12301

FORTOVASE™ (Saquinavir; SQV) Soft Gel Capsule (SGC) in Combination with ZDV and 3TC in Antiretroviral-Naïve HIV-1 Infected Patients

12th World AIDS Conference, Geneva, 28 June–3 July 1998.

C. Farthing[1], M. Sension[2], R. Pilson[3] , and P. Siemon-Hryczyk[3]

[1]AIDS Healthcare Foundation, Los Angeles, CA; [2]North Broward Hosp. District, Fort Lauderdale, FL; [3]Roche Labs Inc., Nutley, NJ

Introduction

Background

There is increasing evidence that the aims of antiretroviral therapy should be to achieve both substantial and prolonged suppression of viral replication.

Multiple clinical trials have reported superiority of triple combination antiretroviral therapies. Several research groups have observed unprecedented beneficial effects on HIV RNA and CD4 cell counts using three drug regimens which incorporate two nucleoside analogue reverse transcriptase inhibitors with an HIV protease inhibitor (PI). Undetectable plasma HIV RNA levels have been achievable with these therapies in a majority of patients. Regimens using combination therapy including PI(s) are now considered the standard of care for the treatment of HIV infection.

Objectives

- To evaluate the efficacy of FORTOVASE™ (saquinavir) SGC in combination with ZDV and 3TC in the treatment of HIV infected patients with no previous antiretroviral drug therapy. Efficacy and duration of antiviral response are evaluated by monitoring of HIV RNA levels and CD4 and CD8 cell counts.
- To collect safety data on FORTOVASE™ in combination with other antiretrovirals.

Methods

Study Design

This was an open-label, non-comparative, two-center study investigating the safety and virologic activity of a triple therapy regimen of FORTOVASE™ (saquinavir) SGC, ZDV, and 3TC in at least 40 HIV infected patients with no previous antiretroviral drug therapy. The duration of the study was 24 weeks. Patients could elect to continue the treatment up to 48 weeks.

Patients who experienced a rebound in viremia to greater than 50% of baseline levels on two consecutive determinations after a minimum of 4 weeks of triple therapy were to be terminated as treatment failures.

Patients were instructed to return all medication bottles to the site at each clinic visit so that the number of capsules returned for each medication could be counted to assess compliance. Patients who were found to be less than 80% compliant at two consecutive visits were considered non-compliant and their data was excluded from the standard population analysis starting at the first of the two noncompliant visits.

Patients received the following 3-drug combination:

- FORTOVASE™ 1200 mg orally TID
- ZDV * 300 mg orally BID
- 3TC 150 mg orally BID

Patients were instructed to take FORTOVASE™ within 2 hours of a meal or substantial snack.

***** Six patients exhibited grade 3 or 4 hematologic toxicity or nausea and were permitted to substitute d4T for ZDV at the investigator's discretion.

Outcome Measures

Patients were assessed for plasma HIV RNA, as measured by Roche Amplicor (lower limit = 400 copies/mL), with determinations at baseline, weeks 1, 2, 4, 6 and 8, then every 4 weeks up till week 24, then every 8 weeks for the duration of the study. Patients below the detectable limit of 400 copies/mL were further analyzed using the Ultra-Direct method with a detection limit of 20 copies/mL.

Immunologic response was assessed by lymphocyte testing (CD4 and CD8 cell counts) at baseline, weeks 1, 2, 4, 6 and 8, then every 4 weeks up till week 24, then every 8 weeks for the duration of the study.

Statistical Considerations and Analytical Plan

The primary variables were the proportion of patients with plasma HIV RNA below the level of quantification and the magnitude of the mean change from baseline of viral RNA over 48 weeks. Secondary variables included immunologic response, specifically CD4 and CD8 counts.

Data analyses were performed on all of the above efficacy variables. Patients enrolled into the study with incorrect diagnosis, those who did not take a minimum of four weeks of study medication, those who took partial doses of study medication (<80% compliance at two consecutive visits) or those who provided no follow-up information after baseline were not included.

Results

Virology

- Mean baseline plasma HIV RNA was 4.8 $\log_{10}$ or 63,757 copies/mL (n=42).
- Mean $\log_{10}$ change in plasma HIV RNA at 48 weeks was -3.48.
- At week 48, 77% of patients (17 of 22) sustained levels of plasma HIV RNA below the level of assay quantification (<400 copies/mL), as measured by Roche Amplicor assay. Using Roche Ultra-Direct assay, 68% (15 of 22) sustained levels of plasma HIV RNA less than 20 copies/mL.

Immunology

- Mean baseline CD4 and CD8 counts and CD4/CD8 ratio were 419 cells/mm^3, 960 cells/mm^3 and 0.5, respectively (n=42).
- Mean changes in CD4 and CD8 counts and CD4+/CD8+ ratio at week 48 were +246 cells/mm^3, -131 cells/mm^3 and +0.32, respectively.

Safety

- FORTOVASE™ (saquinavir) SGC in combination with ZDV and 3TC was well tolerated in the antiretroviral-naïve patients studied.
- Adverse events related to study drug were generally mild; of those adverse events that were considered moderate to severe, the most frequent (≥5%) included nausea, vomiting, diarrhoea, and headaches.
- Laboratory abnormalities included 1 patient with Grade III AST/ALT at week 4 which resolved; 1 patient with Grade IV AST/ALT at week 12 associated with acute hepatitis A infection which resolved; 1 patient with Grade III alkaline phosphatase/Grade III AST/Grade IV ALT and Grade III bilirubin at week 20 associated with acute Hepatitis A infection which resolved; 1 patient with Grade III neutropenia at week 16 which resolved upon replacement of ZDV with d4T; and 1 patient with Grade III triglycerides at week 2 associated with having discontinued cholesterol-reducing medication.
- Five patients had serious adverse events, all unrelated to study drug: 1 patient had hematemesis and gastritis due to alcohol abuse, which resolved; 1 patient had surgery for injuries sustained after being struck by an automobile; 1 patient had surgery for injuries as a result of an automobile accident; 1 patient had surgery for a cervical disc rupture; and 1 patient had a perirectal abscess requiring surgical treatment.

Patients Not Included in Analysis

(Note: Population enrolled at the Florida site included many transient patients).

20 of 42 patients at week 48 were not included in the standard population analysis:

- 2 patients did not cooperate
- 6 patients were non-compliant with study medication
- 5 patients due to refusal of treatment
- 7 patients lost to follow-up

Conclusions

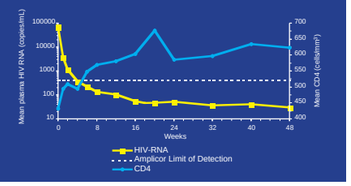
- FORTOVASE™ (saquinavir) SGC in combination with ZDV and 3TC produced a potent and sustained viral load suppression and immunologic response over a 48-week period in antiretroviral-naïve patients.
- The triple antiretroviral combination regimen was well tolerated in the patients studied, with the majority of adverse events being mild. Only 5 patients experienced clinically significant grade III and/or IV laboratory abnormalities through 48 weeks of the study.
- Compliance with the regimen is in line with that reported in other studies with 6/42 (14%) patients being deemed non-compliant.
- After 48 weeks of therapy with FORTOVASE™ (saquinavir) SGC in combination with ZDV and 3TC, 77% of patients (17 of 22) sustained a plasma HIV RNA <400 and 68% (15 of 22) achieved <20 copies/mL.
- The mean change in plasma HIV-1 RNA at 48 weeks was -3.48 $\log_{10}$.
- Immunologic responses at 48 weeks of this triple combination regimen resulted in a mean increase in CD4 levels (+246 cells) and CD4/CD8 ratio (+ 0.32).

The adjacent panel presents the key data to date, with current conclusions.

1 Baseline demographics

	SQV-SGC 1200 mg TID n = 42
HIV RNA (mean, copies/mL)	63,757
HIV RNA (mean, $\log_{10}$ copies/mL)	4.8
CD4 count (mean, cells/mm^3)	419
CD8 count (mean, cells/mm^3)	960

2 HIV-1 RNA and CD4 changes in value over time for standard population

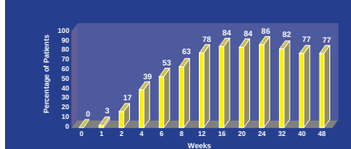


3 $\log_{10}$ HIV-1 RNA change from baseline*

	Week 24	Week 32	Week 40	Week 48
Mean	−3.21	−3.35	−3.30	−3.48
Median	−3.32	−3.19	−3.23	−3.42
Range	−4.78 to -0.41	−4.50 to -2.31	−4.50 to -1.87	−4.50 to −2.14

* limit of detection = 20 copies/mL

4 Proportion of patients with HIV RNA <400 copies/mL



5 Percentage of patients with HIV RNA <400 copies/mL or <20 copies/mL

n=22	Week 24	Week 32	Week 40	Week 48
<400 copies/mL[1]	86	82	77	77
<20 copies/mL[2]	50	63	59	68

[1] As measured by Roche Amplicor Assay
[2] As measured by Roche Ultra-Direct Assay

6 CD4, CD8 and CD4/CD8 ratio mean changes from baseline

	Week 24	Week 32	Week 40	Week 48
CD4 count	+188	+209	+240	+246
CD8 count	-108	-150	-191	-131
CD4/CD8 ratio	+0.24	+0.28	+0.35	+0.32

7 Adverse events* (week 48)

- Nausea 6 pts
- Vomiting 4 pts
- Diarrhoea 4 pts
- Headaches 4 pts

*Moderate to Severe in ≥5% of patients (week 48)

8 Patient withdrawals

Patients prematurely terminated

4 patients terminated due to adverse events
2 patients did not cooperate
5 patients refused treatment
7 patients lost to follow-up
1 patient with an insufficient therapeutic response

6 patients withdrawn from standard analysis due to non-compliance

9 Efficacy summary (week 48)

- 3.48 $\log_{10}$ decrease in HIV RNA
- 77% below the limit of detection (Amplicor)
- 68% achieved <20 copies/mL
- 246 CD4 cell count increase
- Median viral load = 20 copies/mL

10 Safety summary (week 48)

- FORTOVASE™ (SQV-SGC) 1200 mg in combination with NRTIs is well tolerated
- Few AEs reported, no serious AEs related to study drug
- Few laboratory abnormalities

11 Conclusions

- FORTOVASE™ (SQV-SGC) in combination with ZDV + 3TC produced a potent and sustained viral load suppression and immunologic response over a 48 week period in antiretroviral-naive patients
- This combination regimen was well tolerated with the majority of adverse events being mild. Only 5 patients experienced clinically significant grade III and/or IV laboratory abnormalities

12 Conclusions

- After 48 weeks of therapy with FORTOVASE™ (SQV-SGC) in combination with ZDV + 3TC, 77% of patients (17 of 22) sustained a plasma HIV RNA <400 copies/mL and 68% (15 of 22) achieved <20 copies/mL
- The mean change in plasma HIV RNA at 48 weeks was –3.48 $\log_{10}$
- Immunologic responses at 48 weeks showed a mean increase in CD4 levels (+246 cells/mm^3) and CD4/CD8 ratio (+0.32)