

Analysis of drug resistance during HIV RNA viraemia in the MONET trial of darunavir/ritonavir monotherapy

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Introduction

In the MONET trial, 256 patients with HIV RNA levels below 50 copies/mL on antiretroviral treatment, and no history of virological failure, were randomised to receive darunavir/ritonavir (DRV/r) 800/100 mg once daily, either as monotherapy (monotherapy arm) or in combination with two nucleoside analogues (triple therapy arm).

The aim of this analysis was to measure the prevalence of drug resistance during episodes of transient or sustained HIV RNA viraemia.

Methods

Patients attended study visits at screening, baseline and then Weeks 4, 12, 24, 36 and Week 48. After Week 48, patients were assessed every 12 weeks to Week 96.

Plasma HIV RNA was measured using the Roche Amplicor HIV-1 Monitor assay (version 1.5, Roche Molecular Systems, Branchburg, USA (Ref 1)). Viral genotypic tests were performed using standard Virco TYPE HIV-1 assays (Virco BVBA, Mechelen, Belgium).

Genotypic drug resistance was assessed for all patient samples with HIV RNA concentrations above 50 copies/mL, up to September 2009. As a consequence of limited sensitivity, there is a limited success rate for genotyping at low HIV RNA levels. Virtual phenotyping was used to assess phenotypic sensitivity.

Any patient with an HIV RNA result above 50 copies/mL attended a confirmation visit within 2 weeks, for repeated testing of HIV RNA, drug resistance and plasma drug levels.

Pre-trial stored samples were not available for most patients, so it was not possible to determine the baseline genotype for most patients. Therefore, resistance mutations observed during the trial might have been pre-existing.

Genotypic mutations (Ref 2) were defined as follows:

DRV resistance associated mutations: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V

IAS-USA major PI mutations: D30N, V32I, L33F, M46I/L, I47A/V, I50L, I54M/L, L76V, V82A/F/T, I84V, N88S, L90M

NRTI mutations: M41L, A62V, K65R, D67N, K70R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184V, L210W, T215Y/F, K219Q/E

The percentage of patients with each mutation was calculated from the number of patients with at least one successful genotype. The analysis assumed a worst case scenario: if any of a patient samples showed a mutation, the patient was assumed to have this mutation, even if other samples showed wild-type virus.

Results

A summary of the key baseline characteristics from the MONET trial is shown in Table 1. The patients were 78% male and 92% Caucasian, with a median CD4 count of 575 cells/uL at baseline.

There was a longer median duration of prior antiretroviral treatment in the monotherapy arm (7.4 years) compared with the triple therapy arm (5.9 years). There was a diversity of prior antiretroviral treatment, ranging from patients still on their first randomized treatment for eighteen months, to patients with ten or more years of antiretroviral treatment.

Table 1: Baseline characteristics by treatment arm (ITT population)

Baseline data	DRV/r mono n=127	Triple therapy n=129
Mean age, years	43	44
Gender (% male)	78%	83%
Race (% Caucasian)	92%	90%
Mean CD4 count	571	579
HCV antibody Positive	17%	9%
Known duration of HIV infection (years)	9.1	7.5
Duration of prior ARV treatment (years)	7.4	5.9
PI naive at screening (%)	23%	28%
PI-based treatment at screening (%)	56%	57%
NNRTI-based treatment at screening (%)	44%	43%

Table 2: Summary of genotypic resistance detected post randomization (ITT)

Number of Patients with:	DRV/r mono n=129	Triple therapy n=127
at least 1 HIV RNA result \geq 50 post baseline	39 (31%)	31 (24%)
Number of genotypes performed	74	42
Number of successful genotypes	40 (54%)	19 (45%)
at least one successful genotype	24 (19%)	14 (11%)
no primary PI, DRV, NRTIs or M184V mutations	23 (96%)	13 (93%)
1 or more IAS-USA primary PI mutations	1 (4%)	1 (7%)
1 or more DRV mutations	1 (4%)	0
M184V mutation	0	1 (7%)
Other NRTI mutations	0	0

Conclusions

Of 38 patients successfully tested for drug resistance in the MONET trial, 36 (95%) showed no major PI or NRTI mutations.

One patient (triple therapy arm) had re-emergence of pre-existing drug resistance, present in a pre-screening sample – this patient's virus remained phenotypically sensitive to DRV. The patient had sustained HIV RNA suppression to Week 84 after the temporary blip.

Another patient (monotherapy arm) showed a single DRV mutation at the time of a single blip in HIV RNA (63 copies/mL). This virus remained phenotypically sensitive to DRV. The patient had sustained HIV RNA suppression to Week 60, after the single HIV RNA blip.

No patient samples have shown phenotypic resistance to DRV, in either treatment arm of the MONET trial, up to September 2009.

This analysis included testing for drug resistance for all samples with HIV RNA $>$ 50 copies/mL. Normally, resistance testing is only performed for samples with HIV RNA $>$ 400 copies/mL.

References

- Roche Diagnostics GmbH, Mannheim, Germany. COBAS Amplicor HIV-1 MONITOR Test, version 1.5. June 2007, Package Insert. <http://www.fda.gov/Cber/sba/hiv1roc122002S.htm>. Accessed September 2008.
- Hirsch M, Gunthard H, Schapiro J, Brun-Venizet F, Clotet B, Hammer S et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA Panel. Clin Inf Dis 2008, 47: 266-285

After 48 weeks, 86.2% of patients in the monotherapy arm and 87.8% of patients in the triple therapy arm had HIV RNA $<$ 50 copies/mL, in the primary analysis (Per Protocol, Switch equals failure).

There were 7 patients with two consecutive HIV RNA levels above 50 copies/mL in the triple therapy arm versus 11 in the monotherapy arm. However, only two patients per arm showed a confirmed elevation in HIV RNA above 400 copies/mL by Week 48.

Genotypes were available for 38/70 (54%) patients with at least one HIV RNA result $>$ 50 copies/mL. Thirty-six of these 38 patients (95%) showed no major PI mutations, DRV resistance associated mutations or NRTI mutations. There was one patient in each treatment arm who showed at least one IAS-USA mutation associated with resistance to protease inhibitors or nucleoside analogues.

Details of the two patients are shown in Figures 1-2 below.

Details of two patients with DRV or IAS-USA PI mutations

Patient 1. One PI pre-treated patient in the triple therapy arm had a single genotype showing resistance to lamivudine (M184V) and to PIs (V82I/T, L90M). This genotype was detected when the HIV RNA level was 50 copies/mL, after a short interruption of treatment. However the virus was phenotypically sensitive to DRV/r (fold change=1.2). All subsequent visits showed HIV RNA levels $<$ 50 copies/mL, to Week 84 of the trial, on their original randomised treatment (2NRTI + DRV/r).

Re-analysis of the pre-screening HIV RNA sample showed that these mutations were already present before the patient started treatment in the MONET trial.

Patient 2. One PI pre-treated patient in the DRV/r monotherapy arm (Figure 2) had a single HIV RNA result at Week 12, of 63 copies/mL. Genotyping of this sample showed a single DRV mutation – L33F.

The sample was phenotypically sensitive to DRV (fold change =0.8).

All subsequent HIV RNA results for this patient were $<$ 50 copies/mL, to Week 60 of the trial on their original randomised treatment (DRV/r monotherapy).

Figure 1 - Patient 1
Treatment arm: 2NRTI + DRV/r

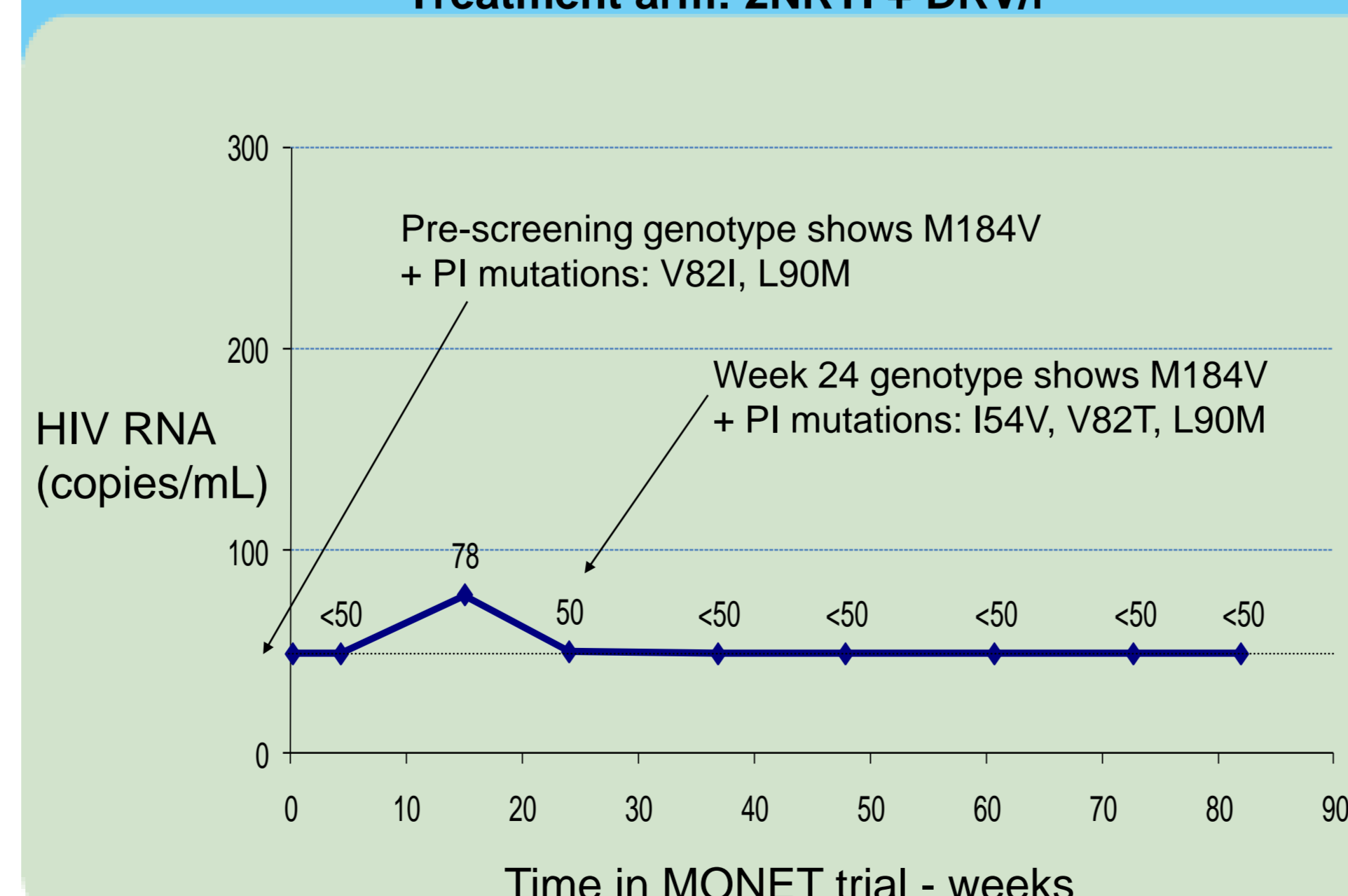


Figure 2 - Patient 2
Treatment arm: DRV/r

