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HIV 감염 환자에서 고활성 항레트로바이러스 요법을 포함한 신기능 장애 위험인자 연구

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Factors Associated with Renal Dysfunction, Including Highly Active Antiretroviral Therapy in Korean HIV-Infected Patients

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HIV 치료를 위한 강력한 항바이러스 약물요법이 널리 사용됨에 따라 HIV에 감염된 상태에서 신장질환 발생 위험성을 지닌 채 오랜 기간 생존하는 환자들이 증가하고 있다. 본 연구는 국립중앙의료원 감염병 센터를 내원한 만18세 이상의 HIV 감염 환자를 대상으로 HIV 감염 환자에게 신기능 장애를 유발하는 위험인자를 평가하고자 환자군 대조군 연구를 후향적으로 실시하였다. 2006년 1월부터 2011년 3월까지 5년 3개월 동안 신기능이 저하된 모든 HIV 감염 환자를 환자군으로 하며, 정상 신기능을 가진 HIV 감염 환자들 중 대조군을 무작위로 선정하여 환자군과 대조군을 1:2의 비율로 하였다. 환자군과 대조군을 비교해 만성신질환을 유발하는 위험인자를 평가하기 위한 분석변수로 성별, 연령, CD4+ 세포수, 혈중 바이러스 수, HAART 56일 이상 여부, 당뇨병과 C형 간염을 선정하였다. 또한 추가적으로 개별 antiretroviral 약물들 사용과 신기능이 얼마나 관련되어 있는지 알아보기 위해 각각의 약물과 eGFR의 상관관계를 분석하였다. 환자군은 CD4+ 세포수가 $<200\times10^6$ cells/l 인 군이 7.7배(OR: 7.7; 95% CI, 1.8-32.9) 단백뇨가 있는 환자의 경우 7.8배(OR: 7.8; 95% CI, 1.6-37.8) 더 유의하게 만성신질환 발생위험이 높았다. 개별 antiretroviral 약물들과eGFR의 상관관계를 분석한 결과, lamivudine 이 eGFR 과 약한 음적 상관관계를 보이는 것으로 나타났으며($r=-.211$, $p<.05$), 다른 약물들의 경우 통계적으로 유의한 값을 보이지 않았다. 이번 환자군-대조군 연구는 HIV 감염 환자들이 만성 신질환으로 발전하는데 여러 인자들의 역할에 대해 평가하고자 하였다. 여러 변수들을 평가해 본 결과, 만성 신질환 환자들의 경우 CD4+ 세포수가 $<200\times10^6$ cells/l 이거나 단백뇨를 동반한 경우가 통계적으로 유의하게 많았다.

□ Key words - chronic kidney disease, highly active antiretroviral therapy, HIV

INTRODUCTION

With the advent of highly active antiretroviral therapy (HAART), morbidity and mortality have decreased among patients with human immunodeficiency virus (HIV) infections. HIV-associated nephropathy (HIVAN) is an important complication in HIV-infected patients, but its prevalence has also been significantly reduced through HAART.[1-2] However, HAART-induced renal dysfunctions such as renal tubular damage and decreased glomerular filtration rate (GFR) have been observed.[3] Approximately 15% of HIV-infected patients have been estimated to have chronic kidney disease (CKD), and HIV-induced metabolic complications such as hypertension and diabetes can contribute to nephropathy.[1, 4] Being of African descent, being male, injection drug use, a low nadir CD4+ cell count, hypertension, and hepatitis C have all been identified as risk factors for HIVAN in several studies.[5-7] In addition, tenofovir, indinavir, and

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stavudine have been found to be associated with CKD in HIV-infected patients.[8)]

Currently, there are over one million HIV-infected patients in the U.S., and they are likely to receive antiretroviral therapy as their disease progresses.[9)] In Korea, a total of 7,656 patients were diagnosed with HIV from 1985 to 2010, and 773 HIV-infected patients were newly diagnosed in 2010. With the significant improvement in life expectancy with the use of HAART, HIV infection has become a chronic disease. Therefore, even HIV-infected patients with normal renal function can develop CKD later in life. To address this situation, guidelines for the management of CKD in HIV-infected patients have been developed.[10)] These guidelines recommend routine urinalysis for eGFR and proteinuria together with monitoring for comorbidities that can contribute to kidney dysfunction.

Most of the previous studies that assessed the risk factors for CKD in HIV-infected patients were conducted on African-Americans or Caucasians, and only several studies have included Asians.[3)] Because many studies have shown racial differences in HIV-infected patients' renal function, the risk factors associated with CKD in Korean HIV-infected patients must be identified to better understand HIV-infected patients in Korea. The objective of this study was to identify risk factors, particularly in the context of HAART, for CKD in patients with HIV in Korea.

METHODS

Study design, setting, and data source

This retrospective case-control study was conducted at the National Medical Center (NMC) in Korea. We identified all adults in the NMC aged 18 years or older who were infected with HIV between January 1, 2006, and March 31, 2011. Case patients were defined as those who experienced CKD during this time frame, and all of these patients were included in this study. Control patients were those who had normal renal function during the same period, and for each case patient, two control patients were randomly selected. Patients were excluded if they visited the NMC less than twice, had decreased renal function when diagnosed with HIV, or did not have laboratory data regarding renal function.

All patients are entered into the Order Communication System (OCS) of the NMC, which is an electronic database with pertinent laboratory, diagnostic, procedural, pharmaceutical, vital sign, and demographic data. We used the OCS data for this study, and the most recent data were selected. The following data were included in this study: age, gender, CD4+ cell count, HIV RNA level, antiretroviral therapy, presence of proteinuria, presence of diabetes, presence of hypertension, and hepatitis C infection status. This study was carried out in accordance with the principles enunciated in the Declaration of Helsinki, and approval to conduct this study was obtained from the NMC institutional review board.

Definitions

CKD

According to the National Kidney Foundation, mild kidney disease (Stage 2) is defined as a GFR of 60-89 mL/min/1.73 m^2, moderate renal insufficiency (Stage 3) is defined as a GFR of 30-59 mL/min/1.73 m^2, severe renal insufficiency is defined as a GFR of 15-29 mL/min/1.73 m^2, and renal failure is defined as a GFR of less than 15 mL/min/1.73 m^2 or treatment with dialysis.[11)] In the present study, a patient with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 for more than 3 months was defined as having CKD. The eGFR used in the data analysis was calculated using the simplified modification of diet in renal disease (MDRD) formula.[12)]

Highly active antiretroviral therapy (HAART)

Based on the antiretroviral therapy guidelines for HIV-infected patients, the combination therapy known as highly active antiretroviral therapy (HAART) was defined as follows:[13)]

1. Two nucleoside reverse transcriptase inhibitors (NRTIs) + one non-nucleoside reverse transcriptase inhibitor (NNRTI)
2. Two NRTIs + one protease inhibitor (PI)
3. Two NRTIs + one integrase strand transfer inhibitor (INSTI)

HAART requires that HIV RNA levels, CD4+ cell counts, and toxicity be monitored before and 2-8 weeks (no later than 8 weeks) after beginning the therapy, followed by monitoring every 4-8 weeks. Therefore, a period of up to 8 weeks was considered to be the minimum for clinical significance.[13] To accurately evaluate the clinical effectiveness of HAART, short-term HAART treatments were not classified separately, and the cases in this study were classified as either 1) receiving HAART treatment for more than 56 days or 2) never receiving HAART treatment or having been treated for fewer than 56 days.

Other factors

CD4+ cell counts and plasma viral loads measured before the renal disease first occurred were taken as the baseline values for the patient group. When there were two or more test measurements taken within a month prior to the onset of CKD, the lowest value was used for the CD4+ cell count, and the highest value was used for the plasma viral load. CD4+ cell counts were classified into $< 200\times10^6$ cells/l, 200 to 349×10^6 cells/l, and $\geq 350\times10^6$ cells/l. Plasma viral loads were classified into $\geq$ 100,000 copies/ml, 10,000 to 99,999 copies/ml, and <10,000 copies/ml (including undetectable values).

The presence or absence of either diabetes or hepatitis C was classified as 'yes' or 'no', respectively, for each disease.

Because angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which are hypertension drugs that exhibit renoprotective effects in diabetic nephropathy, can affect the occurrence of CKD in hypertensive patients, they were classified separately from drugs such as calcium channel blockers (CCBs), beta blockers, and diuretics. Accordingly, hypertensive patients were classified as follows: 1. patients with hypertension who received ACEI and ARB treatments, 2. patients with hypertension who received hypertension drugs other than ACEI and ARB, 3. patients with hypertension who did not receive drug treatments, and 4. patients without hypertension who did not receive drug treatments.

Data analysis

The data analyses were performed with SPSS, version 12.0 (SPSS, Chicago, IL), statistical software. No a priori power calculation was performed because all eligible patients were included in the analysis. The data were analyzed using Fisher's exact test or the chi-squared test for categorical variables. Student's t-test was used to compare continuous variables. Binary logistic regression analysis was used to identify CKD risk factors. After which, only those variables with $p < 0.05$ were retained for multivariate comparisons by using backward stepwise logistic regression to identify risk factors that might be associated with CKD in patients who were HIV positive. The estimates of the relative risk of CKD are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). In addition, bivariate correlation testing was performed to assess the strength of associations between individual antiretroviral agents and eGFR. A p-value of less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

General characteristics of the patient and control groups

The characteristics of the patients in the study are shown in Table 1. Eight patients who visited the hospital less than twice since the start of the study or who had no clinical laboratory values were excluded, as were 4 patients with reduced renal function at the time of their HIV diagnosis. Ultimately, 34 patients were in the CKD group, and 68 people with normal renal function were in the control group. The ages of the patient group and control group were similar with a mean±standard deviation of 52.2±12.3 years old and 51.8±11.6 years old, respectively, which were not significantly different. As for gender, the patient group included 1 female, everyone in the control group was male, and there was no statistically significant difference between the two groups.

The number of people with more than 56 days of HAART was 25 (73.5%) in the patient group and 45

Table 1. A Comparison of Characteristics between the Patient and Control Groups

	Renal disease cases (n=34)		Controls (n=68)		p-value
	n	%	n	%	
Gender					
Female	1	2.9	0	0.0	0.333*
Male	33	97.1	68	100.0	
Age					
20s	1	2.9	2	2.9	
30s	5	14.7	10	14.7	
40s	7	20.6	15	22.1	0.936*
50s	12	35.3	23	33.8	
60s	7	20.6	14	20.6	
70s	1	2.9	4	5.9	
80s	1	2.9	0	0.0	
HAART (≥56 days)£					
Yes	25	73.5	45	66.2	0.451†
No	9	26.5	23	33.8	
CD4+ cell count (nadir)					
<200	10	29.4	7	10.3	0.048†‡
200-349	6	17.6	13	19.1	
≥350	18	52.9	48	70.6	
RNA (highest)					
≥100000	2	5.9	1	1.5	0.477*
10,000-99,999	2	5.9	5	7.4	
<10,000	30	88.2	62	91.2	
Proteinuria					
Yes	10	29.4	5	7.4	0.003†§
No	24	70.6	63	92.6	
Hypertension/treatment					
Yes/ACEI or ARB¶	6	17.6	4	5.9	
Yes/Other treatment	1	2.9	2	2.9	0.219*
Yes/No treatment	0	0.0	1	1.5	
No/No treatment	27	79.4	61	89.7	
Diabetes					
Yes	5	14.7	4	5.9	0.156*
No	29	85.3	64	94.1	
Hepatitis C					
Yes	0	0.0	1	1.5	1.000*
No	34	100.0	67	98.5	

* Fisher's exact test, †Chi-squared test, ‡$p<0.05$, § $p<0.01$, £HAART: highly active anti-retroviral therapy, ¶ACE: angiotensin-converting enzyme

(66.2%) in the control group, but the difference was not statistically significant. Nadir CD4+ cell counts differed significantly between the patient and control groups: in the patient group, 29.4% had $<200\times10^6$ cells/l, 17.6% had 200 to 349×10^6 cells/l, and 52.9% had $\geq350\times10^6$ cells/l. In the control group, the values were 10.3%, 19.1%, and 70.6%, respectively ($p = 0.048$). Regarding plasma RNA viral loads, the percentage of subjects with >100,000 copies/ml was higher in the patient group, but the difference was not statistically significant.

In terms of proteinuria, 29.4% of the patient group exhibited proteinuria compared with only 7.4% in the control group, and the difference between the two groups was statistically significant ($p = 0.003$). Regarding the use of hypertension/antihypertensive drugs, the percentage taking ACEI and ARB was higher in the patient group (17.6% compared with 5.9% in the control group), but the difference was not statistically significant. There were also no statistically significant differences with respect to diabetes or hepatitis C.

Risk factors of the study patients

The results of the risk factor analysis for the patient group are shown in Table 2. The logistic regression analysis of all of the risk factors in the study showed that the patients with CD4+ cell counts of $<200\times10^6$ cells/l had a significantly (7.7-fold) greater risk of developing CKD. However, when only the risk factors that gave significant results in the logistic regression analysis were analyzed, there was an increase in the risk of developing CKD, but it was not statistically significant (OR: 3.2; 95% CI, 1.0-10.3, $p = 0.05$). For patients with proteinuria, the risk of developing CKD was 4.6-fold higher when only the risk factors that had significant results in the logistic regression analysis were analyzed (OR: 4.6; 95% CI, 1.4-15.4, $p = 0.01$). Patients with a history of hypertension had a higher probability of developing kidney disease regardless of the medication taken, but this result was not statistically significant (patients using ACEI or ARB; OR, 5.2; 95% CI, 1.0-26.4, $p = 0.05$; patients using non-ACEI or ARB: OR, 2.7; 95% CI, 0.2-35.0, $p = 0.45$). Having received more than 56 days of HAART and the highest plasma viral load category were found to be unrelated to the risk of developing CKD.

In this study, the correlation between each of the drugs and the eGFR was analyzed to identify the relationships

Table 2. A Comparison of Risk Factors for the Patient and Control Groups

	All variables				Main effect and significant explanatory variables			
	OR*	(95% CL†)	p-value	-2logL	OR	(95% CL)	p-value	-2logL
			105.96				117.60	
Gender								
Male	127200000	(0.0, 0.0)	1.00					
Female	1.0	Referent						
Age								
Under 30	1.5	(0.4, 6.7)	0.56					
40s	0.8	(0.2, 3.7)	0.76					
50s	0.8	(0.2, 2.6)	0.65					
Over 60	1.0	Referent						
HAART(≥56 days)‡								
Yes	1.3	(0.4, 3.9)	0.70					
No	1.0	Referent						
CD4+ cell count (nadir)								
<200	7.7	(1.8, 32.9)	0.01		3.2	(1.0, 10.3)	0.05	
200-349	1.6	(0.5, 5.4)	0.47		1.3	(0.4, 4.0)	0.67	
≥350	1.0	Referent			1.0	Referent		
RNA(highest)								
≥100,000	0.3	(0.0, 10.3)	0.50					
10,000-99,999	0.1	(0.0, 1.4)	0.09					
<10,000	1.0	Referent						
Proteinuria								
Yes	7.8	(1.6, 37.8)	0.01£		4.6	(1.4, 15.4)	0.01£	
No	1.0	Referent			1.0	Referent		
Hypertension/treatment								
Yes/ACEI or ARB§	5.2	(1.0, 26.4)	0.05					
Yes/Other treatment	2.7	(0.2, 35.0)	0.45					
Yes/No treatment	0.0	(0.0, 0.0)	1.00					
No/No treatment	1.0	Referent						
Diabetes								
Yes	1.7	(0.3, 10.6)	0.59					
No	1.0	Referent						
Hepatitis C								
Yes	0.0	(0.0, 0.0)	1.00					
No	1.0	Referent						

* OR: odds ratio, †CL: confidence interval, ‡HAART: highly active anti-retroviral therapy, §ACE: angiotensin-converting enzyme, £p<0.05

between individual drugs (abacavir sulfate, lamivudine, lamivudine/zidovudine complex, lopinavir/ritonavir complex, atazanavir, efavirenz, ritonavir, raltegravir, and didanosine) and renal function. Lamivudine was found to exhibit a weak negative correlation (r=-.211, $p < .05$), as shown in Table 3.

DISCUSSION

This case-control study aimed to identify the risk factors that cause CKD in HIV-infected patients. Logistic regression analyses of all the risk factors in the study revealed that the risk of developing CKD was significantly greater for patients with CD4+ cell counts of

Table 3. The Correlations between Individual Drugs and the eGFR

	eGFR
abacavir	-.163
lamivudine	-.211*
lamivudine/zidovudine complex	.198*
lopinavir/ritonavir complex	-.112
atazanavir	-.039
efavirenz	.233*
ritonavir	-.030
raltegravir	-.084
didanosine	.094
stavudine	.087

* $p<0.05$

$<200\times10^6$ cells/l and for patients with proteinuria. Furthermore, analyses of the correlations between individual drugs and renal function revealed that lamivudine has a weak correlation with reduced eGFR levels.

Many previous studies have also indicated that CD4+ cell count is relevant as a risk factor for the development of chronic kidney disease[4, 9, 14] and several cohort studies have shown that the risk of renal failure and mortality increases when the CD4+ cell count is $<200\times10^6$ cells/l.[15-16] In a recent study, the following were considered to be predictive factors for renal failure: being female, a body mass index (BMI) <18.5, a CD4+ cell count $<200\times10^6$ cells/l, and a clinical stage higher than the World Health Organization (WHO) stage II.[17] Our study also indicated that patients with a CD4+ cell count of $<200\times10^6$ cells/l had a higher risk of developing CKD. Despite the fact that plasma viral load has a direct role in the occurrence of HIV, almost no study has identified it as a risk factor for developing CKD. Similarly, in the present study, plasma viral load was not found to be statistically significant. In addition, several studies have reported that HAART is a useful prognostic factor for renal disease, including non-HIVAN histologies,[18-21] but the present study indicated that performing HAART for more than 8 weeks did not have a statistically significant effect on the occurrence of CKD. This result may have been affected by the fact that drugs that are known to cause a decrease in renal function, such as tenofovir and indinavir, were not used because tenofovir has not yet been released in Korea and indinavir has not ever been used in NMC. In addition, correlations between CKD and comorbidities such as diabetes, hypertension, and hepatitis C were found to be not statistically significant in this study. However, the results of each study vary slightly depending on the race and the characteristics of the patient group. A recent study has also reported that the occurrence of acute renal failure is related to reductions in the CD4+ cell count and eGFR, but race; the presence of hepatitis B or C; exposure to drugs such as indinavir, tenofovir, or atazanavir; and plasma viral load were all found to be irrelevant.[22] Regarding gender, AIDS is generally known to be exceptionally more common in males than in females, and the percentage of male HIV-infected patients who visited this hospital was also significantly higher. Although one female patient was included in the patient group, the control group consisted entirely of males; therefore, the effects of gender on kidney disease could not be analyzed.

Additionally, to determine whether individual drugs influence renal function, this study analyzed the correlation between each drug and the eGFR, but it did not attempt to evaluate whether each of the individual drugs is a risk factor with a direct effect on CKD or the extent of its effects. A recent study of antiretroviral drugs has reported that age, atazanavir treatment, and tenofovir treatment are each significantly related to distal tubular dysfunction.[23] However, in another study that investigated the renal influence of tenofovir in children, adolescents, and young people over a long period, a moderate case of eGFR reduction was observed in only one underweight female; neither proteinuria, hypophosphatemia, nor diabetes occurred, and the eGFR was stable.[24] Thus, risk factor analyses of drugs vary slightly depending on the race and the characteristics of the patient group in each study. Because the drugs that are known to reduce renal function, such as tenofovir and indinavir, have not yet been used in NMC, there has not yet been an opportunity to evaluate them, and additional studies will be necessary after tenofovir and indinavir are introduced in NMC.

An additional limitation of this study is that it was conducted retroactively and consisted of selecting a specific study period and reviewing target patient information and medical records, unlike the approaches used in previous studies. In addition, because the number of target patients was small, it was difficult to draw a statistically significant conclusion when analyzing the differences in the characteristics between the patient group and the control group or when analyzing the risk factors.

Moreover, only eGFR values were monitored and assumed to represent CKD; thus, various renal diseases (including HIVAN) were not accurately classified or evaluated through biopsies. Additionally, the exact mechanisms by which many drugs induce nephrotoxicity remain unidentified; therefore, larger-scale prospective studies that are well designed should be conducted in the future to determine the effects of each risk factor and of each individual drug on the prognosis of the patients.

This study is significant despite its limitations in its use of Koreans as subjects; there has not been sufficient research that targets Asians on the risk factors for developing CKD or the drugs used for HIV-infected patients, and no such study has ever used Koreans as subjects. The results of this study are expected to contribute to the prevention and management of CKD in HIV-infected patients. To validate these results and make them applicable, prospective studies on a larger number of target patients should be undertaken in the future.

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