Original article

A Pilot Study of Efficacy and Safety of Standard Dose of Lopinavir/Ritonavir in Combination with one Nonnucleoside Reverse Transcriptase Inhibitor and one Nucleoside Reverse Transcriptase Inhibitor in well Virology Suppressed HIV Infected Adults

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Abstract

Background : Highly active antiretroviral therapy leads to long life of HIV-infected adults. More patients have co-morbid diseases which cause intolerance of nucleoside reverse transcriptase inhibitor (NRTI) toxicity. Due to limitation of available drug in Thailand, adjusting regimen to nonnucleoside reverse transcriptase inhibitor (NNRTI) plus boosted protease inhibitor is another option.

Objectives: To study the virological control and trough concentration (C_{trough}) of lopinavir (LPV) in a combined regimen of one NNRTI, one NRTI and standard dose of lopinavir/ritonavir (LPV/rtv).

Material and Methods: This study was a 52-week prospective clinical trial. Eligible patients were HIV - infected adults with plasma HIV RNA (pVL) < 50 copies/mL, age > 18 years, no history of LPV resistance and received a combined treatment of one NNRTI, one NRTI and LPV/rtv for at least 3 months. Patients with LPV/rtv 500mg/125 mg were adjusted to 400mg/100 mg. the other combined drugs, 1 NNRTI and 1 NRTI were continued. The primary outcome was virological control (pVL< 50 copies/mL). Secondary outcome was C_{trough} of LPV > 1 mg/L.

Results: Between November 2013 and April 2014, a total of 12 patients were screened and enrolled in this study. Seven patients received LPV/rtv 500 mg/125 mg before enrollment and five patients received LPV/rtv 400 mg/100 mg. Seven patients on nevirapine (NVP) and five patients on efavirenz (EFV). Eleven patients on lamivudine and one patient on tenofovir. Eleven of 12 patients had pVL< 50 copies/mL and their C_{trough} of LPV > 1 mg/L.

Conclusion: NVP or EFV plus standard dose of LPV/rtv in Thai HIV infected adults with well virological suppress had efficacy in virological control with enough level of C_{trough} of LPV.

Keywords : Lopinavir/ritonavir; NNRTI; Ctrough

นิพนธ์ต้นฉบับ

การศึกษานำร่องของประสิทธิภาพและความปลอดภัยในการใช้ยาโลปินาเวียร์/ริโทนาเวียร์ขนาดมาตรฐาน ร่วมกับยานอนนิวคลิโอไซด์รีซิสเทนหนึ่งตัว และยานิวคลิโอไซด์รีซิสเทนหนึ่งตัว ในผู้ป่วยเอชไอวีผู้ใหญ่ที่คุมไวรัสได้ดี

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บทคัดย่อ

ที่มาและความสำคัญ: ยาต้านไวรัสประสิทธิภาพสูงทำให้ผู้ป่วยติดเชื้อเอชไอวีมีอายุยืนยาวขึ้น ผู้ป่วยมีโรคร่วมเพิ่มมากขึ้นทำให้ไม่สามารถทนต่อพิษของยาเอ็นอาร์ทีไอได้ ด้วยข้อจำกัดของยาที่มีในประเทศไทย การปรับสูตรยาเป็นยาเอ็นเอ็นอาร์ทีไอร่วมกับยาพีไอ จึงเป็นทางเลือกหนึ่ง

วัตถุประสงค์: เพื่อศึกษาการควบคุมปริมาณไวรัสและความเข้มข้นของยาโลปินาเวียร์ก่อนเริ่มยามื้อถัดไป ในสูตรยาเอ็นเอ็นอาร์ทีไอ 1 ชนิด เอ็นอาร์ทีไอ 1 ชนิด และยาโลปินาเวียร์/ริโทนาเวียร์ขนาดมาตรฐาน

วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาไปข้างหน้าเป็นเวลา 52 สัปดาห์ ผู้ป่วยที่เข้าเกณฑ์ในการศึกษาคือผู้ป่วยผู้ใหญ่ที่ติดเชื้อเอชไอวี มีปริมาณไวรัสเอชไอวีในน้ำเลือดน้อยกว่า 50 ก๊อปปี้ต่อมิลลิลิตร มีอายุมากกว่าหรือเท่ากับ 18 ปี ไม่มีประวัติดื้อยาโลปินาเวียร์และได้รับการรักษาด้วยยาสูตรรวมที่มียาเอ็นเอ็นอาร์ทีไอ 1 ชนิด ยาเอ็นอาร์ทีไอ 1 ชนิดและยาโลปินาเวียร์/ริโทนาเวียร์ มาอย่างน้อย 3 เดือน ผู้ป่วยที่ได้ยาโลปินาเวียร์/ริโทนาเวียร์ ขนาด 500 มิลลิกรัม/125 มิลลิกรัม จะถูกปรับยาเป็นขนาด 400 มิลลิกรัม/100 มิลลิกรัมร่วมกับได้ยาเดิมคือยาเอ็นเอ็นอาร์ทีไอ 1 ชนิด และยาเอ็นอาร์ทีไอ 1 ชนิด ผลการศึกษาหลักคือการควบคุมปริมาณไวรัสได้น้อยกว่า 50 ก๊อปปี้ต่อมิลลิลิตร และผลการศึกษารองคือความเข้มข้นของยาโลปินาเวียร์ก่อนเริ่มยามื้อถัดไปมากกว่า 1 มิลลิกรัมต่อลิตร

ผลการศึกษา: ในช่วงเดือนพฤศจิกายน พ.ศ. 2556 ถึงเดือนเมษายน พ.ศ. 2557 ผู้ป่วย 12 ราย ได้ถูกคัดกรองและเข้าร่วมการศึกษานี้ ผู้ป่วย 7 ราย ได้รับยาโลปินาเวียร์/ริโทนาเวียร์ ขนาด 500 มิลลิกรัม/125 มิลลิกรัม ก่อนเข้าการศึกษา และผู้ป่วย 5 ราย ได้ยาโลปินาเวียร์/ริโทนาเวียร์ ขนาด 400 มิลลิกรัม/100 มิลลิกรัม ผู้ป่วย 7 ราย ได้รับยาเนวิราพีนและ 5 ราย ได้รับยาอีฟาวาเรน ผู้ป่วย 11 ราย ได้รับยาสามทีซีและ 1 ราย ได้รับยาทีดีเอฟ ผู้ป่วย 11 ราย จาก 12 ราย มีปริมาณไวรัสเอชไอวีในน้ำเลือดน้อยกว่า 50 ก๊อปปี้ต่อมิลลิลิตร และมีความเข้มข้นของยาโลปินาเวียร์ก่อนเริ่มยามื้อถัดไปมากกว่า 1 มิลลิกรัม/ลิตร

สรุป: ยาเนวิราพีนหรือยาอีฟาวาเรนร่วมกับยาโลปินาเวียร์/ริโทนาเวียร์ขนาดมาตรฐาน ในผู้ป่วยติดเชื้อเอชไอวีผู้ใหญ่ชาวไทยที่ควบคุมปริมาณไวรัสได้อย่างดี มีประสิทธิภาพในการควบคุมปริมาณไวรัสและมีระดับยาโลปินาเวียร์ก่อนเริ่มยามื้อถัดไปสูงเพียงพอ

คำสำคัญ: โลปินาเวียร์/ริโทนาเวียร์; เอ็นเอ็นอาร์ทีไอ; ความเข้มข้นของยาก่อนเริ่มยามื้อถัดไป

Introduction

In Thailand, standard treatment of highly active antiretroviral therapy (HAART) is a combination of two nucleoside reverse transcriptase inhibitors (NRTI) and one nonnucleoside reverse transcriptase inhibitor (NNRTI).[1] Potency of this treatment, make a good clinical response and increase life expectancy of patient to nearly normal population. However, long term use of several NRTIs have been associated with metabolic complication such as anemia and renal impairment. Increase in aging, more co-morbid diseases are found and led to limited treatment of NRTIs. Although, new regimens of HAART have lower toxicity, cost of treatment for Thai national health is too high for coverage. Changing regimen to NNRTI and boosted protease inhibitor (PI) is another option.

Recommendation of Department of Health and Human Services guideline 2016 for combination use of NNRTI with boosted lopinavir/ritonavir (LPV/rtv) is increasing dose of LPV/rtv from 400 mg/100 mg (standard dose) to 500 mg/125 mg (high dose) due to drug-drug interaction.[2] Pharmacokinetic studies of several PIs in Thai patients showed that Thai patients had high drug level of PIs with standard dose.[3,4]

Objective

This study was designed to assess the efficacy and safety of standard dose of LPV/rtv in combination with nevirapine (NVP) or efavirenz (EFV) and one NRTI in well virology suppressed HIV infected Thai patients.

Material and Methods

Study design

This was a 52 weeks, pilot, prospective study designed to evaluate the virological efficacy and trough concentration (C_{trough}) of standard dose of LPV in well virology suppressed HIV-infected adults who was treated with standard dose of LPV/rtv in combination with one NNRTI and one NRTI.

Population

Patients were eligible for the study if they were > 18 years and had provided written informed consent, no history of LPV resistance, plasma HIV RNA (pVL) < 50 copies/mL within 12 months prior to screening visit, pVL < 50 copies/mL at screening visit and received combination treatment of one NNRTI, one NRTI and LPV/rtvfor at least 3 months. Patients were not eligible if they had active acquired immune deficiency syndrome defining disease or active opportunistic infections, pregnancy or lactating and use of concomitant medications that may interfere with the pharmacokinetics of LPV including rifampicin or proton pump inhibitors.

Procedures

After screening, patients who received high dose of LPV/rtv were adjust LPV/rtv to standard dose as protocol study. For patients with standard dose of LPV/rtv treatment, the

current regimen with LPV/rtv 400 mg/100mg twice a day, one NNRTI and one NRTI were continued.

Patients were evaluated at baseline and every 13 weeks. pVL was assessed at screening visit, week 13, 26, and 52. At week 0 for patients who received high dose LPV/rtv, and week 13 and 26 for all patients, C_{trough} of LPV were measured. All pVL tests and C_{trough} of LPV were performed at the HIV-NAT research laboratory in Bangkok. CD4+ cell count and urinary analysis were performed at screening and end of the study. Complete blood count, alanine transaminase, creatinine, cholesterol, high-density lipoprotein, triglycerides and fasting blood glucose were performed every 26 weeks. At each study visit, all participants were asked to complete an adherence questionnaire. At week 0, 13 and 52, all participants were asked to complete a questionnaire of gastrointestinal (GI) toxicity.

The primary outcome was virological control (pVL < 50 copies/mL). Secondary outcome was C_{trough} of LPV > 1 mg/L.

Statistical analyses

Categorical data were expressed as proportions. Continuous data were expressed as mean and interquartile range (IQR) as appropriate.

Results

Between November 2013 and April 2014, a total of 12 patients were screened and enrolled in this study. Seven patients received LPV/rtv 500 mg /100 mg before enrollment. Nine patients received LPV/rtv< 1 year, two patients received LPV/rtvfor about 3 years and one patient had no available data. Drugs were adjusted to PI in ten patients due to NRTI toxicity and in two patients due to virological failure from previous dual ARV therapy. Seven patients on NVP and five patients on EFV. Eleven patients on lamivudine (3TC) and one patient on tenofovir (TDF). One patient died 13 weeks after enrollment from septic right prosthetic hip. Demographics data were presented in Table 1.

Table 1. Demographics data

	N = 12
Age (years)	49.4 (43.5-58)
Male [No. (percent)]	9 (75)
Body weight (kg)	55.7 (49-62.5)
Body mass index (kg/m^2)	20.5 (18.0-23.4)
CD4 nadir * (cells/mm^3)	88.3 (5-158)
Duration of HAART prior to screening * (years)	8.3 (4-11)
Previous regimen of NRTI * (No.)	
d4T -> AZT -> TDF	7
d4T -> TDF	2

Table 1. Demographics data

Cause for changing regimen to NNRTI plus PI (No.)	
lipodystrophy	7
renal impairment	6
lactic acidosis	3
neuropathy	3
Fanconi syndrome	2
virological failure from dual therapy	2
anemia	1
Previous major opportunistic infection	8
Comorbid disease	10

Data are mean (IQR) or n (percent), stavudine (d4T), zidovudine AZT), * one data not available.

Eleven patients had pVL< 50 copies/mL. Only one patient had pVL 67 copies/mL at the end of the study. Ctrough of LPV were shown in figure 1. One of twenty three test (4.3 peseent) had Ctrough < 1 mg/L. Eighteen test (78.3 pescent) of Ctrough were measured 12 + 1 hours after the last intake of study medication. Only one male patient, who had Ctrough < 1 mg/L, were meausured Ctrough more than 14 hours after the last intake. His pVL was followed every 13 weeks and all pVL were< 50 copies/mL. All of seven patients who had adjusted LPV/rtv from 500 mg/125 mg to study dose had decreased cholesterol level and four patients had decreased triglyceride level. Five patients had decreased GI disturbance after decreased LPV/rtv dose. They favoured to take study dose because of less pill, less GI toxicity and easy to use (2 tablets versus 2 and a half tablets).

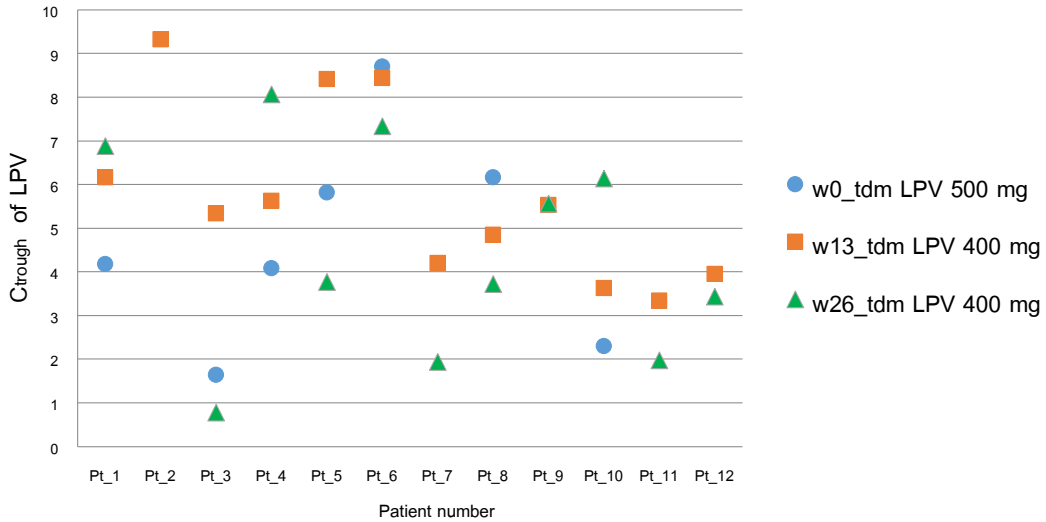

Fig. 1 Ctrough of LPV in 500 mg and 400 mg

Discussion

Standard dose of LPV/rtv combination with NVP or EFV showed efficacy in terms of virological control and less toxicity. One patient who had pVL 67 copies/mL, was followed 1 year later, the result was < 50 copies/mL which suggested the viral blip more than virological failure. The NEKA study and the MULTINEKA study found that standard dose of LPV/rtv combination with NVP had efficacy for virological suppression and improvement of mitochondrial toxicity.[5,6] Increased dose of LPV/rtv combination with EFV in NRTI sparing study showed that some participants were adjusted LPV/rtv to standard dose due to GI toxicity and high drug level.[7] As shown in figure 1, C_{trough} of LPV 400 mg was above the therapeutic concentration except one patient who had C_{trough}< 1 mg/L. The low C_{trough} could explained by delay measurement of the last intake of LPV. Pharmacokinetic studies found higher drug level of standard dose of PIs in Asian including Thai than Caucasian.[3,4] High drug level of PI had related higher toxicity.[7, 8] Four patients who received LPV/rtv 500 mg / 100 mg before adjust to standard dose, had low C_{trough} level at week 0 than week 13 which explained by delay measurement. In our study, C_{trough} level had both interpatient and intrapatient variability. Body weight and genetic traits may influence interpatient variability.[9,10] Environment such as food, concomitant medication, treatment adherence and time of measurement may influence intrapatient variability.[9,10]

In Thailand the first line treatment of HAART is a combination of two NRTI and one NNRTI. Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2014 recommended that the NRTI backbone is TDF plus 3TC, another alternatives are Abacavir (ABC) and AZT.[1] Increase in aging and co-morbid diseases led to limitation of NRTI therapy. TDF has long term renal and bone toxicities. A novel prodrug of tenofovir, Tenofovir alafenamide (TAF), had non inferiority in viral suppression when compared with TDF.[11,12] TAF has a favourable long term renal and bone safety profile.[11-13] ABC has controversial data in associated increased risk of myocardial infarction.[14-17] Long term tolerability in HAART is a heart issue. Simple regimens for well controlled HIV-infected patients were studieds. The OLE and the SALT study found that dual therapy with 3TC and one boosted PI had efficacy comparable with triple therapy.[18,19]

Although small number of participants is the limitation of this study, data of C_{trough} which shown adequate C_{trough} in PI naïve patient support the virological suppression in our study. NVP or EFV plus standard dose of LPV/rtv can be an alternative therapy in Thai patients who are intolerance with NRTI.

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