Long-term efficacy and safety of first-line therapy with once-daily saquinavir/ritonavir

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Background: The aim of this study was to assess the long-term efficacy and safety of first-line treatment with once-daily saquinavir/ritonavir plus two nucleoside reverse transcriptase inhibitors (NRTIs).

Methods: A total of 272 antiretroviral-naive patients with a CD4+ T-cell count of 200–350 cells/mm³ were treated with two NRTIs and saquinavir/ritonavir 1,600/100 mg per day for ≥24 weeks. Patients were followed up every 12 weeks for CD4+ T-cell counts, HIV RNA levels, clinical and laboratory toxicities. Intention-to-treat analyses were used for the first 24 weeks of treatment and as-treated analysis after week 24.

Results: The median baseline CD4+ T-cell count was 269 cells/mm³ and HIV RNA was 4.7 log₁₀ copies/ml. At a median follow-up time of 56 (interquartile range [IQR] 25–113) weeks, 262/272 (96.3%) had HIV RNA <400 copies/ml, with a median HIV RNA decline of −2.89 (IQR 3.31–3.27) log₁₀ copies/ml (P<0.001) and a median rise in CD4+ T-cell count of 192 (IQR 117–317) cells (P<0.001). At weeks 24, 48, 72 and 96, 249/272 (91.5%), 157/164 (95.7%), 113/126 (89.7%) and 84/90 (93.3%) had HIV RNA <400 copies/ml, respectively; at the same time points, 83.8%, 92.7%, 85.7% and 85.6% had HIV RNA <50 copies/ml. Drug-related adverse events were reported in 6.3%. Significant rises in total cholesterol, triglyceride, low-density lipoprotein and high-density lipoprotein were seen.

Conclusion: First-line highly active antiretroviral therapy with once-daily saquinavir/ritonavir plus two NRTIs showed strong antiviral efficacy.

Introduction

First-line highly active antiretroviral therapy (HAART) combines two nucleoside reverse transcriptase inhibitors (NRTIs) with protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) [1–3]. Ritonavir-boosted saquinavir is recommended as a first-line option especially for those judged as at risk for hyperlipidaemia according to the United States International AIDS Society guidelines [1].

Since 2005, saquinavir has been available in 500 mg tablets, reducing pill burden and side effects compared with the older capsule and soft-gel formulations. The standard dosing of saquinavir/ritonavir is 1,000/100 mg twice daily; however, pharmacokinetic studies have shown that in Thais, therapeutic saquinavir drug levels are achieved at a 1,600/100 mg once-daily dosing [4]. In addition, the 1,000/100 mg
twice-daily [5] dosing results in higher drug levels in Thais than in Caucasians [6]. Our group previously illustrated excellent efficacy and safety at 24 weeks of the once-daily boosted saquinavir treatment in the first 200 Thai patients enrolled in the Staccato trial [7]. The goal of this paper is to study the long-term efficacy and safety of this regimen in all 272 antiretroviral (ARV)-naive Thai patients enrolled in Staccato.

Methods

The Staccato trial is an international randomized evaluation of continuous versus CD4\(^+\) T-cell count guided HAART, for patients with full viral suppression at baseline [8]. Before the randomized phase, ARV-naive patients with a baseline CD4\(^+\) T-cell count of 200–350 cells/mm\(^3\) were treated at seven Thai centres with once-daily ritonavir-boosted saquinavir and two NRTIs, for at least 24 weeks. Once patients obtained HIV RNA levels <50 copies/ml and a CD4\(^+\) T-cell count >350 cells/mm\(^3\), they were randomized to either continuous, CD4\(^+\) T-cell count guided or 1 week on/1 week off treatment. The 1 week on/1 week off treatment was prematurely terminated due to high rates of virological failure [9]. Figure 1 shows patient disposition. Of the 272 ARV-naive Thai patients included, 47 were never randomized into the continuous arm, 143 were randomized into the CD4\(^+\) T-cell count guided arm, and nine were randomized to the 1 week on/1 week off arm for a maximum of 12 weeks and were treated with continuous HAART thereafter. Therefore, the length of continuous HAART varies in each patient depending on the randomized arm they were assigned to.

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 at the beginning of the trial in 2001 was stavudine plus enteric-coated didanosine at standard weight-adjusted doses plus saquinavir/ritonavir. Patients received 200 mg saquinavir hard gel capsules with ritonavir in a once-daily dose of saquinavir/ritonavir at 1,600/100 mg until 2005, after which patients were switched to the new saquinavir 500 mg tablet formulation at 1,500/100 mg once-daily dosing. In addition, the NRTI backbone of stavudine/didanosine was used until March 2003 and tenofovir/lamivudine or tenofovir/emtricitabine was used thereafter. The changes were per protocol amendment to lower saquinavir pill burden and stavudine/didanosine-related toxicity. The switch occurred after a median exposure duration on stavudine/didanosine of 32 (interquartile range [IQR] 17–53) weeks.

Patients attended study visits at screening, baseline, weeks 8, 16, 24 and then every 12 weeks. Patients were assessed for CD4\(^+\) T-cell count, HIV RNA (Roche
ampiclon Ultra-sensitive assay, Roche, Nutley, NJ, USA), fasting lipids, haematology, clinical chemistry, adverse events and HIV disease progression. Clinical and laboratory adverse events were graded by severity.

The primary endpoint was the proportion of patients with HIV RNA levels <400 copies/ml at the last week of continuous HAART regardless of temporary discontinuations or dose modifications of the study drugs. We presented several analyses. Firstly, an intention-to-treat (ITT) analysis was performed until week 24 using the last observation carried-forward method with missing observations equating to failure. After week 24, this approach was no longer feasible because patients were randomized to either continuous treatment or to treatment interruptions. Thus, for later time points we used an as-treated analysis. However, ITT was used for all the patients supposed to be on continuous treatment until the end of the trial.

Data were analysed using SPSS for Windows, version 9.0 software (SPSS Inc., Chicago, IL, USA) and Stata version 8 (STATA Corp., College Station, TX, USA).

Results

A total of 272 ARV-naive Thai patients were enrolled in Staccato and included in the analyses. Baseline characteristics are shown in Table 1. There were more females than males, with a mean age of 34.3 years and a median body weight of 56 (IQR 49–63) kg. The majority had mild or no HIV symptoms (Centre for Disease Control and Prevention clinical class A) with a median baseline CD4 + T-cell count of 269 cells/mm3 (IQR 224–322) and a median CD4+ T-cell change from baseline of 269 cells/mm3 at baseline to 464 cells/mm3 (83.8%).

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>272</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>34.3 (8.3)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>107/165 (39/61)</td>
</tr>
<tr>
<td>CDC class</td>
<td>75 (27.6)</td>
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<tr>
<td>CD4+ T-cell count, cells/mm³</td>
<td>269 (224–322)*</td>
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<tr>
<td>HIV RNA, log₁₀ copies/ml</td>
<td>4.7 (4.2–5.1)*</td>
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Adverse events and HIV disease progression. Clinical and laboratory adverse events were graded by severity. Adherence and five for virological failure). One patient switched from saquinavir/ritonavir to nevirapine for virological failure. Thirty-two patients had saquinavir dose adjustments: 16 received a lower dose of saquinavir (one for mitochondrial toxicity and 15 changed from 1,600 mg to 1,500 mg per protocol) and 15 received a higher dose (from 1,600 mg to 2,000 mg) of saquinavir (three for virological failure, one for concomitant rifampin treatment, nine for low Cmin and two for unspecified reasons). Switching from stavudine/didanosine to tenofovir/lamivudine or emtricitabine per protocol occurred in 139 (51.1%) patients.

The median CD4+ T-cell count rose from 269 cells/mm³ at baseline to 464 cells/mm³ (P<0.001) with a median CD4+ T-cell change from baseline of 192 (IQR 117–317) cells/mm³. HIV RNA fell by a median of –2.89 (IQR 3.31–-2.37) log₁₀ copies/ml (P<0.001). At week 24, 249/272 (91.5%) and 228/272 (83.8%), had HIV RNA levels suppressed to <400 and <50 copies/ml, respectively. Afterwards, 157/164 (95.7%), 113/126 (89.7%) and 84/90 (93.3%) had HIV RNA levels <400 copies/ml at 48, 72 and 96 weeks, respectively. At the same time points, 152/164 (92.7%), 108/126 (85.7%) and 77/90 (85.6%) had HIV RNA levels suppressed to <50 copies/ml. The proportions of patients with CD4+ T-cell counts >350 cells/mm³ at these time points are also shown (Figure 2).

When patients from the CD4+ T-cell count guided arm were excluded, ITT analyses showed that 110/129 (85.3%) at week 24, 103/129 (79.4%) at week 48, 94/129 (72.9%) at week 72 and 80/129 (62.0%) at week 96 had HIV RNA <400 copies/ml; 99/129 (76.7%) at week 24, 102/129 (79.1%) at week 48, 89/129 (69.0%) at week 72 and 73/129 (56.6%) at week 96 had HIV RNA <50 copies/ml. Virological failure defined as two consecutive HIV RNA levels (TC <200 mg/dl; TG <130 mg/dl and LDL <160 mg/dl in 6.3%, LDL <200 mg/dl, TG <130 mg/dl and LDL <160 mg/dl in 3.7% and TG <200 mg/dl in 1.1%). At the end of Staccato, the median time of follow up was 56 (IQR 25–113) weeks.

Of the 272 patients, 47 (17%) could not be randomized to continuous versus interrupted treatment because of loss to follow-up (6%), CD4+ T-cell count <350 cells/mm³ (6%) and HIV RNA >50 copies/ml (5%). Ten patients switched from saquinavir/ritonavir to efavirenz (three for gastrointestinal toxicity, one for weight loss, one for poor adherence and five for virological failure). One patient switched from saquinavir/ritonavir to nevirapine for virological failure. Thirty-two patients had saquinavir dose adjustments: 16 received a lower dose of saquinavir (one for mitochondrial toxicity and 15 changed from 1,600 mg to 1,500 mg per protocol) and 15 received a higher dose (from 1,600 mg to 2,000 mg) of saquinavir (three for virological failure, one for concomitant rifampin treatment, nine for low Cmin and two for unspecified reasons). Switching from stavudine/didanosine to tenofovir/lamivudine or emtricitabine per protocol occurred in 139 (51.1%) patients.
RNA measurements >400 copies/ml was found in 11 (4%) patients. Genotyping and outcome of nine of these 11 patients have previously been reported, showing no major PI mutations [10]. The remaining two patients also showed similar results.

Seventeen (6.3%) patients had ARV-related adverse events (AEs): grade I (n=2), grade II (n=4), grade III and no grade IV (n=11). The grade III AEs comprised pancreatitis (n=1), neuropathy (n=1), nausea/vomiting (n=1), flu-like symptoms (n=1), urinary tract infection (n=1), convulsion (n=1), vascular ischaemia (n=1), high lactate levels (n=2) and high lipase levels (n=2). Overall, the AEs were related to didanosine (n=8), stavudine (n=7), saquinavir (n=3), ritonavir (n=2), lamivudine (n=1) and tenofovir (n=1).

Lipid profiles at the end of the study differ significantly from baseline (paired Student’s t test, P<0.001 for TC, TG and HDL and P<0.03 for LDL) with a rise in median TC of 8 (IQR -5–34) mg/dl, median TG of 11 (IQR -15–53) mg/dl and median LDL of 1.5 (IQR -12–20) mg/dl. The HDL did not decline, but rather a median rise of 4 (IQR 0–15) mg/dl was seen. At the last visit, the proportions of patients with TC≥200 mg/dl and ≥240 mg/dl were significantly related to didanosine (n=8), stavudine (n=7), saquinavir (n=3), ritonavir (n=2), lamivudine (n=1) and tenofovir (n=1).

Discussion

Once-daily saquinavir/ritonavir at 1,600 or 1,500 mg/100 mg with two NRTIs resulted in excellent antiviral efficacy with 96% of patients achieving HIV RNA <400 copies/ml and a CD4+ T-cell rise of almost 200 cells at a median follow-up of 56 weeks. The antiviral efficacy was sustained; 93.3% and 85.6% of those followed for 96 weeks had HIV RNA suppression to <400 and <50 copies/ml, respectively.

Saquinavir/ritonavir was well tolerated with few losses to follow-up, virological failure and need to switch to a different ARV. When the CD4+ T-cell count guided arm patients were excluded, the ITT analysis showed a significantly lower rate of viral suppression. This is due in part to the over representation of patients who fail to reach the Staccato randomization criteria (HIV RNA <50 copies/ml and CD4+ T-cell count >350 cells/mm3).

In our previous publication of the first 200 Staccato patients followed to week 24, we showed that 96% had HIV RNA <400 copies/ml and 89% had HIV RNA <50 copies/ml with a median CD4+ T-cell count rise of 100 copies/ml [7]. This study illustrated the durability
of a once-daily saquinavir/ritonavir regimen in controlling HIV viraemia and raising CD4+ T-cell count. Whether this outcome applies to North American or European patients whom in general weigh more than Thais is uncertain. The pharmacokinetic parameters are acceptable in Thais who are treated with saquinavir/ritonavir 1,600 mg/100 mg once-daily [11,12]. Thais have higher plasma saquinavir levels than UK patients when the same saquinavir/ritonavir dosing is used [12].

Lopinavir, atazanavir, fosamprenavir and saquinavir, all boosted with ritonavir, are PIs recommended for use as first-line therapy [1]. Lopinavir/ritonavir is the preferred PI because of its long-term efficacy data with 95% and 59% of patients maintaining HIV RNA <50 copies/ml by on-treatment and ITT analyses, respectively, at 7 years [13]. Lopinavir/ritonavir has; therefore, been used as a comparator drug for current PI studies. In the GEMINI study, lopinavir/ritonavir was compared with saquinavir/ritonavir, used at the standard dosing of 1,000/100 mg twice daily. The planned analysis of 337 patients who reached 24 weeks reported similar viral suppression rates of <50 copies/ml in both arms: 69% in lopinavir/ritonavir versus 70% in saquinavir/ritonavir arms. More patients taking lopinavir/ritonavir had elevated TC (27% in lopinavir/ritonavir and 22% in saquinavir/ritonavir) and TG (9% in lopinavir/ritonavir and 1% in saquinavir/ritonavir)[14]. The KLEAN study showed similar antiviral efficacy and lipid profiles in patients randomized to either fosamprenavir/ritonavir or lopinavir/ritonavir [15]. Around 70% achieved viral suppression <50 copies/ml after 1 year and about 10% had abnormal fasting TC and TG. The ALERT study showed no difference in antiviral efficacy with 80% of patients achieving HIV RNA <50 copies/ml at 24 and 48 weeks in fosamprenavir/ritonavir- and atazanavir/ritonavir-treated patients, but the latter group had a more favourable TG profile [16]. In comparison with these studies, our patients achieved similar or better virological response at a longer follow-up time. However, hyperlipidaemia appears to be more common. The choice of NRTI in our study may have driven some of the lipid findings, as stavudine has been associated with lipid elevations. In contrast with Staccato, stavudine was not used in GEMINI, KLEAN or ALERT, which may explain some of the different findings across studies. The hypercholesterolaemia rate in our study is similar to other studies in Thais using indinavir/ritonavir, but higher than those using unboosted saquinavir and indinavir [17–19]. The differences in how hyperlipidaemia is defined and in the duration of follow-up between studies lead to some difficulties in data comparison and interpretation, nevertheless, it is surprising to see that hyperlipidaemia, even before ARV, is not uncommon in Thais as Thais have a lower body mass index compared with Caucasians [20]. This is further confirmed by a recent study showing that 66% of Thai men and women undergoing routine health examination had hypercholesterolaemia [21]. The rise in HDL after ARV in our study, however, is reassuring, as low HDL is a marker for coronary heart disease [22]. In addition, significantly high lipid levels above grade II in our study were uncommon both before and after ARV.

In a recent meta-analysis of 53 trials enrolling 14,264 patients, ritonavir-boosted PI- and NNRTI-based regimens had superior virological efficacy compared with ritonavir-unboosted PI- and triple NRTI-based regimens. An advantage of PIs is that PI resistance is rare and there is lower risk of NRTI resistance in early virological failure [10,23–25], which allows more options for second-line regimens [26]. In our patients who failed virologically, we did not see any major PI mutations and almost all patients achieved virological suppression following saquinavir dose increase or switching to NNRTI regimens [10]. Our study has two main limitations. Firstly, we do not have a comparison group using either standard dosing of saquinavir or other PI-containing regimens. Secondly, the follow-up time on continuous saquinavir/ritonavir treatment varied significantly among patients due to the interrupted nature of the structured treatment in this study.

Durability of first-line HAART depends on its ability to reach and maintain HIV RNA <50 copies/ml. We have demonstrated the durability of once-daily saquinavir/ritonavir with two NRTIs in controlling HIV viraemia. The use of 500 mg saquinavir tablet formulation at a dose of 1,500 mg with ritonavir 100 mg once-daily offers a regimen with good efficacy, lower pill burden and that is easy to take. Hyperlipidaemia is, however, common and warrants close follow-up.

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Disclosure statement

Jintanat Ananworanich has received travel grants and honoraria from Roche and Gilead. Kiat Ruxrungtham has received travel grants, consultancy fees and speakers’ honoraria from Roche, Abbott and Bristol-Myers Squibb. Ploenchit Chetchotisakd has received travel grants from Abbott. Malte Schutz is a current employee of Roche. Bernard Hirschel has received travel grants and speakers’ honoraria from Roche, Abbott and Gilead. Other authors declare no conflict of interest.

Additional file

The additional file ‘Staccato Thailand Study Group’ can be accessed via the Volume 13 Issue 3 contents page for Antiviral Therapy, which can be found at www.intmedpress.com (by clicking on ‘Antiviral Therapy’ then ‘Journal PDFs’).

References


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