A Randomized, Open-Label, Comparative Trial of BID and TID Dosing of Saquinavir Enhanced Oral Formulation as Part of a Triple Therapy for Advanced AIDS Patients

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Abstract

Objective : To compare the efficacy and safety of 1,400 mg BID and 1,200 mg TID of saquinavir soft gel given with zidovudine and lamivudine in antiretroviral-naïve, advanced AIDS patients.

Method : A randomized, open-label study conducted at a university hospital.

Results : Forty cases were enrolled in the study, 20 cases in each group. The mean CD4 cell count was 29 cells/mm^3. The mean $\log_{10}$ HIV-1 RNA was 5.27 copies/mL. Using an on-treatment analysis, the reduction in plasma $\log_{10}$ HIV-1 RNA of BID and TID groups was not statistically significant at -2.44 *vs* -2.60 copies/mL (-0.16, 95% CI -0.63 to 0.30; p= 0.48). The mean increase in CD4 cell counts was not statistically significant at +144 and +159 cells/mm^3 (11, 95% CI -75 to 97; p=0.79).

Conclusion : The preliminary data suggests that in antiretroviral-naïve, advanced AIDS patients, 1,400 mg BID of saquinavir soft gel given with two nucleoside analogues might be as effective as the standard 1,200 mg TID.

Key word : Saquinavir-Soft Gel Capsule, BID Dose, Highly Active Antiretroviral Therapy, Advanced AIDS

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A protease inhibitor given with two nucleoside reverse transcriptase inhibitors (NRTI) is the current treatment for human immunodeficiency virus type 1 (HIV-1) infected patients. Saquinavir (SQV), a protease inhibitor, has shown significant antiretroviral activity, which is directly related to its plasma concentration. The bioavailability of saquinavir in hard gel capsules (SQV-HGC) is 3 to 5 per cent (1). Notwithstanding, the enhanced soft gel capsule (SQV-SGC) formulation at a dose of 3.6 g/d achieves plasma concentrations 10 times greater than SQV-HGC at a dose of 1.8 g/d. The recommended dose of SQV-SGC is 1,200 mg TID(2). The IC_{90} of SQV was 12 ng/mL, when 1.6 g of SQV-SGC was given BID to HIV-infected patients and the C_{min} of SQV 246 ng/mL remained above the IC_{90}(3). Data from the United States suggests that comparable HIV-1 RNA suppression may be obtained with 1600 mg BID(4). Since Thai HIV-1 infected patients weigh an average 10 kg less than American patients, a dose of 1,400 mg BID might be as effective in a triple therapy. Moreover, taking medication BID is more convenient than TID, especially in the long-term, and might improve compliance. SQV use in advanced acquired immunodeficiency syndrome (AIDS) patients is not documented, so the authors evaluated the efficacy and safety of SQV-SGC BID *vs* TID when given with 2 NRTIs in advanced AIDS patients.

METHOD

Study Design and Treatment Regimens

This was a randomized, open-label, comparative trial of BID *vs* TID dosing of SQV enhanced oral formulation as part of a highly active antiretroviral therapy (HAART) for advanced AIDS patients. Patients with a documented HIV-1 infection, aged >15 years, CD4 <200 cells/mm^3, HIV-1 RNA >20,000 copies/mL, and antiretroviral-naïve were eligible. Patients with acute opportunistic infections or other serious AIDS-defining illnesses were excluded. Those with unexplained chronic diarrhea, a history of or active malignancy, those pregnant, lactating or using inadequate contraception, those having grade III or higher laboratory or clinical abnormalities, and taking medications metabolized by cytochrome P_{450} (because it interferes with SQV metabolism) were also excluded. The study was approved by the Institutional Review Board and all participants gave informed consent. After being enrolled, patients received open-label zidovudine (AZT 300 mg BID for body weights >60 kg and 200 mg BID for <60 kg) and lamivudine (3Tc 150 mg BID). They were then randomly assigned SQV-SGC 1,400 mg BID or SQV-SGC 1,200 mg TID. The patients were followed-up every 4 to 8 weeks to monitor the occurrence of any adverse events. The CD4 cell counts and viral load (Roche Molecular System Amplicor® HIV-1 monitor) were determined at the start (i.e. the baseline) and at weeks 4, 12, 24, 36, and 48, respectively.

Analysis

Plasma HIV-1 RNA levels and CD4 cell counts for each time point were analyzed using an on-treatment basis. Information missing, for whatever reason, was not included in the analysis.

RESULTS

Forty patients enrolled in the study between July 1999 and November 2000, providing 20 cases in each group. The baseline characteristics are presented in Table 1. The mean age and body weight of the 32 (80%) males and 8 (20%) females were 35 years and 55 kg. All but one patient had contracted the HIV-1 infection through heterosexual activity. The patients were all advanced AIDS patients, whose mean CD4 cell count was 29.5 cells/mm^3 (range, 0 to 123 cells/mm^3; median, 18 cells/mm^3). According to the clinical classification, 29 cases (73%) had AIDS, 7 (17%) were symptomatic HIV and 4 (10%) were asymptomatic HIV. Among the AIDS patients, many had multiple opportunistic infections (OI): 15 with cryptococcosis, 11 with *Pneumocystis carinii* pneumonia, 9 with tuberculosis, 5 with cytomegalovirus infection, 4 with toxoplasmosis, 2 with penicilliosis, 2 with esophageal candidiasis, and 1 each with nocardiosis and salmonellosis. Ten cases had 2 previous OIs, 4 had 3 and 1 had 4. Viral loads were high with a mean $\log_{10}$ HIV-1 RNA of 5.27 copies/mL (geometric range, 29,734 to >750,000 copies/mL; median, 232,142 copies/mL).

Safety Analysis

Adverse events were very common (42 events in 40 patients) (Table 2) and included: anemia, nausea/vomiting, elevated liver enzymes and hyperlipidemia. Sixteen patients (8 in each group) developed anemia (i.e. Grades II to IV) necessitating a reduced

Table 1. Baseline characteristics of the patients.

Characteristic	TID n = 20	BID n = 20	All patients n = 40
Sex			
Male : Female	18 : 2	14 : 6	32 : 8
Age			
Mean year (SD)	33.9 (5.6)	36.5 (9.9)	35.2 (8.1)
Weight			
Mean kg (SD)	55.8 (8.0)	53.6 (10.8)	54.7 (9.5)
HIV risk factor			
Heterosexual	19	20	39
Blood transfusion	1	0	1
Disease staging			
Asymptomatic	2	2	4
Symptomatic	3	4	7
AIDS	15	14	29
HIV-1 RNA levels			
Mean $\log_{10}$ copies/mL (SD)	5.32 (0.34)	5.22 (0.39)	5.27 (0.36)
Geometric median copies/mL	233,969	216,377	232,141
Geometric range, copies/mL	40,936 - >750,000	29,734 - 384,682	29,734 - >750,000
CD4 count (cells/mL)			
Mean (SD)	27.0 (33.6)	32.0 (34.3)	29.5 (33.6)
Median	12.0	25.7	18.0
Range	0 - 123	0 - 120	0 - 123

Table 2. Adverse events and reasons for premature discontinuation of study.

Treatment group	TID n = 20	BID n = 20	Total n = 40
Adverse events			
Anemia Grades II-IV	8 (40)	8 (40)	16 (40)
Severe nausea / vomiting	3 (15)	4 (20)	7 (17.5)
Elevated SGOT Grade II-III	2 (10)	4 (20)	6 (15)
Elevated SGPT Grade II-III	2 (10)	4 (20)	6 (15)
Cholesterol Grade II	2 (10)	0 (0)	2 (5)
Triglyceride Grade II	3 (15)	0 (0)	3 (7.5)
Alkaline phosphatase grade II	1 (5)	1 (5)	2 (5)
Total events	21	21	42
Out of study			
Severe nausea / vomiting	3 (15)	4 (20)	7 (17.5)
Lost to follow-up	1 (5)	3 (15)	4 (10)
Died	0 (0)	1* (5)	1 (2.5)
Total	4 (20)	8 (40)	12 (30)

*Suicide

dose of AZT in 6 cases (4 in the TID group and 2 in the BID group) and a change from AZT to stavudine (d4T) or didanosine (ddI) in 10 cases (4 in the TID and 6 in the BID). The anemia was severe enough in 4 cases (3 in the TID and 1 in the BID) that a blood transfusion was needed. At the end of week 48, 12 patients withdrew from the study, 7 due to severe nausea and vomiting (3 in the TID and 4

in the BID); 4 due to loss of contact (1 in the TID and 3 in the BID), and one, in the BID group, who committed suicide.

Efficacy Data

The response of the plasma HIV-1 RNA concentrations to the treatments are presented in Table 3 and Fig. 1. Using an on-treatment analysis, at week 48, the mean $\log_{10}$ HIV-1 RNA reduction was not statistically significant at -2.60 *vs* -2.4 copies/mL in the TID and BID groups (-0.16, 95% CI -0.63 to 0.30; p = 0.48). The overall viral suppression was remarkable in these patients, the mean reduction $\log_{10}$ HIV-1 RNA was -2.53 copies/mL. At week 48, the mean increase in CD4 was not statistically significant at +159 *vs* +144 cells/mm^3 in the TID and BID groups (11, 95% CI -75 to 97; p = 0.79) (Table 3 and Fig. 2).

Three cases in the TID group had clinical progression, disseminated *Penicillium marneffei* infection, relapse of cryptococcal meningitis and progressive multifocal leukoencephalopathy (PML).

Table 3. Outcomes of patients in both groups at week 48.

Treatment group	TID n = 16	BID n = 12	Total n = 28
HIV-1 RNA (mean log10 copies/mL ± SD)			
Baseline	5.32 ± 0.34	5.22 ± 0.39	5.27 ± 0.36
At week 48	2.72 ± 0.33	2.75 ± 0.50	2.73 ± 0.40
Decreased	-2.60 ± 0.53	-2.44 ± 0.66	-2.53 ± 0.59
CD4 count (mean cells/mm3 ± SD)			
Baseline	27.0 ± 33.6	32.0 ± 34.3	29.5 ± 33.6
At week 48	185.5 ± 94.5	176.0 ± 145.3	181.4 ± 116.5
Increased	158.1 ± 95.7	147.0 ± 126.8	153.3 ± 108.0

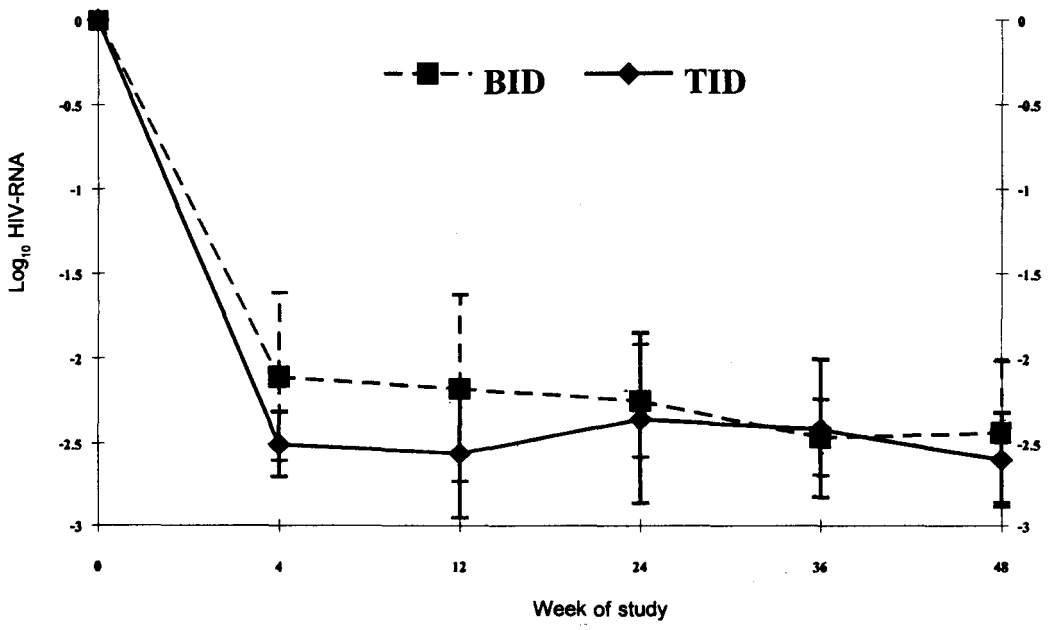

Fig. 1. The response of the plasma HIV-1 RNA concentrations to treatment.

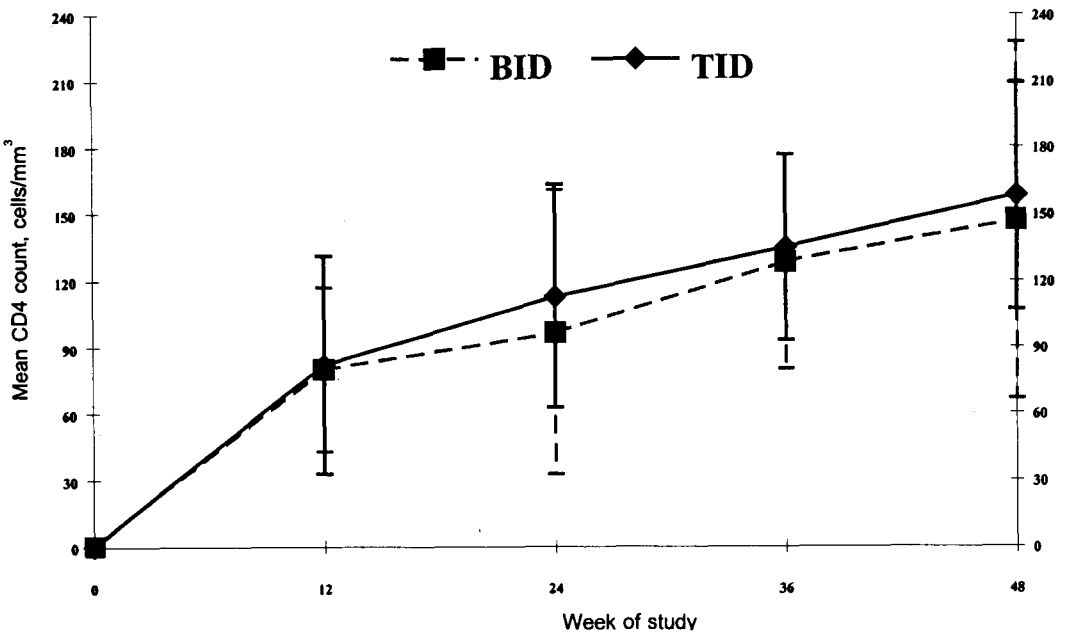

Fig. 2. The response of CD4 cell counts to treatment.

Disseminated penicilliosis occurred 2 weeks after starting HAART (the baseline CD4 was <1 cells/mm^3). PML occurred 5 months after starting HAART, the viral load was <400 copies/mL but the CD4 was only 42 cells/mm^3. Relapse of cryptococcosis occurred in a patient who had poor compliance to the HAART and fluconazole (antifungal drug use for maintenance therapy). One case in the BID group developed tuberculosis at the end of the 48 weeks, the viral load was <400 copies/mL but the CD4 was only 48 cells/mm^3. None of the patients died from clinical HIV-related diseases during the study.

DISCUSSION

Patients who participated in this study were considered advanced HIV-infected cases because their CD4 cell count averaged 29 cells/mm^3 (range, 0 to 123 cells/mm^3). All of them had AIDS according to the CDC's criteria[5] (i.e. CD4 cell count <200 cells/mm^3). Twenty-nine (73%) cases had AIDS diagnosed by having opportunistic infections - the mean $\log_{10}$ HIV-1 RNA was 5.27 copies/mL, the geometric range 29,734 to >750,000 copies/mL. A substantial number of patients developed adverse events when taking the triple combination of antiretroviral drugs, most commonly: anemia (40%), nausea/vomiting (17.5%) and elevated liver enzymes (15%). The anemia was severe enough to require the AZT to be replaced by d4T and blood transfusions were given. Severe nausea and vomiting were the most common symptoms resulting in withdrawal from the study.

Among patients who tolerated the antiretroviral therapy, 25 (89%) of them had viral suppression (HIV-1 RNA <400 copies/mL). The mean CD4 cell count increased to 181 cells/mm^3 and the mean $\log_{10}$ HIV-1 RNA decreased by up to -2.53 copies/mL. There was no significant difference between the BID and TID groups in terms of viral suppression (-2.44 and -2.60 copies/mL, $p = 0.48$) nor in the increment of CD4 cell counts (+144 and +159 cells/mm^3, $p = 0.79$). the present results are similar to a study of HIV-NAT[6], where 1,400 mg BID *vs* 1,200 mg TID of saquinavir were combined with 2 NRTIs in HIV-infected patients pretreated with AZT/ddC. They found the two regimens had the same efficacy. However, the present study is the

first on the effect of SQV in advanced AIDS patients who are antiretroviral-naïve. Opportunistic infections occurred in the patients in the present study even though they responded to HAART (viral suppressed) because their CD4 cell counts remained very low.

Improving the use of the currently approved agents to treat HIV-1 infection remains a challenge. Minimizing the dose and number of pills might improve adherence to treatment and contribute to more prolonged viral suppression during HAART. Co-administration of SQV with ritonavir (RTV), a potent inhibitor of cytochrome P450, causes serum concentrations of SQV to increase markedly compared to higher and more frequent doses of SQV alone[7]. In several clinical trials, the combination of SQV (400 mg to 800 mg) and RTV (400 mg to 600 mg), both administered twice daily, is a well-tolerated and potent regimen effective in the treatment of both naïve and protease-inhibitor-experienced patients[8-12]. A recent pharmacokinetic study of 1,600 mg of SQV plus 100 mg RTV has shown a promising once-daily dosing[13]. A positive preliminary result in clinical trials of HIV-NAT [14] is also encouraging.

The presented preliminary data suggests that in antiretroviral-naïve, advanced AIDS patients, 1,400 mg BID of saquinavir soft gel given with two nucleoside analogues might be as effective as the standard 1,200 mg TID of saquinavir.

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การศึกษาแบบสุ่ม เปิด เปรียบเทียบระหว่างการใช้ยาซาควินาเวียร์แบบวันละสองครั้งกับวันละสามครั้งในสูตรยาสามตัวในการรักษาผู้ป่วยเอดส์ระยะสุดท้าย

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วัตถุประสงค์ : เปรียบเทียบประสิทธิภาพและความปลอดภัยของการใช้ยาซาควินาเวียร์ขนาด 1,400 มก วันละ 2 ครั้งกับขนาด 1,200 มก วันละ 3 ครั้ง โดยใช้ร่วมกับไซโดวูดีนและลามิวูดีนในผู้ป่วยเอดส์ระยะสุดท้ายที่ไม่เคยได้รับยาต้านไวรัสเอ็ชไอวีมาก่อน

วิธีการ : การศึกษาแบบสุ่ม เปิด (randomized, open-label) ในโรงพยาบาลศรีนครินทร์มหาวิทยาลัยขอนแก่น

ผลการศึกษา : ผู้ป่วยจำนวน 40 รายเข้าร่วมการศึกษาโดยมีผู้ป่วย 20 รายในแต่ละกลุ่ม ค่าเฉลี่ยของจำนวน CD_4 เซลล์เท่ากับ 29 ตัว/มม^3 ค่าเฉลี่ยของ $\log_{10}$ HIV-1 RNA เท่ากับ 5.27 ก็อปปี้/มล วิเคราะห์โดย on-treatment analysis การลดลงของ log10 HIV-1 RNA ทั้ง 2 กลุ่มไม่แตกต่างคือ -2.44 เปรียบเทียบกับ -2.66 ก็อปปี้/มล (-0.16, 95% CI -0.63 ถึง 0.30; p=0.48) ค่าเฉลี่ยของการเพิ่มขึ้นของ CD_4 เซลล์ไม่แตกต่างอย่างมีนัยสำคัญทางสถิติคือเพิ่มขึ้น 144 และ 159 เซลล์/มม^3 (11, 95% CI-75 ถึง 97; p=0.79)

สรุปผล : การศึกษาเบื้องต้นนี้พบว่าในผู้ป่วยเอดส์ระยะสุดท้ายที่ไม่เคยได้รับยาต้านไวรัสเอ็ชไอวีมาก่อนการใช้ยาซาควินาเวียร์ขนาด 1,400 มก วันละ 2 ครั้ง โดยใช้ร่วมกับยาในกลุ่มนิวคลีโอไซด์ อนาล็อคอาจให้ผลเท่ากับใช้ยาซาควินาเวียร์ในขนาด มาตรฐานคือ 1,200 มก วันละ 3 ครั้ง

คำสำคัญ : ซาควินาเวียร์, วันละสองครั้ง, ยาต้านไวรัสเอ็ชไอวีในผู้ป่วยเอดส์

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