SHIFTING PARADIGMS: Doravirine's Potential in Treating Non-group M HIV-1, the DORAVI-O study

740

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BACKGROUND

According to the current HIV-1 virus classification, groups O, N, and P (also called HIV-1 non-group M) are highly genetically divergent from the pandemic group M. They are also relatively rare and mainly restricted to West-Central Africa, where they account for 1% of HIV-1 infections.

The natural genetic polymorphism of HIV-1 group O (HIV-1/O) in the reverse transcriptase region harbors the Y181C mutation, which is associated with NNRTI resistance. However, Doravirine's resistance profile challenges this assumption, as it remains effective against viruses with the unique Y181C mutation.

OBJECTIVES

To assess the phenotypic sensitivity to Doravirine (DOR) in clinical strains of HIV-1/non-M

To search for potential genotypic determinants associated with DOR phenotypic resistance

The DORAVI-O study challenges current therapeutic recommendations for HIV-1 group O infection

- Doravirine unique NNRTI resistance profile may allow its use in HIV-1/O, despite natural Y181C natural resistance mutation
- Most of HIV-1/O clinical strains showed **phenotypic susceptibility** to DOR, except 25% with IC_{50} over 1,000 nM
- No clear correlation between genotypic profile and phenotypic **resistance** have been showed yet

METHODS

6x10e6 human mononuclear cells from healthy donors were infected with 100 TCID50 of supernatant of 28 HIV-1 non-M strains *(Fig.1)* for 2 h, then exposed to 5 increasing concentrations of Doravirine (0.1 to 1,000 nM) kindly provided by MSD Laboratories in quadruplicates at 37°C under 5% CO2 for 3 to 4 days.

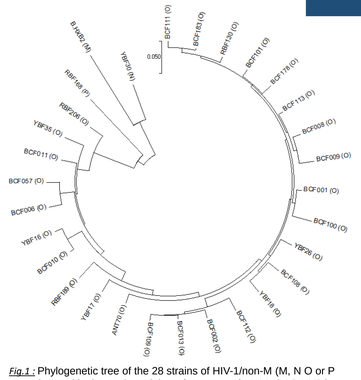


Fig.1 : Phylogenetic tree of the 28 strains of HIV-1/non-M (M, N O or P group) tested in the study and the reference strain HIV-1/M B.HXB2, based on a 705 nucleotides sequence in the reverse transcriptase region (Neighbor-joining method, 500 bootstraps, kimura 2 parameters analyzed with MEGA 7)

Viral RNA was extracted (EZ1 Qiagen) from the supernatant and quantified by qRT-PCR ("in house" for HIV-1/O or HIV-1 Aptima Hologic) to determine the inhibitory concentration 50 (IC50), maximum percentage inhibition (MPI) and Fold Change (FC calculated by comparing the IC_{50} of the strain to the IC50 of the reference strain M, set at 12 nM in the literature.

Amino acid sequences of the reverse transcriptase region of each strain (CEQ8000 Beckman) were compared with the updated ANRS french resistance interpretation algorithm.

RESULTS

In total, 28 phenotypes were obtained from 26 group O strains, 1N, 1P strains respectively, and corresponded to Y181C isolates for 75% *(Table1).*

Phenotypic susceptibility:

Seven (25%) isolates (6O, 1P) had a FC > 1000 and were considered phenotypically resistant to DOR. From the 21 remaining strains the *mean and median IC_{50} were at 132.9 and 37.4 nM* respectively. *Eight (28.5%) group O isolates had a FC < 1* and could be considered as phenotypically highly sensitive to DOR.

Reverse transcriptase genetic profile:

Most of the strains were classified as intermediate for DOR sensitivity by the algorithm due to mutations A98G (96%) and Y181C (75%).

Notably, only one isolate (HIV-1/O BCF108) expressed the mutations associated with DOR resistance (A98G, Y181C, G190A and H221Y) for HIV-1 group M, in accordance with its phenotypic resistance (IC_{50} > 10,000 and FC > 1000).

For the other strains there were *no correlation between the mutations of the genotypic prediction algorithm and the phenotypic susceptibility to DOR*, suggesting the potential existence of non-M viruses specific genotypic determinants not covered by the ANRS algorithm designed for M variants.

Table.1 : Synthetic results of phenotypic data obtained among the 28 HIV-1 non-M clinical isolates

HIV1 group	Strain identity	Tropism	HIV-1 O subgroup	Y181	IC50 (nM)	MPI (%)
O	RBF130	R5	H	C	0.204	87.3
O	BCF057	R5	T	Y	0.619	84.6
O	BCF001	R5	H	C	1.15	92.9
O	BCF100	R5	H	C	1.73	68.8
O	BCF006	DM	T	Y	2.67	97.8
O	BCF112	R5	H	C	3.44	68.1
O	RBF189	R5	H	C	5.28	94.1
O	BCF178	R5	H	C	9.18	82.3
O	BCF113	R5	H	C	25.6	81.8
O	BCF183	R5	H	C	30.1	78.7
O	BCF002	R5	H	C	37.4	60.5
O	BCF010	R5	T	Y	62	85.1
O	YBF16	R5	T	Y	64.1	95.7
O	BCF011	R5	T	Y	130	71.7
N	YBF30	R5		Y	147	96.4
O	BCF009	R5	H	C	225	74.2
O	YBF26	R5	H	C	232	75.9
O	YBF35	R5	T	Y	302	64.9
O	ANT70	R5	H	C	416	71.4
O	YBF17	R5	H	C	498	54.3
O	BCF111	R5	H	C	597	77.9
O	BCF008	R5	H	C	>1,000	90.4
O	BCF013	R5	H	C	>1,000	61.3
O	YBF18	DM	H	C	>1,000	66
O	BCF101	R5	H	C	>1,000	54.2
O	BCF108	R5	H	C	>10,000	60
P	RBF168	R5		Y	>10,000	34.4
O	BCF109	R5	H	C	>10,000	50.5

CONCLUSIONS

The DORAVI-O study revealed **wide phenotypic susceptibilities of HIV-1/non-M to DOR**, **regardless of the natural presence of the Y181C mutation**. These preliminary results may prompt a reconsideration of systematically excluding the DOR from the treatment regimen for some HIV-1/O infected patients.

However, as the French ANRS algorithm failed to find mutations associated with phenotypic resistance for some isolates, we still have to search for a potential genotypic pattern dedicated to non-M strains (beyond the reverse transcriptase region or other regions ?) Site-directed mutagenesis assay would also enable us to study the impact of specific mutations described for HIV-1/M viruses.

Additional Resources: *Plantier et al., Nat. Med. 2009 ; Descamps et al. J Virol. 1997*

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