

Abstract: 38

Pharmacokinetics and Pharmacodynamics of Drug Efficacy and Toxicity



Impact of age on renal function in patients receiving tenofovir

L. Goeddel¹, K.W. Crawford², R. Moore³, D.M. Fine⁴, M. Atta⁴, C. Flexner²

¹Johns Hopkins University School of Medicine, Medicine, Baltimore, USA; ²Johns Hopkins University School of Medicine, Clinical Pharmacology, Baltimore, USA; ³Johns Hopkins University School of Medicine, Infectious Diseases, Baltimore, USA; ⁴Johns Hopkins University School of Medicine, Medicine Div. of Nephrology, Baltimore, USA

Background: Tenofovir is an acyclic phosphonate nucleotide analogue eliminated by glomerular filtration and active tubular secretion. A small fraction of patients experience acute renal toxicity and a Fanconi-like syndrome. In most studies, chronic use of tenofovir is safe and produces a small, clinically insignificant reduction in renal function. Tenofovir use is also associated with mild tubular toxicity resulting in sub-clinical loss of phosphate, protein, and glucose. There is a well-recognized age-related decline in renal function, and HIV-infected individuals are living significantly longer as a result of HAART utilization. Older individuals may display differences in pharmacokinetic parameters which could affect drug toxicity. We explored the impact of age on tenofovir-mediated effects on estimated glomerular filtration rate (eGFR).

Methods: The analysis used all patients included in a single clinic database between 2002 and 2009 who received tenofovir as part of their HAART regimen. Serum creatinine values collected at clinic visits from the start of tenofovir to discontinuation or end of study period were used to compute eGFR by the MDRD method. A repeated measures analysis was performed using mixed-effects regression modeling. Statistical analysis performed with STATA IC.

Results: 1031 patients were included in the analysis with a total of 17383 observations. The composition of the cohort was as follows: 67.24% male, 32.1% Caucasian, 67.9% African-American. The median number of clinic visits was 10 (IQR= 4-16) and the mean time on tenofovir was 700 days. The average eGFR at baseline was 112.7 ml/min. The median age was 43 years. In a univariate analysis, there was a decrease in eGFR [MA1] of 0.016 ml/min (-0.017- -0.014, P<0.000) for each day of tenofovir use, an effect that persisted after controlling for age, baseline MDRD, race and gender. When age was added to a model controlling for days of tenofovir use, eGFR decreased by 0.638 ml/min (-1.037 - -0.239, p=0.002) for each year increase in age. Individuals > 50 years had an average eGFR 16 ml/min (-22.01, -10.29, p<0.000) lower than individuals < 50 years, which reduced to 4 ml/min (-7.83—0.15, p=0.042) lower than those < 50 years after controlling for baseline eGFR. When subjects were further stratified by age as <30 years, 30-45 years and >45 years, individuals aged 30-45 had an average eGFR 9.54 (-15.9-3.1, p=0.004) ml/min less compared to those <30, and individuals >45 had an average eGFR 11.9 (-18.5 - -5.3, p<0.000) ml/min less than those <30 years, after controlling for eGFR at baseline. The following multivariate model was developed: Average eGFR = 118 ml/min -0.016 (days on tenofovir) -9.5 (age 30-45) -11.9 (age>45) + 0.645 (baseline MDRD) -4.71 (concurrent protease inhibitor use) (R² =0.32).

Conclusion: We observed an effect of tenofovir on eGFR related to the duration of exposure, consistent with previous studies. Age independently affected eGFR in patients on tenofovir, both as a continuous variable and when stratified by age category. Other important covariates included baseline eGFR, co-morbidities that affect renal function, and concomitant exposure to protease inhibitors. Tenofovir may require closer monitoring in older individuals.

No conflict of interest