Poster #470-M

Impact of Baseline CD4 Cell Count and Viral Load on Durability of Virologic Response Through 96 Weeks for Lopinavir/ritonavir and Nelfinavir in a Phase III Clinical Trial

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BACKGROUND

In several studies, the ability to achieve viral suppression and/or the duration of virologic response with a protease inhibitor-based regimen has been shown to be affected by baseline CD4 cell count and baseline viral load (Staszewski 1999, Paredes 2000, Grabar 2000, LeMoing 2002). In a phase II study of lopinavir/ritonavir (LPV/r, Kaletra) in 100 antiretroviral-naive patients, virologic response through 3 years was not decreased among patients with lower CD4 cell count or higher viral load at baseline (White 2001). The impact of baseline CD4 cell count and viral load on response to LPV/r therapy was further evaluated in a randomized, phase III comparative study.

METHODS

Study Design

Study 863 was a phase III, randomized, double-blind clinical trial comparing the safety and antiviral activity of Kaletra (LPV/r) + d4T + 3TC vs. that of nelfinavir (NFV) + d4T + 3TC in antiretroviral-naive patients. There was no minimum CD4 cell count or maximum viral load restriction in this study. 653 patients were randomized to receive

- LPV/r 400/100 mg BID + NFV placebo TID + d4T/3TC (n=326) or
- LPV/r placebo BID + NFV 750 mg TID + d4T/3TC (n=327)

Patients were allowed to switch NFV/NFV placebo dosing from TID to BID after FDA approval of the BID dosing regimen, which occurred after all patients reached Week 24.

After all patients reached Week 60, patients were unblinded and continued on open-label randomized therapy.

Efficacy

Durability of response for the two treatment regimens was assessed by examining the time to loss of virologic response. This was defined as the first of two consecutive viral load measurements above 400 copies/mL following any value <400 copies/mL. If the final available value was the first rebound value above 400 copies/mL, the patient was considered a virologic failure at that point. Patients who never achieved viral load <400 copies/mL were considered virologic failures on Day 0. Data through Week 96 are presented in this analysis.

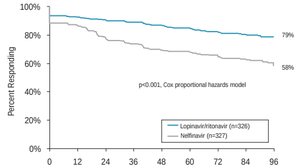
The effects of baseline CD4 cell count and baseline viral load on the time to loss of virologic response were analyzed using the Cox proportional hazards model within each treatment group. Kaplan-Meier response rates through Week 96 were examined within each treatment group by 5 commonly used categories of CD4 cell counts (<50 cells/mm^3, 50 to <200 cells/mm^3, 200 to <350 cells/mm^3, 350 to <500 cells/mm^3, and 500 or more cells/mm^3) and by approximate quintiles of baseline viral load.

RESULTS

Overall Virologic Response

Through up to 96 weeks of treatment, LPV/r-treated patients demonstrated significantly longer time to loss of virologic response than NFV-treated patients (p<0.001, Cox proportional hazards model, Figure 1).

Figure 1. Time to Loss of Virologic Response



RESULTS

Baseline CD4 Cell Count and Viral Load as Univariate Predictors of Response

The Cox proportional hazards model was used to assess the relationship between baseline CD4 cell count/viral load and virologic response within each treatment group. In univariate analyses, lower baseline CD4 count and higher baseline viral load were statistically significantly associated with a higher risk of failure for NFV-treated patients but not for LPV/r-treated patients (Table 1).

Table 1. Univariate Analysis of Virologic Response and Baseline Viral Load or CD4 Cell Count

	Risk Ratio (95% Confidence Interval)	
Univariate Analysis	**NFV (n=327)**	**LPV/r (n=326)**
Baseline CD4 cell count (per 100 cells/mm^3 decrease)	1.29 (1.15, 1.44)	1.10 (0.97, 1.25)
	p<0.0001	p=0.146
Baseline viral load (per 1.0 $\log_{10}$ copies/mL increase)	1.98 (1.55, 2.53)	1.36 (0.96, 1.92)
	p<0.0001	p=0.082

Kaplan-Meier response rates by baseline CD4 cell count category are shown for NFV-treated patients in Figure 2a and for LPV/r-treated patients in Figure 2b.

Figure 2a. Time to Loss of Virologic Response for NFV Patients by Baseline CD4 Cell Count

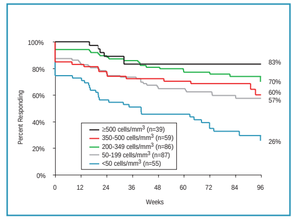
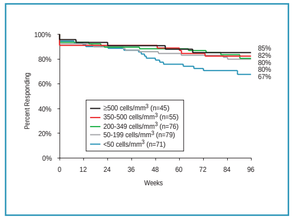


Figure 2b. Time to Loss of Virologic Response for LPV/r Patients by Baseline CD4 Cell Count



Kaplan-Meier response rates by baseline viral load category are shown for NFV-treated patients in Figure 3a and for LPV/r-treated patients in Figure 3b. Notably, among LPV/r-treated patients, the highest viral load stratum (baseline viral load >350,000 copies/mL) demonstrated the second-highest response rate (85%) through 96 weeks.

Figure 3a. Time to Loss of Virologic Response for NFV Patients by Quintiles of Baseline Viral Load

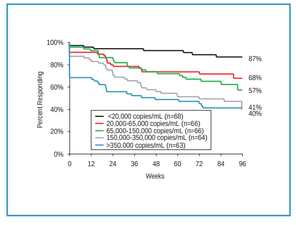
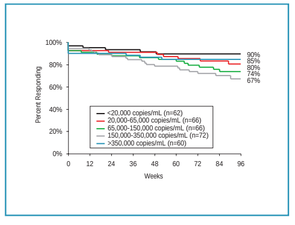


Figure 3b. Time to Loss of Virologic Response for LPV/r Patients by Quintiles of Baseline Viral Load



Baseline CD4 Cell Count and Viral Load as Multivariate Predictors of Response

The Cox proportional hazards model was used to assess the relationship between baseline CD4 cell count/viral load and virologic response within each treatment group. In a multivariate model, lower baseline CD4 count and higher baseline viral load were statistically significantly associated with a higher risk of failure for NFV-treated patients. Neither variable was significantly associated with response among LPV/r-treated patients (Table 2).

Table 2. Multivariate Analysis of Virologic Response and Baseline Viral Load/CD4 Cell Count

	Risk Ratio (95% Confidence Interval)	
Multivariate Analysis	**NFV (n=327)**	**LPV/r (n=326)**
Baseline CD4 cell count (per 100 cells/mm^3 decrease)	1.15 (1.01, 1.30)	1.05 (0.90, 1.22)
	p=0.035	p=0.543
Baseline viral load (per 1.0 $\log_{10}$ copies/mL increase)	1.70 (1.28, 2.26)	1.27 (0.84, 1.91)
	p=0.0002	p=0.265

To explore the relationships demonstrated in the analysis shown in Table 2, patients were stratified by baseline CD4 cell count (above or below 200 cells/mm^3) and viral load (above or below 100,000 copies/mL). Kaplan-Meier response rates through Week 96 are shown for each stratum in Figure 4a for NFV-treated patients and Figure 4b for LPV/r-treated patients.

Figure 4a. Time to Loss of Virologic Response for NFV Patients by Baseline CD4 Cell Count and Baseline Viral Load

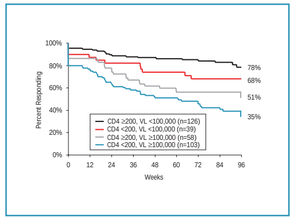
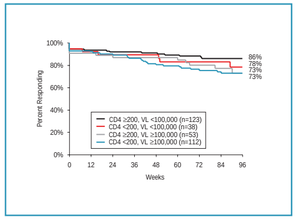


Figure 4b. Time to Loss of Virologic Response for LPV/r Patients by Baseline CD4 Cell Count and Baseline Viral Load



Week 96 response rates demonstrating the independent effects of baseline CD4 cell count and viral load on virologic response to NFV are shown in Figure 5a. Week 96 response rates for LPV/r-treated patients by baseline CD4 cell count and viral load categories are shown in Figure 5b.

Figure 5a. NFV Week 96 Response Rates by Baseline CD4 Cell Count and Baseline Viral Load

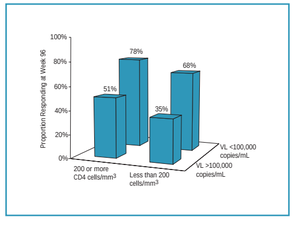
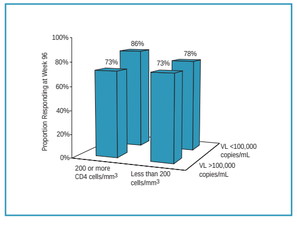


Figure 5b. LPV/r Week 96 Response Rates by Baseline CD4 Cell Count and Baseline Viral Load



Discussion

In accordance with several previous reports (Staszewski 1999, Paredes 2000, Grabar 2000, LeMoing 2002), this analysis demonstrates that among NFV-treated patients, those with lower baseline CD4 cell counts and higher baseline viral loads had a significantly shorter time to loss of virologic response compared to other patients. In contrast to this, and similar to a previous analysis of a phase II study of LPV/r, baseline CD4 cell count and viral load did not demonstrate a statistically significant effect on response among LPV/r-treated patients. Differences between treatment groups in the time to loss of virologic response were largest among patients most likely to initiate treatment based on current treatment guidelines. For example, among patients with baseline CD4 <200 cells/mm^3, a group for whom guidelines universally recommend therapy initiation (DHHS 2002, Pozniak 2001, Carpenter 2000), the percentages of patients maintaining response through Week 96 were 74% for the LPV/r group vs. 44% for the NFV group (p<0.001). At CD4 counts above 200 cells/mm^3, guidelines vary, but treatment initiation is generally recommended or considered for patients with CD4 <350 cells/mm^3 or viral load >55,000 copies/mL; in this subgroup, the percentages of patients maintaining response through Week 96 were 76% for the LPV/r group and 53% for the NFV group (p<0.001).

In some of these analyses of LPV/r-treated patients, a trend toward statistical significance was observed, suggesting that with a longer duration of follow-up, the effect of baseline characteristics on response to LPV/r may become statistically significant. In fact, if the subgroups in Figure 2b are combined so that patients with <50 CD4 cells/mm^3 are compared to the remaining LPV/r-treated subjects, a statistically significant difference is observed (Week 96 response rates were 67% [n=55] vs. 82% [n=271], p=0.03, Cox proportional hazards model). The relative impact of baseline CD4 cell count on response to other agents, such as efavirenz, indinavir, atazanavir, and indinavir/ritonavir, has been less well characterized, since subjects with very low CD4 cell counts have commonly been excluded from participation in these trials (Tashima 2001, Sanne 2001, Schranz 2001).

Both the risk and the consequences of treatment failure should be considered in evaluating antiretroviral regimens. For example, even if criteria for virologic failure are met, isolated viral “blips” or viral rebound during a temporary treatment interruption may not represent a “true” virologic failure. In a recent report on the current study (Bernstein 2001), among patients with detectable viral load and available genotype at any time during Weeks 24-96, significantly more NFV-treated than LPV/r-treated patients demonstrated protease inhibitor resistance (43% vs. 0%, p<0.001) and lamivudine resistance (81% vs. 37%, p<0.001) These findings suggest that in addition to the less durable virologic response observed in the NFV group compared to the LPV/r group in this study, response to subsequent treatment regimens for NFV-treated patients may be undermined due to the higher rate of protease inhibitor and lamivudine resistance.

CONCLUSIONS

- The effects of lower baseline CD4 cell counts and higher baseline viral load levels on the durability of virologic response to a LPV/r-based regimen were generally nonsignificant.
- Among NFV-treated patients, durability of virologic response was highly statistically significantly associated with lower baseline CD4 cell counts and higher baseline viral load levels.
- Clinical trial designs that do not reflect current guidelines for treatment initiation in antiretroviral-naive patients have important limitations:
  - Inclusion of patients with higher CD4 cell counts focuses on a population less likely to initiate therapy and may undermine the ability to detect differences between treatment groups.
  - Similarly, exclusion of patients with advanced HIV disease, such as those with CD4 counts <50 cells/mm^3, may overestimate the treatment effect and decrease the ability to differentiate between treatment regimens.
- Both the risk and the consequences of virologic failure should be considered in evaluating treatment regimens.

REFERENCES

1. Bernstein B, et al. 41st ICAAC, Chicago 2001, Abstract I-1768.
2. Carpenter CCJ, et al. *JAMA* 2000, 283:381-390.
3. Department of Health and Human Services. http://www.hivatis.org, updated 4 February 2002.
4. Grabar S., et al. *AIDS* 2000, 14:141-149.
5. LeMoing V., et al. *AIDS* 2002, 16:21-29.
6. Paredes R., et al. *Arch Int Med* 2000, 160:1123-1132.
7. Pozniak A., et al. *HIV Medicine* 2001, 2:276-313.
8. Sanne I., et al. 41st ICAAC, Chicago 2001, Abstract I-667.
9. Schranz J., et al. 1st IAS Conf. on HIV Pathogenesis and Treatment, Buenos Aires 2001, Abstract 416.
10. Staszewski S., et al. AIDS 1999, 13:367-373.
11. Tashima K., et al. 1st IAS Conf. on HIV Pathogenesis and Treatment, Buenos Aires 2001, Abstract 224.
12. White A.C., et al. 1st IAS Conf. on HIV Pathogenesis and Treatment, Buenos Aires 2001, Abstract 217.