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Nucleoside-associated mutations cause hypersusceptibility to etravirine (ETR)

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Abstract

Background

Nucleoside associated mutations (NAMs) have been implicated in hypersusceptibility (HS) to first-generation NNRTIs; HS has been associated with better clinical responses to NNRTIs. In-vitro HS to etravirine (ETR; TMC125) was investigated.

Methods

A panel of 29 HIV-1 recombinant clinical isolates with well-characterised HS to nevirapine (NVP) and efavirenz (EFV) was tested for ETR phenotypic susceptibility (PhenoSense™, Monogram Biosciences). The panel consisted of four groups: a) isolates with no mutations in reverse transcriptase (RT) (n=8); b) isolates with M184V alone (n=6); c) isolates with NAMs + M184V (n=8); d) isolates with NAMs (n=7). NAMs included amino acid changes at positions: 41, 65, 67, 69, 70, 115, 118, 151, 210, 215, and/or 219. In addition, isolates carrying the K103N mutation (n=11), with or without NAMs and other NNRTI mutations, as well as 1,027 wild-type routine clinical samples with no known NRTI-, NNRTI- or protease inhibitor (PI)-resistance mutations were tested. HS was defined as a fold-change in 50% effective concentration (FC) ≤0.4.

Results

The proportion of samples with HS to ETR, EFV and NVP, respectively, in each group was: a) 0%, 62.5% and 100%; b) 100%, 100% and 100%; c) 75%, 100% and 87.5%; d) 100%, 71% and 85.7%. Median FC values to ETR, EFV and NVP, respectively, in each group were: a) 0.53, 0.4 and 0.3; b) 0.27, 0.25 and 0.25; c) 0.29, 0.27 and 0.26; d) 0.26, 0.33 and 0.34. In addition, one sample with K103N and NAMs showed HS to ETR (FC=0.24). However, none of 10 samples with K103N alone (n=4) or with K103N + other NNRTI mutations, but no NAMs (n=6) showed HS to ETR. The median FC among samples with K103N was 1.18 (range 0.49–2.22) for ETR in contrast to 49 for EFV and >100 for NVP. Among wild-type samples, 2.8%, 3.1% and 9.0% showed HS to ETR, EFV, and NVP, respectively.

Conclusions

Among the HIV-1 isolates studied, HS to ETR was mainly observed among those carrying NAMs and/or M184V. K103N-containing isolates did not exhibit HS to ETR; nevertheless, FC values were below the PhenoSense™ clinical cut-off for ETR (2.9). The potential impact of HS on response to ETR deserves further investigation.

Please note that these data have been updated following the submission of this abstract

Background and objectives

- NAMs have been implicated in HS to the first-generation NNRTIs NVP and EFV
- HS has been associated with better clinical responses to NNRTIs
- The objective of this study was to investigate *in-vitro* HS to ETR

NAMs = nucleoside associated mutations; HS = hypersusceptibility

Methods

- A panel of 29 HIV-1 recombinant clinical isolates with well-characterised HS to NVP or EFV was tested for ETR phenotypic susceptibility (PhenoSense™, Monogram Biosciences)
- The panel consisted of four groups:
  - A) isolates with no mutations in RT (n=8)
  - B) isolates with M184V alone (n=6)
  - C) isolates with NAMs + M184V (n=8)
  - D) isolates with NAMs (n=7)

Methods (cont'd)

- NAMs included amino acid changes at positions
  - 41, 65, 67, 69, 70, 115, 118, 151, 210, 215 and/or 219
- In addition, isolates carrying the K103N mutation (n=11), with or without NAMs and other NNRTI mutations, as well as 1,027 wild-type routine clinical samples with no known NRTI-, NNRTI- or PI-resistance mutations were tested
- HS was defined as a FC ≤0.4

Panel A: isolates with no mutations in RT (n=8)

Sample ID	Mutations	ETR FC	EFV FC	NVP FC
1A	none	0.73	0.44	0.31
2A	none	0.50	0.39	0.30
3A	none	0.56	0.42	0.25
4A	none	0.57	0.37	0.21
5A	none	0.41	0.37	0.27
6A	none	0.48	0.40	0.29
7A	none	0.48	0.43	0.30
8A	none	0.56	0.36	0.34
Isolates with HS to ETR, EFV or NVP (FC ≤0.4) are highlighted		Median FC		
		0.53	0.40	0.30
		HS (%)		
		0	62.5	100

Panel B: isolates with M184V alone (n=6)

Sample ID	Mutations	ETR FC	EFV FC	NVP FC
1B	184V	0.40	0.31	0.31
2B	184V	0.24	0.24	0.16
3B	184V	0.32	0.26	0.27
4B	184V	0.24	0.21	0.20
5B	184V	0.28	0.26	0.29
6B	184V	0.26	0.21	0.22
Isolates with HS to ETR, EFV or NVP (FC ≤0.4) are highlighted		Median FC		
		0.27	0.25	0.25
		HS (%)		
		100	100	100

Panel C: isolates with NAMs plus M184V (n=8)

Sample ID	Mutations	ETR FC	EFV FC	NVP FC
1C	69D, 70R, 184V	0.34	0.33	0.24
2C	41L, 184V, 210W, 215Y	0.24	0.30	0.31
3C	41L, 67N, 69D, 184V, 210W, 215Y, 219Q	0.30	0.24	0.21
4C	65R, 184V	0.28	0.24	0.28
5C	115Y, 151M, 184V	0.54	0.39	0.20
6C	41L, 67N, 118I, 184V, 215Y	0.11	0.16	0.20
7C	41L, 67N, 118I, 184V, 210W, 215Y	0.17	0.22	0.44
8C	65R, 115F, 184V	0.59	0.37	0.29
Isolates with HS to ETR, EFV or NVP (FC ≤0.4) are highlighted		Median FC		
		0,29	0,27	0,26
		HS (%)		
		75	100	87,5

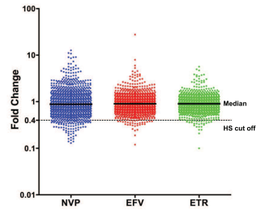
Panel D: isolates with NAMs (n=7)

Sample ID	Mutations	ETR FC	EFV FC	NVP FC
1D	41L, 67N, 69D, 210W	0.26	0.33	0.30
2D	210W, 215Y	0.31	0.41	0.42
3D	41L, 67N, 118I, 210W, 215Y	0.16	0.15	0.19
4D	69, 70R	0.31	0.34	0.38
5D	41L, 67N, 118I, 210W, 215Y	0.20	0.27	0.34
6D	41L, 67N, 118I, 210W, 215Y	0.15	0.18	0.20
7D	41L, 210W, 215Y	0.29	0.42	0.38
Isolates with HS to ETR, EFV or NVP (FC ≤0.4) are highlighted		Median FC		
		0.26	0.33	0.34
		HS (%)		
		100	71	85.7

Isolates with K103N with or without NAMs or other NNRTI mutations (n=11)

Sample ID	Mutations	ETR FC	EFV FC	NVP FC
1	103N, 41L, 67N, 118I, 184V, 210W, 215Y, 225H	0.24	115.00	183.00
2	103N	1.17	69.00	>156.00
3	103N, 101Q	2.21	117.00	>156.00
4	103N	0.49	16.00	40.00
5	103N	0,80	17,00	76,00
6	103N	1,26	30,00	>156,00
7	103N, 106I	1,18	24,00	125,00
8	90V/I, 108I, 179I, 103N	2.22	68.00	>156.00
9	179V/I, 103N	0.85	17.00	32.00
10	238N, 103N	1.35	>209.00	>156.00
11	108I, 238T, 103N	0.97	>209.00	>156.00
Isolates with HS to ETR, EFV or NVP (FC ≤0.4) are highlighted		Median FC		
		1,18	49,00	156,00
		HS (%)		
		9,1	0	0

Wild-type clinical isolates with no known NRTI-, NNRTI- or PI-resistance mutations (n=1,027)



Wild-type clinical isolates with no known NRTI-, NNRTI- or PI-resistance mutations (n=1,027) (cont'd)

FC	NVP	EFV	ETR
Median	0.88	0.90	0.90
Mean	1.20	1.06	0.99
99th PC	5.90	3.67	3.03
Min	0.13	0.12	0.10
Max	12.67	27.67	5.67
	HS (%)		
	9	3.1	2.8

PC = percentile

Conclusions

- HS to ETR was mainly observed among HIV-1 isolates carrying NAMs, M184V, or both
- K103N-containing isolates did not exhibit HS to ETR
  - nevertheless, the median (1.18) and individual FC values were below the PhenoSense™ clinical cut-off for ETR (2.9)[1]
- The potential impact of HS on response to ETR deserves further investigation

References

1. Coakley, et al. IHDRW 2008, Abstract 122.

Supported by Tibotec

Presented at the XVIIth International Drug Resistance Workshop, Sitges, Spain, 10–14 June 2008.

This poster is available on-line at www.tibotec.com