Atazanavir (ATV)-Containing Antiretroviral Treatment is not Associated with an Increased Risk of Cardio- or Cerebro-Vascular Events (CVE) in the D:A:D Study

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BACKGROUND

Prior findings from the D:A:D study suggest that the duration of exposure to protease inhibitor (PI)-containing ART is associated with an increased risk of myocardial infarction (MI) (1). Further analyses suggested that this association was present with some individual PIs (lopinavir and indinavir), but was not present with other PIs (saquinavir or nevirapin). An association with atazanavir (ATV) usage has not previously been investigated due to the limited follow-up among persons exposed to ATV. However, sufficient person-years of follow-up (PYFU) have now accrued among those exposed to ATV to permit an investigation of the association between ATV and the risk of MI and stroke.

AIM OF THE STUDY

The aim of this analysis is to evaluate whether exposure to ATV-containing ART is associated with an increased risk of cardio- and cerebro-vascular events (CVE) defined as the occurrence of MI and stroke, according to the MONICA study definition (2). Other factors associated with MI and stroke were also investigated, including a possible inverse relationship between bilirubin levels and the risk of MI (such a finding has previously been described in HIV-negative subjects) (3-5).

METHODS

The D:A:D is an observational study of >49,000 HIV-infected patients from 11 cohorts from Europe, Australia, and the United States. The aim of the study is to investigate associations between use of antiretroviral drugs and risk of cardiovascular and other major disease events. In this analysis we evaluate a possible association between cumulative exposure to ATV and the rate of MI or stroke. Poisson regression was used to investigate the association between cumulative exposure to ATV and MI and stroke after adjusting for known demographic and clinical confounders, cumulative exposure to antiretroviral drugs and recent exposure to nucleoside reverse transcriptase inhibitors. Follow-up started on the date of enrolment in the D:A:D Study and ended at the earliest of: (i) a new MI/stroke, (ii) death, (iii) six months after last clinic visit, or (iv) 1st February 2011. A sensitivity analysis was performed to investigate a potential modifying association with the latest bilirubin level, included as a categorical covariate, based on the inverse association between bilirubin level and risk of MI reported in HIV-negative persons.

RESULTS

A total of 844 cases of MI (301,907 PYFU) and 532 strokes (303,118 PYFU) have been reported, with a rate of 2.80 [95% CI: 2.6, 2.3]/1000 PYFU in those with no exposure to ATV to 2.0 [1.2, 3.2]/1000 PYFU in those with >3 years exposure, with the rate of stroke being 1.7 [1, 1.9] and 1.7 [1.0, 2.7]/1000 PYFU in these two groups (Figure 1 and 2).

Longer exposure to ATV was not associated with an increased risk of either MI or stroke either in univariate or in multivariable analyses (Table 3). After excluding patients from three cohorts that did not provide any bilirubin measurements, there was a total follow-up of 278,845 person-years. Estimates of the rate of MI, stratified by latest bilirubin level in this subgroup of patients are shown in Table 2. The rate of MI varied from 2.80 [95% CI: 2.6, 2.3]/1000 PYFU in those with no exposure to ATV to 2.0 [1.2, 3.2]/1000 PYFU in those with >3 years exposure, with the rate of stroke being 1.7 [1, 1.9] and 1.7 [1.0, 2.7]/1000 PYFU in these two groups (Figure 1 and 2).

CONCLUSIONS

ATV was not associated with an increased risk of CVE, suggesting that previously reported associations in the D:A:D Study with lopinavir and indinavir are unlikely to reflect a class-wide association. We found no evidence that these findings were altered by adjustment for the latest bilirubin level, although only limited data were available. Our findings may be strengthened by the inclusion of all patients exposed to ATV for longer periods of time.

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