GENOTYPIC INHIBITORY QUOTIENT AS BEST PHARMACOKINETIC / PHARMACODYNAMIC PREDICTOR OF VIROLOGIC RESPONSE TO A LOPINAVIR / SAQUINAVIR DUAL RITONAVIR-BOOSTED REGIMEN IN PATIENTS WITH MULTIRESISTANT HIV-1

S Lam[1,2], MS Delisle[1,2], L Labbé[2], GHR Smith[3], CJL la Porte[4], DM Burger[5], RG Lalonde[1], NL Sheehan[1,2]
[1]McGill University Health Centre, [2]Université de Montréal, Montréal, Canada; [3] Maple Leaf Clinic, Toronto, Canada, [4]Ottawa Hospital, Ottawa, Canada, [5]Radboud University Medical Centre, Nijmegen, the Netherlands

Poster
7th International Workshop on Clinical Pharmacology of HIV Therapy
Lisbon, Portugal
April 20-21, 2006

CONTACT INFORMATION

Nancy Sheehan: Faculty of Pharmacy, Université de Montréal,
C.P. 6128, Succursale Centre-Ville, Montréal, Québec,
H3C 3J7, Canada, @: nancy.sheehan@umontreal.ca

BACKGROUND

- Dual ritonavir (RTV)-boosted protease inhibitor (PI) regimens including lopinavir (LPV) and saquinavir (SQV) have provided acceptable virologic and immunological benefits in patients with multiresistant HIV-1.[1]
- LPV and SQV are synergistic *in vitro*[2] and are known to not interact unfavourably together.[3]
- Many pharmacokinetic / pharmacodynamic (PK/PD) parameters are associated with virologic response in the HIV literature, including minimal concentration (Cmin) and genotypic inhibitory quotient (GIQ).
- The best PK/PD parameter predictive of virologic response and the suggested targets are unknown in the context of LPV / SQV dual RTV boosted salvage regimens in heavily ARV experienced HIV-1 infected patients.

STUDY OBJECTIVES

- To determine the best PK/PD parameter for LPV and SQV predictive of virologic response in patients with multiresistant HIV-1 receiving a LPV / SQV dual-RTV boosted regimen.
- To suggest targets for LPV and SQV for the best PK/PD parameter identified.

METHODS

- Observational 48-week PK / PD substudy from a prospective open-label study[1]
- Patients receiving LPV 400mg / SQV-sgc 1000mg / RTV 100 mg BID and lamivudine and one or more additional nucleoside reverse transcriptase inhibitors (NRTIs)
- Treatment intensified at week 4 by adding efavirenz and increasing LPV / RTV to 533 / 133 mg BID if patients failed to show a drop in viral load of 0.8 $\log_{10}$ copies/mL

Inclusion criteria:

- HIV – 1 infected individuals ≥ 18 years old
- Triple class multiresistant HIV-1
- Previous failure to ≥ two ARV regimens and on a failing regimen at baseline
- At least one PK sample taken at week 24 or 48
- Given written informed consent

Exclusion criteria:

- Liver dysfunction
- Pregnancy or breastfeeding

Viral genotyping and other assessments

- Viral load (VL) and CD4+ lymphocyte cell counts measured at weeks 24 and 48
- Viral genotyping (Virco, McGill AIDS Center) was available at baseline and could be repeated throughout the study. Genotypes were interpreted independantly by three co-investigators. LPV mutations and SQV minor and major mutations were those specified by the IAS-USA mutation tables in 2005[4]. Phenotypic data was not available.

Pharmacokinetic sampling and analysis

Blood samples were collected at weeks 24 and 48 as close as possible to 12 hours post-dose to measure LPV and SQV concentrations in mg/L with a validated and accurate HPLC/UV assay (Radboud University Medical Centre, Nijmegen, the Netherlands)[5].

Time intervals between the last dose and sampling were recorded and C_{12} were extrapolated.

PK / PD parameters

- LPV C_{12}, SQV C_{12}, LPV GIQ, SQV GIQ, modified SQV GIQ (mGIQ), sum of GIQ (∑ GIQ)
- GIQ = C_{12} / # mutations related to the specific PI
- SQV mGIQ = SQV C_{12} / [(2 x # SQV major mutations)+ # SQV minor mutations]
- ∑ GIQ = LVP GIQ + SQV GIQ

Statistical Analyses

Virologic endpoints studied were viral load < 400 copies/mL and < 1000 copies/mL at weeks 24 and 48. Logistic binary regressions and Fisher's exact tests were used for these endpoints and ROC curves were studied to identify target values. Linear regression (results not shown) and Mann-Whitney U tests were used to explore the relationship between drop in viral load ($\log_{10}$) and PK/PD parameters.

RESULTS

26 patients were included. 24 and 21 patients had PK/PD data available at weeks 24 and 48, respectively.

Table 1: Study demographics [median(range)]

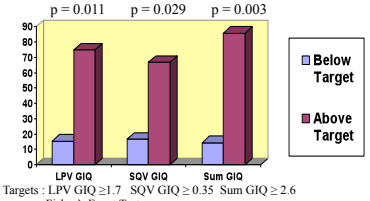
	Baseline n = 26	Week 24 n = 24	Week 48 n = 21
Baseline Age (yrs)	40 (19-50)	40.5 (19-50)	39.5 (19-49)
Gender (% male)	84.6	83.3	85.7
Ethnicity (%)			
- Caucasian	80.8	79.2	81.0
- African	11.5	12.5	9.5
Baseline VL ($\log_{10}$)	4.5 (3.2-6.0)	4.5 (3.2-5.6)	4.6 (3.2-6.0)
Baseline CD4$^+$ (cell/mm^3)	103 (1-358)	119 (1-358)	123 (1-358)
# Previous HAART	7 (1-10)	7 (1-9)	7 (1-9)
# active ARV	1.4 (0-4)	1 (0-4)	1 (0-4)
% SQV resistance	73.1	79.2	81.0
% LPV resistance	19.2	29.2	42.9
# SQV mutations	4 (2-8)	4 (2-8)	5 (2-8)
# LPV mutations	5 (2-9)	5 (3-9)	6 (2-9)

Table 2: Summary of response and PK / PD parameters [median(range)]

	Week 24 N = 24	Week 48 N = 21
% VL (copies/mL)		
< 400	33.3	38.1
< 1000	37.5	38.1
Drop in VL from baseline ($\log_{10}$) copies/mL	-0.9 (-3.8, 0.6)	-0.6(-4.3, 1.3)
VL ($\log_{10}$) copies/mL	3.5 (1.7 - 5.3)	3.8 (1.7-5.6)
CD4$^+$ (cell/mm^3)	161 (1 - 623)	216 (12-708)
C_{12} (mg/L)		
SQV	2.0 (0.3 - 7.3)	1.5 (0.08-7.8)
LPV	7.9 (0 - 23.1)	8.6 (0.5-16.0)
GIQ (mg/L)		
SQV	0.5 (0.05 – 2.2)	0.29 (0.01-1.4)
LPV	1.7 (0 - 7.4)	1.2 (0.08-5.6)
∑	2.2 (0.2 – 9.6)	1.4 (0.09-6.2)

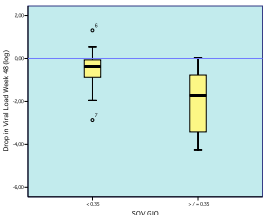
Logistic regression analyses at week 48 show that for a VL < 400 and < 1000 copies/mL, only the ∑ GIQ (p=0.044) and LPV GIQ (p=0.049) predict virologic response. ROC curves suggest LPV GIQ, SQV GIQ, and ∑ GIQ targets of ≥ 1.7, 0.35, and 2.6, respectively. The number of active ARV at week 48 was also related with virologic response (p=0.047).

Figure 1: Percent of patients with viral load < 400 copies/mL at week 48 as a function of week 48 LPV GIQ, SQV GIQ and ∑ GIQ

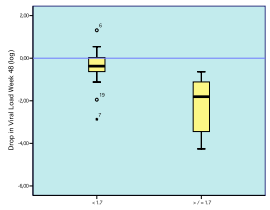


Targets : LPV GIQ ≥1.7 SQV GIQ ≥ 0.35 Sum GIQ ≥ 2.6
Fisher's Exact Test

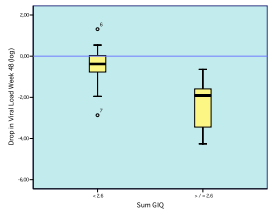
Figure 2: Median (95%CI, range) drop in viral load ($\log_{10}$ copies/mL) at week 48 as per week 48 SQV GIQ, LPV GIQ, and ∑ GIQ



SQV GIQ
p =0.019



LPV GIQ
p = 0.004



∑ GIQ
p = 0.004

Mann-Whitney U Test

CONCLUSIONS

- LPV GIQ and ∑ GIQ are the strongest PK/PD predictors of virologic response in our study in this heavily experienced population with multi-resistant HIV-1 receiving LPV and SQV.
- ∑ GIQ, representing the contribution of both PIs, was slightly more predictive of efficacy, though LPV may be a greater contributor.
- The clinical impact of using the suggested targets in the context of therapeutic drug monitoring needs to be further evaluated.

ACKNOWLEDGMENTS

We graciously thank the patients for participating; the physicians and research nurses at the Montréal Chest Institute; the staff at the laboratory (Pharmacy Department, Nijmegen) including Rob Aarnoutse for the PK analyses; Rolf van Heeswijk; Tanya Murphy, Nicolas Moreau and Djamal Berbiche for statistical assistance; Hoffman-La Roche Canada for an unrestricted educational grant; and Abbott Laboratories Ltd for access to Kaletra through an expanded-access program.

REFERENCES

1. Smith et al, HIV Clinical Trials 2005; 6: 63-72.
2. Molla et al, AAC 2002; 46: 2249-53.
3. la Porte et al, AIDS 2003; 17: 1700-2.
4. Johnson et al, Topics in HIV Medicine 2005; 13: 51-7.
5. Droste et al, Ther Drug Monit 2003; 25: 393-9.