proviral integration under drug pressure and this might be confirmed by the proviral DNA quantification.