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two nucleoside reverse transcriptase inhibitors
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A prospective study of efficacy and safety of once-daily saquinavir/ritonavir plus two nucleoside reverse transcriptase inhibitors in treatment-naive Thai patients

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Objective: To assess the efficacy and safety of first-line treatment with once-daily saquinavir/ritonavir with two nucleoside reverse transcriptase inhibitors (NRTIs), as induction therapy before enrollment in a randomized trial of structured treatment interruption strategies.

Design: Two-hundred antiretroviral-naive patients with CD4+ cell counts between 200–350 at screening were enrolled in this open-label 24week study.

Methods: Patients were followed up every 8 weeks for CD4+ cells, HIV RNA, and clinical and laboratory toxicities.

Results: Two-hundred patients were enrolled with median baseline CD4+ cell count of 267 cells/µl and HIV RNA 50 118 (4.7 $\log_{10}$) copies/ml. After 24 weeks of treatment, 191 of 200 (96%) patients had below 400 copies/ml HIV RNA, with 177/200 (89%) below 50 copies/ml (intent to treat, missing equals failure method), with a median rise in CD4+ cell count of 122 cells/µl. There was no significant correlation between the minimum concentration of saquinavir and HIV RNA reductions at week 8 (P=0.957) or absolute HIV RNA at week 24 (P=0.77).

Conclusion: First-line highly active antiretroviral therapy (HAART) with once-daily saquinavir/ritonavir plus two NRTIs showed strong antiviral efficacy over 24 weeks, and should be evaluated in larger prospective randomized clinical trials.

Introduction

Treatment guidelines recommend first-line HAART with the combination of two nucleoside analogues (NRTIs) plus either a non-NRTI or a boosted protease inhibitor (PI) [1,2]. Ritonavir-boosted saquinavir is a recommended component of first-line highly active antiretroviral therapy (HAART) [1,2] and for treatment with PIs in developing countries [3]. Saquinavir is available in two formulations – soft gelatin capsules (Fortovase) and hard gelatin capsules (Invirase).

Pharmacokinetic studies have shown that similar saquinavir drug levels are achieved with the two formulations when boosted with ritonavir at doses of 1600/100 mg once daily [4] and 1000/100 mg twice daily [5]. The hard gelatin capsule formulation is preferred because of its smaller size, room temperature storage and improved tolerability; a 500mg tablet with similar composition to the hard gelatin capsule is recently approved for use in the United States [6].

However, until now the formulation used most widely in randomized clinical trials has been the soft gelatin capsules [7–9]. Withdrawals owing to gastrointestinal adverse events were recorded in these studies, which may have been associated with the excipients in the soft gelatin saquinavir formulation used. The induction phase of the Staccato trial in Thailand was the first large-scale evaluation of once-daily ritonavir-boosted saquinavir using the hard gelatin formulation. The dosage of 1600/100 mg once daily was chosen based on previous experience with this dosage in studies in Thailand [10,11] and North America [9].

The pharmacokinetics of saquinavir/ritonavir at the 1600/100 mg once-daily dosage [12,13] do suggest that a proportion of patients would have trough levels below the minimum effective concentration of 50 ng/ml [14]. However this minimum effective concentration was established for unboosted saquinavir treatment. When boosted with ritonavir, at the 1600/100 mg once-daily dosage, higher maximum concentration levels are achieved, and saquinavir shows strong intracellular accumulation [15]. If the intracellular saquinavir shows sustained antiviral activity when plasma drug levels are low, the previously established minimum effective concentration may need to be revised. This study also re-evaluated trough saquinavir levels in the context of a once-daily ritonavir-boosted dosage of saquinavir hard gel capsules.

Methods

The Staccato trial is an ongoing international randomized evaluation of continuous versus CD4-guided HAART, for patients with full viral suppression at baseline. Before the randomized phase, antiretroviral-naive patients in seven Thai centres were treated with HAART including once-daily boosted saquinavir hard gelatin capsules plus ritonavir, with two NRTIs, for an induction phase of 24 weeks. Adherence to study medication   was monitored and assessed by dedicated staff. Patients with HIV RNA levels below 50 copies per ml at week 24 are then randomized to continuous versus CD4-guided treatment.

The trial enrolled HIV-1 infected, treatment-naive adults with screening CD4+ cell counts of 200–350 cells/ml. The first 200 patients are included in this planned analysis. The trial was approved by local and national ethics committees, and all patients signed written informed consent at screening. The HAART regimen used for all patients was two nucleoside analogues (NRTIs) plus saquinavir/ritonavir 1600/100 mg once daily. Saquinavir hard gelatin 200 mg capsules with standard ritonavir 100 mg capsules were used. The NRTI combination was initially d4T plus enteric-

Table 1. Baseline characteristics and patient disposition

Baseline characteristic	
Age, mean years (SD)	33.94 (8.55)
Sex, male:female (%)	89:111 (44.5:55.5)
CDC class, n (%)	
A	176 (88)
B	20 (10)
C	4 (2)
Median CD4+ cell count, $\times 10^6$ cells/l (IQR)	267 (220–315.3)
Median HIV RNA, $\log_{10}$ copies/ml (IQR)	4.7 (4.2–5.1)
Patient disposition	
Patients switched to TDF/3TC by week 24 (%)	23 (11.5)
Patients lost to follow-up by week 24 (%)	2 (1)
Patients still receiving SQV/r at week 24 (%)	198 (99)

A total of 200 patients were included in the analysis. IQR, interquartile range; SQV/r, saquinavir/ritonavir; TDF, tenofovir disoproxil fumarate.

coated ddI at standard weight-adjusted doses and was later switched to tenofovir plus 3TC by a protocol amendment. A total of 23 patients (11.5%) made this switch of NRTIs by week 24, of whom four switched because of d4T-related toxicities (peripheral neuropathy, high lactate and/or weight loss). A pharmacokinetic substudy showed no clinically significant effect of the switch in NRTIs on plasma saquinavir levels [16], and these results have been confirmed by independent pharmacokinetic trials [17,18].

Patients attended study visits at screening, baseline, and weeks 8, 16 and 24. Patients were assessed for CD4+ cell count, HIV RNA (Roche Amplicor Ultrasensitive assay), fasting lipids, haematology, clinical chemistry, adverse events and HIV disease progression. Clinical and laboratory adverse events were graded by severity.

For pharmacokinetic assessments, samples were taken at routine study visits, and the time of last dose intake recorded. The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) was the only study site with capability to perform pharmacokinetic assessments; therefore, only the patients who were followed at HIV-NAT during the 3-month pharmacokinetic assessment period (n=47) had their samples collected. Blood samples were then centrifuged at 3800 rpm for 10 min at 4ºC on the day of sample collection. Plasma saquinavir and ritonavir were measured in all available samples by means of a validated HPLC method. To test for a correlation between saquinavir drug levels and HIV RNA response, Spearman's rank correlations were used for continuous measures, and Chi-square tests for categorical measures.

The primary endpoint was the proportion of patients with HIV RNA levels under 50 copies per ml at week 24 using the intent-to-treat, missing equals

Figure 1. Median CD4$^+$ cell change from baseline

for two patients owing to concerns over low saquinavir plasma levels. Finally, four patients switched NRTIs owing to NRTI toxicity.

The median CD4$^+$ cell count rose from 267 cells/µl at baseline to 386 cells/µl at week 24 ($P<0.001$) with a median CD4$^+$ cell change from baseline of 122 cells at week 24 (Figure 1). HIV RNA levels fell by a median 2.9 $\log_{10}$ copies per ml to week 24 ($P<0.001$). At week 24, 191/200 patients 96% had HIV RNA levels suppressed below 400 copies per ml, with 177/200 (89%) below 50 copies per ml (Figure 2). High baseline HIV RNA did not predict HIV RNA above 50 copies per ml at week 24.

Forty-seven patients had their minimum concentration (Cmin) of saquinavir measured. The median saquinavir Cmin was 270 ng/ml (IQR 110–550). Six of forty-seven (12.9%) patients had saquinavir Cmin levels below 50 ng/ml. Of these six patients with low saquinavir Cmin, two of two (100%) and none of four (0%) patients failed virologically at week 8 and 24, respectively. Several analyses were conducted to investigate the correlation between saquinavir Cmin and reductions in HIV RNA during the trial. For the 21 patients with saquinavir Cmin recorded during the first 8 weeks of the trial, there was no correlation between saquinavir Cmin and the $\log_{10}$ reduction in HIV RNA from baseline to week 8 ($r=0.012$, $P=0.957$). Whether patients had higher or lower saquinavir Cmin compared with the median value, the HIV RNA reductions were the same (Table 2). For 47 patients with saquinavir Cmin recorded at any time during the 24 week trial, there was no correlation between saquinavir Cmin and the HIV RNA level achieved at week 24 ($r=-0.043$, $P=0.777$) or with body weight ($r=-0.024$, $P=0.872$). These 47 patients

failure method, regardless of temporary discontinuations or dose modifications in the study drugs. In addition, switches in NRTI without previous virological failure were not classified as treatment failure in this analysis. Changes from baseline to week 24 were analysed by the Wilcoxon signed ranks test for continuous variables and the McNemar test for categorical variables. Data were analysed using SPSS for Windows, version 9.0 software (SPSS Inc., Chicago, IL, USA).

Results

The first 200 patients were included in the analysis. Baseline characteristics are shown in Table 1. Overall, there were 89 males and 111 females, with median age 34 years and median body weight of 55 kg. Most patients were either in CDC stage A (88%) or B (10%) at baseline. Median baseline CD4$^+$ cell count was 267 [interquartile range (IQR) 220–316] and HIV RNA 4.7 (IQR 4.2–5.1) $\log_{10}$ copies per ml.

Two of the 200 patients (1%) discontinued the trial (owing to difficulty in complying with the follow-up schedule). All other patients completed 24 weeks of treatment. Nineteen of the 200 patients (9.5%) modified their HAART regimen during the trial. There were temporary interruptions of treatment for nine patients (three for gastrointestinal side effects, two for neurological side effects, one for mitochondrial toxicity with weight loss and high lactate levels, three for other reasons) and four dose reductions [all for d4T/ddI treatment, owing to either hyperlactataemia ($n=1$) or falling body weight ($n=3$)]. Five patients increased their drug dosage – d4T/ddI doses were increased for three patients owing to rising body weight, and saquinavir/ritonavir was switched to twice-daily dosing

Figure 2. Proportion of patients with HIV RNA levels under 50 copies per ml (solid line) and under 400 copies per ml (dotted line) versus time
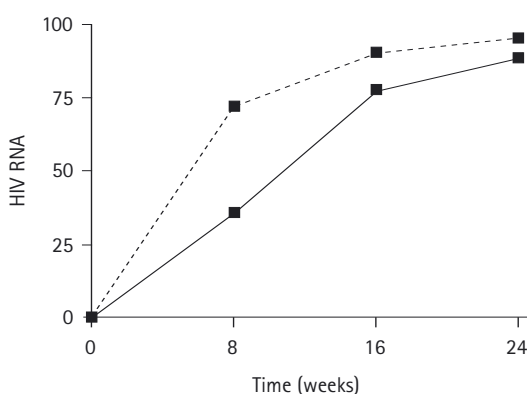
Table 2. Comparison of median HIV RNA reduction at week 8 (n=21) and week 24 (n=19) in two groups of patients

HIV RNA reduction	Saquinavir Cmin	
	High Cmin*	Low Cmin**
HIV RNA reduction at week 8, median (IQR)	–2.32 (–2.54 to –2.04)	–2.41 (–2.57 to –2.26)
HIV RNA reduction at week 24, median (IQR)	–3.0 (–3.49 to –2.60)	–2.79 (–2.99 to –2.43)

*Patients with a minimum concentration (Cmin) of saquinavir higher than the median value (n=13 at week 8 and n=12 at week 24). **Patients with saquinavir Cmin lower than the median value (n=8 at week 8 and n=7 at week 24). Median saquinavir Cmin for all patients is 0.27 mg/L.

had similar median HIV RNA at time of saquinavir Cmin (1.7 $\log_{10}$) and mean body weight (59.3 kg) as the whole cohort.

There were no CDC C (AIDS-defining) events during the 24-week trial. Adverse events of Grade 1 (mild) or Grade 2 (moderate) severity were recorded for 76 patients (38%) and 16 patients (8%), respectively. Of the adverse events recorded, the majority were gastrointestinal (34%; diarrhoea, nausea or vomiting) or neurological (15%; predominantly peripheral neuropathy). There were no adverse events of Grade 3 or 4 (serious or life-threatening) severity recorded, and no patients permanently withdrew from the trial owing to adverse events.

Discussion

In this 24-week study of 200 antiretroviral-naive Thai patients, treatment with two NRTIs plus once-daily saquinavir/ritonavir led to HIV RNA suppression <400 copies per ml for 96% of patients and RNA levels below 50 copies per ml for 89% of patients, with a median rise in CD4$^+$ cell count of 122 cells/µl. These results compare favourably with the efficacy seen for non-NRTI-based HAART [19,20] or boosted-PI-based HAART [21,22] as well as boosted saquinavir soft gelatin capsules in antiretroviral-experienced Thai patients [11]. The lack of correlation between plasma saquinavir drug levels and HIV RNA reductions suggests that, using the 1600/100 mg once-daily dosage, saquinavir exposure is high enough to achieve viral suppression for this population of antiretroviral-naive Thai patients. Almost half of the patients experienced antiretroviral-related side effects. Although the side effects were mostly mild, they may affect the efficacy and adherence to this regimen in longer follow-up.

The Thai treated population is typically highly adherent to treatment. Patient adherence was monitored closely with adherence support in this trial. Strong effi-

cacy has been seen for trials of other HAART regimens among Thai patients [11,23]. Even so, the efficacy seen in this trial of boosted-saquinavir-based HAART also compares favourably with the on-treatment analysis from clinical trials of HAART in North America and Europe, including only those who remained on randomized treatment [6,19].

Previous randomized trials of boosted saquinavir have evaluated the soft gelatin formulation, which contains an excipient (capmul) that is associated with additional gastrointestinal side effects in a randomized study [5]. This may explain the results from some of the randomized trials. In the FOCUS trial, comparing once-daily soft gelatin saquinavir/ritonavir with efavirenz, the on-treatment analysis for the two arms was similar, whereas there were excess withdrawals for gastrointestinal adverse events in the saquinavir arm, leading to inferiority of the saquinavir arm in the intent-to-treat analysis [9]. Similarly, in the MaxCmin2 trial, comparing twice-daily soft-gelatin saquinavir/ritonavir with lopinavir/ritonavir, the antiviral efficacy was similar in the two arms in the on-treatment analyses, whereas a difference in withdrawal rates (mainly for mild to moderate gastrointestinal toxicity in the saquinavir arm) led to a lower overall response rate in the boosted saquinavir arm in the intent-to-treat analysis [8]. The absorption of saquinavir/ritonavir is depended on food, which may affect treatment adherence.

Higher efficacy has been correlated with lower pill count [24]. A 500 mg formulation of saquinavir was recently approved by the US Food and Drug Administration. It has been found to lower the daily pill count for saquinavir by 60% and is similar in composition to saquinavir hard gel capsules [6]. However, this formulation needs to be evaluated in randomized clinical trials versus other boosted PIs, to determine whether lower pill count and better-tolerated formulation can indeed improve the overall treatment efficacy of boosted saquinavir.

The saquinavir drug levels achieved for Thai patients [4,10], measured as either area under the curve (AUC) or Cmin, appear to be higher than those seen in studies of Caucasian patients [13]. The cause of this apparent difference is unknown, but may include a lower body weight, different routine food intake, or possibly genetic factors. Given this apparent difference in pharmacokinetics, a typical Caucasian patient may need to take a once-daily saquinavir/ritonavir dosage of 2000/100 mg, to achieve a similar AUC and Cmin to a typical Thai patient given the 1600/100 mg once-daily dosage [10,13]. With the new 500 mg formulation of saquinavir, a lower dosing of saquinavir/ritonavir 1500/100 once daily may be acceptable for Thai

patients. Saquinavir/ritonavir is approved and used most frequently at the dose of 1000/100 mg twice daily. A study that is currently enrolling will compare this dose versus lopinavir/ritonavir 400/100 mg twice daily in antiretroviral-naive HIV patients. The nucleosides for this study are tenofovir/emtricitabine in both arms. There are several smaller investigator-initiated studies either ongoing or in the planning stages for saquinavir/ritonavir once daily in Europe and North America. These studies are using the 2000/100 mg once-daily dose.

Other studies have shown no significant correlation between plasma saquinavir drug levels and efficacy – in the FOCUS trial, the saquinavir Cmin did not correlate with HIV RNA reductions or the likelihood of HIV RNA undetectability [25]. In the MaxCmin1 trial, virological failure did not correlate with saquinavir trough levels, grouped as quartiles [26]. In the era of unboosted saquinavir, a subset of patients was identified with long-term HIV RNA suppression despite low plasma saquinavir drug levels [27]. However, in these studies, as well as the Staccato induction trial, samples were collected for drug level evaluation without prior observed dosing, or control for food intake, which can influence saquinavir plasma levels [28]. A similar lack of correlation between drug levels and HIV RNA response was also seen in a randomized trial of lopinavir/ritonavir for treatment-naive patients [29]. Saquinavir is known to achieve higher concentrations within cells than plasma, and has a longer half-life within cells at the 1600/100 mg once-daily dosage [15]. For PI-naive patients, the intracellular saquinavir level 24 h after dosing may still be sufficient to allow persistent viral suppression, even when plasma levels are suboptimal. However, this effect may not be true for treatment of PI-experienced patients, in which higher drug levels may be required.

In summary, first-line HAART including once-daily saquinavir/ritonavir and two NRTIs achieved strong antiviral efficacy at week 24, which appeared to be independent of the plasma saquinavir Cmin levels for this dosage. This once-daily combination should be evaluated in new randomized trials, including the new 500 mg formulation of saquinavir.

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Conflict of interest (in order according to author list)

Jintanat Ananworanich has received travel grants and honoraria from Hoffmann-LaRoche
Andrew Hill is a former employee of Hoffmann-LaRoche and now consults for the same company.
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