HIV Resistance Collaborative Group

Data Analysis Plan:

Baseline Genotype as a Predictor of Week 24 HIV RNA $\geq$ 500 copies/mL in ACTG 333

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1 Analysis Overview

This report summarizes the results of the HIV Resistance Collaborative Group's Data Analysis Plan (DAP; 8/31/99) as applied to ACTG 333. The report evaluates baseline HIV genotype in the protease gene as a predictor of week 24 HIV RNA suppression below 500 copies/mL. See the DAP for full details regarding the analysis methods.

ACTG 333, Version 3.0, was a 48 week randomized three-arm open-label trial in saquinavir-experienced subjects. The study recruited subjects who had a total of least 48 weeks of prior saquinavir, at a dose of 1,800 mg/day, but who were naive to all other protease inhibitors. The study sought to evaluate the effect of switching from saquinavir (SQVhc) to either an investigational, more bioavailable formulation of saquinavir (SQVsgc) or to indinavir (IDV).

Subjects recruited to the study remained on their non-protease anti-HIV therapy regimen and were randomized with equal likelihood to one of three arms. Arm 1 had subjects remain on SQVhc at 600 mg every 8 hours. Arm 2 had subjects substitute SQVhc with SQVsgc taken at a dose of 1200 mg every 8 hours. Arm 3 replaced SQVhc with indinavir taken at 800 mg every 8 hours. The randomization was stratified by screening HIV-RNA ($<$ 50,000 copies per ml vs. $\geq$ 50,000) and number of concomitant nucleosides at baseline (0-1 vs. 2 or more).

The study focused on the effect of the drugs on plasma HIV-RNA (measured by RT-PCR) during the first 8 weeks of therapy and collected HIV-RNA at baseline and weeks 2, 4, 6, and 8 following randomization. A subject's short-term RNA change is defined to be the difference between the log baseline value and the average of a subject's log RNA values at weeks 4, 6, and 8. After week 8 subjects randomized either to SQVsgc or IDV were evaluated for their short-term RNA change. If their short-term RNA change did not show a decrease from baseline, they were then crossed over to the other therapy (SQVsgc to IDV or IDV to SQVsgc). All subjects randomized to SQVhc crossed over to IDV at week 8.

The primary objective of the study was to determine, if after prolonged use of SQVhc, recipients had a short-term decrease in plasma HIV-RNA following the substitution of SQVhc with IDV or the SQVsgc. Secondary objectives included assessing the longer-term (48 week) effect of the drugs on plasma HIV-RNA and determining if genotypic and phenotypic characteristics of viral isolates at baseline predict the effect of therapy on plasma HIV-RNA. The study also sought to determine the safety and the tolerability of these drugs and to assess the influence of SI/NSI phenotype on the development of protease resistance. The primary analysis of ACTG 333 was based on 89 subjects who were randomized between August 1996 and Feburary 1997.

HIV genotyping on baseline specimens was performed separately at two laboratories:

- Roche (Netherlands) by Charles Boucher using a population methodology
- Merck by Jon Condra using a clonal methodology

Discrepancies in results between the two methods were resolved during team conference calls and by the reassaying of a few samples. Genotype data is only available on the protease gene at this time.

2 Baseline Characteristics

Baseline characteristics for the subjects in this DAP analysis are given in Table 1. The median CD4+ cell count for this population was 240 cells/mm^3 , while the median HIV-1 RNA level was 12,000 copies/ml. Subjects in the IDV and SQVsgc arms received one new drug, while subjects remaining on SQVhc received no new medications (subject were requested to stay on the same RT regimen). There were 60 patients in these two arms. A total of 53 subjects had at least one mutation from the list in the DAP.

Patients were heavily pretreated with ZDV, ddC, and SQV prior to entering this study. There was not much experience with other RT inhibitors nor any with NNRTIs or protease inhibitors other than SQV.

3 Failure Rates

See the DAP for definitions of the endpoints and covariates. Table 2 displays the observed failure rates for the dropouts-as-failures (DAF) and the dropouts-as-censored (DAC) endpoints, by the DAP-specified covariates of interest.

4 Logistic Regression Models

P-values were obtained via likelihood-ratio tests and confidence intervals were obtained via profile-likelihood. Only genotype data was available, and only for the protease gene. The number of new drugs was not used in analyses because only three subjects from the SQVhc arm (the arm to receive no new drugs) were uncensored with respect to either of the endpoints of interest.

Table 3 summarizes logistic regression analyses for the week 24 DAF endpoint. The baseline $\log_{10}$ HIV-1 RNA and the number of PI mutations are highly associated with failure (RNA: $p<0.001$; odds ratio: 12.99. Number of PI mutations: $p=0.0015$; odds ratio: 2.71).

Table 4 summarizes logistic regression analyses for the week 24 DAC endpoint. Odds ratios and p-values are of similar magnitude as for the week 24 DAF endpoint.

Table 1: Baseline Characteristics

	Total $n = 89$	
CD4+ Cell Count (cells/mm^3)		
Median	240	
≤ 100	13	(15%)
101 - 200	24	(27%)
201 - 300	24	(27%)
301 - 400	17	(19%)
> 400	11	(12%)
HIV-1 RNA Copy Number (copies/ml)		
Median	12451	
≤ 500	10	(11%)
501 - 5000	21	(24%)
5001 - 50000	31	(35%)
> 50000	22	(25%)
Missing	5	(6%)
Number of New Drugs		
0	29	(33%)
1	60	(67%)
Number of PI Mutations		
0	28	(31%)
1	5	(6%)
2	5	(6%)
3	17	(19%)
4	11	(12%)
5	7	(8%)
6	7	(8%)
7	1	(1%)
Missing	8	(9%)

Table 1: Baseline Characteristics (continued)

	Total $n = 89$	
Prior ZDV		
< 1 week	1	(1%)
1 week–1 year	13	(15%)
> 1 year	75	(84%)
Prior d4T		
< 1 week	71	(80%)
1 week–1 year	16	(18%)
> 1 year	2	(2%)
Prior ddI		
< 1 week	65	(73%)
1 week–1 year	15	(17%)
> 1 year	9	(10%)
Prior ddC		
< 1 week	21	(24%)
1 week–1 year	10	(11%)
> 1 year	58	(65%)
Prior 3TC		
< 1 week	29	(33%)
1 week–1 year	53	(60%)
> 1 year	7	(8%)
Prior SQV		
< 1 week	3	(3%)
1 week–1 year	1	(1%)
> 1 year	85	(96%)