HIV-1 NON-GROUP M PHENOTYPIC SUSCEPTIBILITY TO IBALIZUMAB

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BACKGROUND

While HIV-1 group M is responsible for the large majority of HIV infections worldwide, 3 other groups named O, N and P (HIV-1 non-M) are more genetically divergent and endemic in West-central Africa, mainly in Cameroon.

Due to the natural genetic polymorphisms associated with HIV-1 non-M, fully-active antiretrovirals are more restricted than for HIV-1/M.[1] Therefore, novel drugs such as Ibalizumab (IBA), the first-in-class long-acting CD4-directed post-attachment inhibitor, could provide important alternatives for treatment regimens.[2]

OBJECTIVES

→ To determine the phenotypic susceptibility of HIV-1/non-M clinical isolates to IBA

METHODS

7 clinical isolates of HIV-1/non-M were tested
- 5 HIV-1/O (4 subgroup H and 1 subgroup T)
- 1 HIV-1/N
- 1 HIV-1/P

and BRU-HXB2 HIV-1 reference strain.

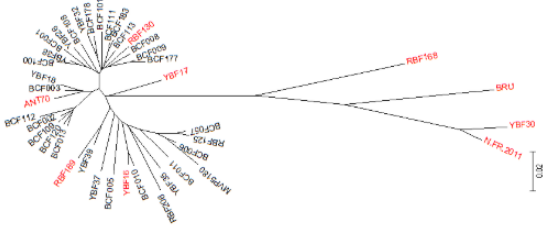

Figure 1 : Phylogenetic tree representing the diversity of the studied strains (in red)
(Analysis made with Mega7.Evolutionary history was inferred using the Neighbor-Joining method and evolutionary distances using Kimura 2-parameter method)

For the phenotypic assay PHA stimulated-PBMC from healthy donors were preincubated with IBA for 1h. Then, $2.5x10^5$ PBMC previously infected for 2h with 100 $TCID_{50}$ of each viral supernatants, were incubated (37°C, 5% CO_2) in quadruplicate in a 96-wells plate with 5 increasing concentrations of Ibalizumab (from 1 to 10 000 ng/ml) for 3 days.

Viral RNA was extracted from 200µl of supernatant by EZ1 advanced XI Qiagen® and quantified by various methods described as following[3]: Integrase-based specific in house qRT-PCR (HIV-1/O), LTR-M Biocentric® (HIV-1/M and N) and Aptima HIV-1 Quant Dx Hologic®, for the calculation of inhibitory concentrations 50% (IC_{50}), maximum percent inhibition (MPI) and fold-change (FC) calculated from BRU-HXB2 IC_{50}.

The highest IC_{50}values were controlled for reproducibility.

IBA demonstrated *in vitro* susceptibility of HIV-1/O while phenotypic results with HIV-1/P suggest potential resistance

RESULTS

Five clinical isolates (4 HIV-1/O and 1 HIV-/N) had a **mean IC_{50} (min; max) of 0.119 ($6x10^{-11}$; 0.227) ng/ml** and median **MPI of 96.9%,** comparable to those of the HIV-1/M reference (IC_{50} and MPI of 0.186 ng/ml and 90.9% respectively).

In contrast with these results, the RBF168 clinical **isolate of HIV-1/P was naturally resistant** (IC_{50}>10 000 ng/ml and MPI<25%), in two independent experiments.

Finally, YBF17, a divergent clinical isolate of HIV-1/O subgroup H, had a FC of 824 (IC_{50} of 153 ng/ml) with intermediate MPI (75.9%) but within the susceptibility range defined in the literature for HIV-1/M (max at 600 ng/ml). This strain also showed high intra-group O genetic diversity (Fig1).

Table 1 : Phenotypic results of the 7 HIV-1/non-M strains and BRU.HXB2

Group	Strain	IC_{50} (ng/mL)	MPI	FC
M	**BRU.HXB2**	0.186	90.9	-
N	**YBF30**	0.216	98.1	1.16
O	**RBF189**	$6.19x10^{-11}$	93.6	< 0.01
O	**RBF130**	0.0644	94.0	0.35
O	**ANT70**	0.0089	96.9	0.48
O	**YBF16**	0.227	98.5	1.22
O	**YBF17**	153	75.9	824
P	**RBF168**	> 10 000	< 25	-

CONCLUSION

Our results demonstrate the susceptibility of HIV-1 non-M to Ibalizumab with **100% of HIV-1/O and N isolates tested being susceptible, while IBA had no activity against the single HIV-1/P isolate tested**.

These results should now be confirmed in a larger panel and potential N-linked glycosylation sites (PNGS) should be assessed to determine their potential role in resistance of HIV-1/non-M to IBA.

REFERENCES & FUNDINGS

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