Association between *ABCC2* -24C>T Polymorphism and Tenofovir-Related Renal Damage in Patients with HIV Infection

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Background

Tenofovir (TFV) is a nucleotide reverse-transcriptase inhibitor used as one of the first-line agents in various combination antiretroviral therapies. It is a popular choice due to its high efficacy and once-daily dosing regimen. However, renal toxicity has been related to the use of TFV including tubular dysfunction and the development of Fanconi's syndrome. Concerns have been raised regarding the long term effects of TFV on kidney functions. TFV undergoes renal clearance via both glomerular filtration and active tubular filtration. However, the mechanism of TFV-associated renal toxicity is largely unknown.

The *ABCC2* gene is located on chromosome 10q24 specifically coding multidrug resistance protein 2 (MRP2). MRP2 is expressed in the canalicular (apical) part of the liver cells and proximal renal tubule endothelial cells. Since MRP2 is involved in the renal excretion of TFV, differential expression of this protein might contribute to TFV-associated renal toxicity as a result of single nucleotide polymorphisms in *ABCC2.* The C>T variant at the -24 position in the promoter region of the *ABCC2* has been associated with functional changes of MRP2.

Therefore, our central hypothesis is that *ABCC2 -24C>T polymorphism is associated with renal toxicity of TFV*.

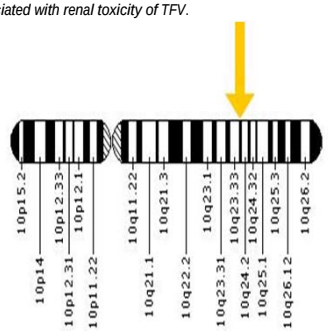

Figure 1: ABCC2 location: 10q24
Genetics Home Reference, US National Library of Medicine

Materials & Methods

- This was a retrospective study in HIV+ patients (n=40) treated with tenofovir for over 6 months.
- Patient DNA samples were obtained from clinical centers in New York, Rochester, Cleveland and Miami. Genotyping will be performed using real-time PCR with Taqman® probes.
- The subjects were divided into two groups with relatively matched demographics (Table 1): control (n=20) and renal damage (n=20). The renal damage criteria were as follows: BUN > 20.0 mg/dL , [Na+] > 145 mEq/L , [K+] > 5.0 mEq/L and [Creatinine] > 1.2 mg/dL .

Results

Table 1. Demographics of study subjects (N=20 per group)

Characteristics (Patients with Renal Damage)	Results
Median age – years (range)	46 (31-62)
Female/Other sex – n (%)	5 (25)
Race – n (%)	
Caucasian	9 (45)
African American	4 (20)
Hispanic/Other	7 (35)
Substance Abuse – n (%)	9 (45)
Characteristics (Control Group)	**Results**
Median age – years (range)	47 (34-61)
Female/Other sex – n (%)	7 (35)
Race* – n (%)	
Caucasian	4 (22)
African American	6 (33)
Hispanic/Other	8 (44)
Substance Abuse – n (%)	12 (60)

* Race: N=18, two subjects race UNKOWN

Results

- Significantly higher indicator levels were noted in patients with renal damage [Table 2, median (IQR)].
- Pharmacogenomic analysis is currently ongoing.

Table 2. Presence of Renal Damage Indicators in Patient Groups

	Renal Damage	Control	p
BUN-mg/dL	22.0(19.3, 25.5)	14.0(14.0, 15.8)	<0.01
[Na+]-mEq/L	139(137, 141)	140(139, 142)	0.067
[K+]-mEq/L	4.7(4.5, 5.0)	4.2(3.9, 4.4)	<0.01
[Creatinine]-mg/dL	1.2(1.1, 1.5)	0.8(0.8, 0.9)	<0.01

Conclusions

- The data indicates a significant association between the indicators of renal damage including BUN, [K+] and [creatinine] levels, and tenofovir-containing treatment in HIV+ patients, which is consistent with previous findings from previous studies.
- The presence of this association suggests the potential connection between SNP of the *ABCC2* gene (*e.g.* at the -24 C/T), MRP2 function and renal clearance of tenofovir, which might partially explain the long-term renal toxicity of this agent.
- Review of the patients' genotypes will help optimize and individualize tenofovir-containing regimens, therefore further investigation is warranted in this area.

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Acknowledgments & References

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