Hepatotoxicity during therapy with Tipranavir, Citalopram and Finasterid – a case report

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Background

Tipranavir (TPV) is a new potent protease inhibitor. Side effects like hepatotoxicity have been described, whereas severe elevation of liver enzymes has been noticed in about 10% within 24 weeks of treatment. Various interactions of co-medication with TPV can be found in literature. They are hard to predict before and are even little investigated so far. In combination with Ritonavir (r), TPV itself inhibits cytochrome P450-CYP3A. Combination of TPV/r with drugs metabolized via CYP3A can cause interactions like elevated plasma levels of the co-medication and consequently lead to side effects. We report one case of severe hepatotoxicity during therapy with TPV/r and a backbone of Tenofovir (TDF) and Emtricitabin (FTC) and co-medication with the antidepressant Citalopram and the hair restorer Finasterid.

Case report

A 38-years old male HIV-positive patient was planned to have a new antiretroviral therapy (ART). He has already taken various HAART regiments during the past six years. Due to insufficient medical adherence, various resistances against all three ART classes and missing sufficient therapeutic options, he was not taking any medication from April 2004 onwards. During the next months, the lab results showed elevating viral load and a decreasing CD4 cell count (figure 1 and 2).

Therefore, treatment with Tenofovir (TDF), Emtricitabin (FTC) and the recently available Tipranavir (TPV) combined with Ritonavir (r) was started in January 2006, whereas TDF and FTC had already been prescribed before. In the course, blood results showed elevating liver enzymes with a peak (GOT 168U/l, GPT 654U/l, GGT 454U/l) approximately six months after starting the ART.

Other causes of elevated liver enzymes like alcohol, viral hepatitis or opportunistic infections could be excluded. The patient mentioned concomitant use of the antidepressant Citalopram and the hair restorer Finasterid. Elevation of liver enzymes is considered to be a rare side effect of these drugs and has been little investigated. As both drugs are metabolized via CYP3A4, inhibition of this cytochrome can increase their plasma concentration. Due to this knowledge and the rather low TPV-levels at that time (see below), the comedication has been stopped in July 2006 whereas the ART has been retained unchanged. GOT and GPT decreased during time (GOT 31 UI, GPT 54 UI at a six-months-follow up), and GGT decreased to 342 UI six months later.

Due to resistance against TPV and intermediate susceptibility towards the backbone with consequently increasing viral load and a decreasing CD4 cell count, medication had to be modified again in March 2007 and an until today successful combination of TMC-125 / Darunavir / Saquinavir / r has been started. After having stopped TDF/FTC/TPV/r, even GGT decreased to normal levels.

During the period when these severe elevated liver enzymes could be determined, therapeutic drug monitoring (TDM, an example of High performance liquid chromatography (HPLC) results is shown in fig. 4) showed low plasma levels of TPV (8.1 to 18.5µg / ml, see fig. 5) and Ritonavir (57 to 303 ng / ml). On account of this, these antiretroviral agents were not supposed to have caused the observed severe hepatotoxicity.

Conclusion

The reported case shows that hepatotoxicity during therapy with Tipranavir can be observed, but it also shows that not only the antiviral drug should be considered as the causative drug. Drug interactions are very complex, but should always be kept in mind when confronted with side effects like hepatotoxicity. Thus, co-medication and especially free available or herbal drugs should be always be asked for.

As GOT only decreased to its normal level after having stopped the TPV-containing drugs, one might assume that TPV itself might have partially caused the hepatotoxicity. However, normal or even low plasma levels of TPV undermines that hypothesis. We therefore suggest that TDM helps to find or exclude the causative drug, and cases like the reported one emphasises its importance.