551

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Predictors of HIV RNA Suppression on Darunavir/Ritonavir Monotherapy or triple therapy in the MONET and PROTEA Trials

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Background

In previous studies of protease inhibitor (PI) monotherapy, patients with low nadir CD4 counts, HCV co-infection, poor adherence to treatment, or detectable baseline levels of HIV RNA or DNA have been the most likely to show treatment failure:

Predictors of Treatment Failure in PI monotherapy trials:

MONOI: Baseline HIV RNA detected (>1 copy/mL)
Shorter duration of prior treatment
Poor adherence
Higher baseline HIV DNA
OK-04: Nadir CD4 count <100 cells/uL
Poor adherence (self-reported missed doses)
Kalesolo: Older age at baseline
MOST: Nadir CD4 count <200 cells/uL

In the MONET and PROTEA trials, 529 patients with HIV RNA <50 copies/mL at screening switched to DRV/r 800/100 mg once daily, either as monotherapy (n=264) or as triple therapy with 2NRTIs (n=265).

The objective of this analysis was to identify the main predictors of treatment failure on DRV/r monotherapy at Week 48 in the combined MONETand PROTEA trials.

Methods

Patients with CD4 nadir <100 cells/μL were excluded from the MONET and PROTEA studies. At the screening visit, patients were taking either 2 NRTIs plus either NNRTI- based or non-NNRTI based treatment (typically 2NRTI/PI or 2NRTI/Integrase).

Treatment response was defined as HIV RNA<50 copies/mL at week 48 (FDA Snapshot method).

Multivariate logistic regression was used to identify factors predictive of treatment failure in the two combined clinical trials by Week 48:

baseline HIV RNA (target not detected), age, gender, race, HCV co-infection, nadir CD4 count, duration of diagnosis, time to ARV use, treatment group, baseline CD4 count and time to start of ART treatment.

For the univariate model, used to evaluate the impact of baseline factors of response (as defined above), all factors were retained, irrespective of statistical significance.

For the final multivariate model, factors significant at the 0.10 level following stepwise selection with backward elimination procedure were retained.

Results

In the MONET and PROTEA trials, there were 224/264 patients on DRV/r monotherapy (85%) with HIV RNA <50 copies/mL at Week 48, versus 240/265 (91%) on triple therapy.

Predictors of response are shown in Table 1. In the combined triple therapy arms of the PROTEA and MONET trials, there were three predictors of HIV RNA suppression at Week 48: older age (p=0.09), baseline HIV RNA <50 copies/mL (p=0.03) and no prior NNRTI use (p=0.008).

In the PI monotherapy arms, there were two significant predictors of HIV RNA suppression: CD4 nadir ≥200 cells/uL (p=0.01) and no prior use of NNRTIs (p-0.06).

Table 1: Predictors of HIV RNA <50 copies/mL at Week 48 – Pooled MONET/PROTEA Univariate and Multivariate logistic regression analysis

Factor	Univariate analysis Odd Ratio (95% CI)	Multivariate analysis Odds Ratio (95% CI)	p value
Triple therapy arms (n=265)			
Age (per 1 year older)	1.03 (0.99-1.08)	1.04 (0.99-1.10)	p=0.09
HCV antibody positive	0.55 (0.12-2.65)		
Baseline CD4 count	1.00 (1.00-1.00)		
Baseline HIV RNA<50 c/mL	8.05 (1.69-38.3)	6.19 (1.23-31.1)	p=0.03
CD4 nadir ≥200 cells/uL	1.39 (0.59-3.31)		
Female gender	0.58 (0.22-1.54)		
Prior NNRTI use	0.27 (0.10-0.69)	0.27 (0.10-0.71)	p=0.008
Prior PI use	2.08 (0.87-4.99)		
Black race	0.52 (0.14-1.94)		
Years since HIV diagnosis	0.97 (0.90-1.04)		
Years on ARV treatment	0.93 (0.85-1.02)		
Monotherapy arms (n=264)			
Age (per 1 year older)	0.98 (0.95-1.01)		
HCV antibody positive	0.98 (0.21-4.60)		
Baseline CD4 count	1.00 (1.00-1.00)		
Baseline HIV RNA<50 c/mL	0.69 (0.08-5.69)		
CD4 nadir ≥200 cells/uL	2.48 (1.25-4.91)	2.45 (1.23-4.88)	p=0.01
Female gender	1.25 (0.52-3.01)		
Prior PI use	1.92 (0.92-4.01)		
Prior NNRTI use	0.50 (0.25-1.01)	0.51 (0.25-1.04)	p=0.06
Black race	0.79 (0.25-2.46)		
Years since HIV diagnosis	0.97 (0.91-1.03)		
Years on ARV treatment	0.97 (0.89-1.04)		

Results

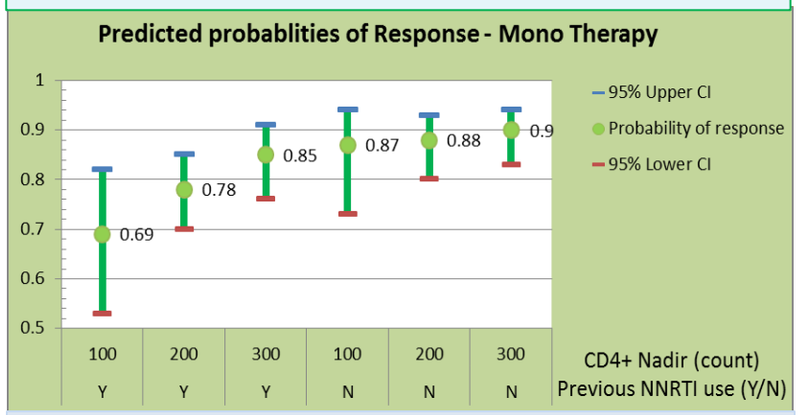
Table 2 shows the response rates in each treatment arm in the subgroups of patients with CD4 nadir above or below 200 cells/uL and by prior use of NNRTIs

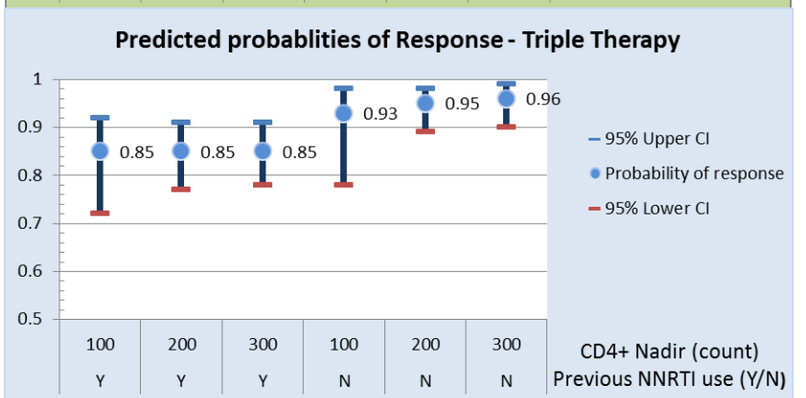
The efficacy of DRV/r monotherapy ranged from 69% for those with CD4 nadir <200 cells/μL and prior NNRTI treatment, to 91% for those with CD4 nadir ≥200μL and no prior NNRTI treatment

The Figures show the predicted probabilities of HIV RNA suppression by baseline CD4 nadir and prior use of NNRTIs. There was no further improvement in efficacy for patients on DRV/r monotherapy with CD4 nadir categories above 200 cells/uL

Table 2: HIV RNA <50 copies/mL at Week 48, By CD4 nadir and prior NNRTI use

CD4 nadir	Prior NNRTI	DRV/r	2NRTI+DRV/r
≥200	no NNRTI	80/88 (91%)	96/99 (97%)
<200	no NNRTI	36/42 (86%)	34/37 (92%)
≥200	prior NNRTI	75/86 (87%)	75/88 (85%)
<200	prior NNRTI	33/48 (69%)	35/41 (85%)
Overall		**224/264 (85%)**	**240/265 (91%)**





Conclusions

In the combined MONET and PROTEA trials, patients with CD4 nadir above 200 cells/uL and no prior NNRTI-based treatment were most likely to show sustained HIV RNA suppression on DRV/r monotherapy at Week 48 (91%).

The FDA snapshot method used in this analysis includes treatment failure as either HIV RNA elevations, or discontinuation of randomised treatment for adverse events or other reasons.

CD4 nadir may be an indirect marker of prior disease severity. Prior NNRTI use might be a marker of the acceptability of taking a protease inhibitor during the trials.

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