1. BACKGROUND

Efavirenz (EFV) 600mg is currently recommended by WHO as a first-line antiretroviral agent in HIV infected adults. A dose reduction to 400mg EFV has been proposed because of concerns regarding toxicity and costs. EFV is widely used during pregnancy in those countries where HIV infection is most common. Pregnancy can reduce exposure to antiretroviral agents with a corresponding risk of poor maternal virological control and MTCT. Pharmacokinetics (PK) of EFV 600 mg have been previously studied in pregnancy with contradictory results.

Both the IMPAACT P1026 protocol and the PANA network have been established to describe the pharmacokinetics of antiretroviral agents in HIV-infected pregnant women in comparison to post-partum pharmacokinetics (www.impactnetwork.org and www.panacad.org).

Objectives:
1. To further investigate the PK of EFV 600 mg in pregnant women.
2. To describe the safety of the antiretroviral agents during pregnancy and monitor viral load response and pregnancy outcomes.

2. METHODS

Data presented were collected in two studies: PANA Pharmacokinetics of Antiretroviral Agents in HIV-infected Pregnant Women (Europe) and IMPAACT study P1026. “PK Properties of ARVs Drugs During Pregnancy” (US, Argentina) (ClinicalTrials.gov identifiers NCT00285929 and NCT00042289).

Both studies are non-randomized, open-label, parallel, multi-center phase IV studies in HIV-infected pregnant women. PANA recruits patients from HIV treatment centers in Europe; IMPAACT recruits patients from sites in the US, South America, Thailand and Africa.

Here, we report on pregnant HIV-infected patients treated with EFV 600mg as part of their ART.

Blood was collected for 24h pharmacokinetic curve (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24) after observation of intake of the medication in the second and third trimester. After at least 2 weeks continuation of therapy post-partum, intensive PK sampling was repeated. Where possible a cord blood sample and matching maternal blood sample were taken to allow delivery of placental sampling.

Safety and antiviral parameters were evaluated.

EFV plasma concentrations were determined by validated methods of bioanalytical Pharmacokinetic parameters were calculated using Phoenix (Certara) version 6.3. Bioequivalence analysis was conducted using Phoenix. Subjects with concurrent rifampicin were not included in this analysis, but presented separately.

3. RESULTS

1. Thirty-four HIV-infected pregnant women were included in this study. Thirteen in the PANA network and 21 in the IMPAACT P1026 network.

2. Subject characteristics per trimester and pregnancy outcomes are shown in Table 1.

3. Pharmacokinetics

a. Geometric mean (GM) concentration-time profiles of EFV 600 mg QD during second trimester, third trimester and postpartum are shown in Figure 1.

b. GM pharmacokinetic parameters of EFV 600 mg QD during second trimester, third trimester and postpartum are shown in Table 2.

c. GM ratios and 90% confidence intervals (90%CI) of pharmacokinetic parameters of EFV 600 mg QD in second and third trimester compared to postpartum are shown in Table 3.

3. RESULTS (continued)

4. Infant birth weight (grams)

Safety

a. Three pregnancy-related serious adverse events were reported including pre-eclampsia, vaginal bleeding, and pregnancy induced hypertension.

b. In newborn congenital abnormalities were reported, including meningomyelecele, polydactily, and bilateral polydactily.

c. Five pregnant births were observed with a median (range) gestational age of 34 (33-36) weeks.

3. RESULTS (continued)

Figure 1: Geometric mean (±CV) concentration-time profile after administration of EFV 600 mg QD during third trimester and postpartum

Figure 2: EFV 600 mg QD individual pharmacokinetic parameters during second trimester (2nd), third trimester (3rd) and postpartum (PP).

Discussion

3. Conclusions

4. Overall EFV exposure was similar during pregnancy compared to postpartum. Although the Cmax was not bioequivalent, postpartum exposure compared to postpartum, EFV 600mg led to adequate drug exposure during pregnancy.

Prospective evaluation of the proposed EQF dose reduction to 400mg is warranted in pregnant women.

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Abstract # 433

Pharmacokinetics of Efavirenz 600 mg QD during Pregnancy and Postpartum

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