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L76V – clinically relevant resensitization of the protease inhibitors (PIs) saquinavir (SQV) and atazanavir (ATV)

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Background

The mutation L76V is selected under lopinavir (LPV)-, amprenavir (APV)- and darunavir (DRV)-containing regimens with increasing prevalence. L76V decreases susceptibility to LPV and APV, and increases susceptibility to SQV and ATV. However, little is known about the clinical implication of this mutation in the response to PI-containing regimens in patients with strongly limited therapy options.

Methods

Virological, immunological and genotypical data of 22 HIV-1 multiclass-resistant L76V-positive patients were collected retrospectively. All patients were pre-treated for a mean duration of 87 months, with a mean CD4 cell count of 299 ± 221 cells/mL and a mean VL of 26,450 copies/mL. Thirteen patients switched to ATV or SQV plus LPV or APV to maintain selection pressure on L76V and nine patients received ATV and/or SQV only. Ten patients had three-class resistant viruses, three had viruses with resistance to NRTI and PI. Ten patients received an optimized background therapy and another three received double-PIs only. Viral load and CD4 counts were determined at baseline and week 12–96 to assess therapy success (VL<50). Stanford HIVdb 4.2.6, REGA v7.0 and HIV-GRADE 06–2007 were used for resistance predictions. Phenotypic analyses in 10 patients were performed to verify the effects of resistance and resensitization.

Summary of results

Sustained therapy success was observed in 8/13 (61.5%) patients, where selection pressure on L76V was constantly maintained (one included new drug classes), while only 2/9 patients (22.2%) with ATV/SQV regimens only and without selection pressure on L76V were successful (three of them received supplemental new drug-classes). There was a moderate increase of mean CD4 cell counts observable in all patients with successful therapy follow-up. Eight patients with failing treatment received a second resistance test. While L76V was then undetectable in patients without selection pressure, it persisted in patients with LPV- or APV-containing regimens.

Conclusion

The co-existence of the L90M mutations was mostly responsible for failure of therapy in these patients. L76V was detected under LPV-, APV- and DRV-containing regimens. ATV and/or SQV are encouraging options in deep salvage-situations with viruses carrying the L76V mutation. Maintenance of selection-pressure on L76V with APV or LPV is beneficial for a sustained therapy success in ATV- and/or SQV-containing regimens.