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Improvement of atazanavir-induced hyperbilirubinaemia following TDM-guided atazanavir dose reduction

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Purpose of the study

To confirm in our cohort of patients the correlation between hyperbilirubinaemia (defined as unconjugated bilirubin >2 mg/dL and/or total bilirubin >2.5 mg/dL) and elevated atazanavir (ATV) trough levels (i.e. >750 ng/mL), and to assess the efficacy of a therapeutic drug monitoring (TDM)-guided ATV dose reduction in order to improve the clinical impact of this adverse event.

Methods

41 HIV-1 positive adult patients were included in this study (30 males and 11 females; age = 44 ± 5.28 years; body weight = 69 ± 11.3 kg). All of them received an antiretroviral therapy (ART) including ATV 300 plus ritonavir (RTV) 100 mg once daily and had an hyperbilirubinaemia, defined as above. ATV trough concentrations (Ctrough) were measured for each patient by High Performance Liquid Chromatography (HPLC).

Summary of results

In 31 out of 41 patients (75.6%), the ATV Ctrough was >750 ng/mL. The correlation between ATV Ctrough and bilirubinaemia was highly significant by linear regression analysis for both unconjugated and total bilirubin ($p < 0.0001$). The 31 patients showing increased ATV Ctrough and hyperbilirubinaemia were included in the second part of our study. ATV daily dose was therefore reduced to 200 mg with RTV 100 mg, and ATV Ctrough and bilirubinaemia were reassessed after 15 days. ATV Ctrough was significantly lower after the dose reduction, passing from 1382 ± 484.3 ng/mL to 929.2 ± 383.2 ng/mL ($p < 0.0001$); total bilirubin passed from 3.3 ± 0.9 mg/dL to 2.3 ± 0.9 mg/dL ($p < 0.0001$) and unconjugated bilirubin from 2.9 ± 0.9 mg/dL to 2 ± 0.8 mg/dL ($p = 0.0001$). Three months after the ATV dose reduction, the immuno-virologic parameters were also re-assessed; the rate of patients with undetectable HIV-RNA did not show a statistically significant difference (passing from 92.8% to 88.8%), whereas CD4 cell numbers showed a significant increase from 505.7 ± 288.6 cells/mmc to 602.6 ± 343.8 cells/mmc ($p = 0.0016$); the CD4 percentage, on the other hand, did not differ significantly, passing from 24 ± 9.3% to 24.6 ± 9.5%.

Conclusion

Our data confirm a strong correlation between ATV Ctrough and hyperbilirubinaemia, and more interestingly, support a reduction in the ATV dosage from 300 mg to 200 mg (both plus RTV 100 mg) once daily in hyperbilirubinaemic patients with an ATV Ctrough >750 ng/mL. By this approach, we were able to reduce significantly the bilirubin levels, maintaining an optimal HIV suppression and a satisfactory immunologic competence.