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Chapter 3:
Saquinavir trough concentration before and after switching NRTI to tenofovir in patients treated with once-daily saquinavir hard gel capsule/ritonavir 1600 mg/100 mg

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Letter

Saquinavir trough concentration before and after switching NRTI to tenofovir in patients treated with once-daily saquinavir hard gel capsule/ritonavir 1600 mg/100 mg

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Pharmacokinetic evaluations have indicated that tenofovir disoproxil fumarate (TDF) influences the plasma levels of some co-administered protease inhibitors (PIs). In particular, TDF has been shown to lower the plasma Cmin of unboosted atazanavir (300 mg once daily) by 60% [1] and atazanavir/ritonavir (300/100 mg once daily) by 23% [2]. An 11% reduction in plasma maximum concentrations of unboosted indinavir (800 mg three times daily) has also been reported for TDF co-administration [3]. Tenofovir exposure is also affected by some PIs, with a 22% increase in tenofovir Cmin and a 24% elevation in the area under the tenofovir concentration–time curve reported for co-administration with unboosted atazanavir [1], while administration with lopinavir/ritonavir elevates these parameters by 51% and 32%, respectively [3].

It has been reported recently that TDF does not influence saquinavir (SQV) exposure in patients taking SQV hard gel/ritonavir (SQV-hg/r) on a twice-daily schedule of 1000/100 mg [4]. The influence of TDF on once-daily SQV has not been established.

We have examined the effect of TDF on SQV-hg trough concentration in adult patients taking once-daily SQV-hg/r (1600/100 mg) in the Staccato trial. During May–July 2003, 14 patients (nine females) underwent a routine assessment of SQV trough after receiving SQV-hg/r with body weight-based doses of stavudine (d4T; 30/40 mg twice daily) and didanosine (ddI; 250/400 mg once daily) for at least 8 weeks [median 24 weeks, interquartile range (IQR): 2–10 months]. In August 2003, the nucleoside background in these patients was switched to TDF 300 mg plus lamivudine (3TC) 300 mg once daily and SQV levels were subsequently reassessed. Samples were drawn immediately before the next SQV dose and 24 h after the last SQV dose. The median time between the first and second assessments was 6 months (IQR: 4–11 months) and the median total time on SQV-hg/r at the second assessment was 14 months (IQR: 7–18 months). Plasma samples for analysis were taken 24 h after the last reported dose on both occasions and plasma SQV concentrations measured using a validated high-performance liquid chromatography assay [5]. Differences in SQV trough before and after switching to TDF were analysed by the Wilcoxon signed-rank test.

There was no significant change in SQV trough before and after switching from d4T/ddI to TDF/3TC (median 0.28 mg/l vs 0.31 mg/l, respectively; P=0.925) (see Table 1), and no significant change in patient body

<table>
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<tr>
<th>Table 1. SQV trough [mg/l]</th>
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<tbody>
<tr>
<td>Before TDF</td>
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<tr>
<td>(d4T/ddI)</td>
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<tr>
<td>n=14</td>
</tr>
<tr>
<td>Mean (so)</td>
</tr>
<tr>
<td>Median (IQR)</td>
</tr>
<tr>
<td>% CV</td>
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<td>% SQV ≤0.10 mg/l (n)</td>
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Trough: SQV concentration immediately before the next SQV dose and 24 h after the last SQV dose. so, standard deviation; IQR, interquartile range. CV, coefficient of variation (ratio of the standard deviation to the mean).
weight between the first and second assessments was noted that might have influenced drug levels. The median change in trough between the first and second assessments was +0.05 mg/l (IQR: –0.15 to +0.38). Three subjects exhibited SQV trough levels below the 50% inhibitory concentration of wild-type HIV of 0.10 mg/l prior to switching, and one after. We conclude, therefore, that TDF does not influence minimum steady-state plasma concentrations of SQV in a once-daily SQV-hg/r 1600/100 mg combination.

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References

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