PRO 140 IN VITRO ACTIVITY IN HTE SUBJECTS WITH A 4-CLASS DRUG-RESISTANT HIV-1 VIRUS

0524

Boston, Massachusetts
March 8–11, 2020

Contact information:
Arianna Gabrieli, Ph.D./Stefano Rusconi, M.D.
Infectious Diseases Unit, DIBIC Luigi Sacco
University of Milan, Milan, Italy
E-mail: arianna.gabrieli@asst-fbf-sacco.it
stefano.rusconi@unimi.it

Stefano Rusconi[1] , Francesco Saladini[2], Silvia Barbaliscia[3] , Andrea Poli[4] , Laura Galli[4] , Roberta Gagliardini[5] , Lidia Gazzola[6] , Daniela Francisci [7], Francesca Vichi[8] , Emanuele Focà[9] , Maurizio Zazzi[2] , Maria M. Santoro[3] , Arianna Gabrieli[1] , Antonella Castagna[4] , for the PRESTIGIO Registry study group

[1]University of Milan, Milan, Italy;[2] University of Siena, Siena, Italy; [3]University of Rome Tor Vergata, Rome, Italy; [4]San Raffaele Vita-Salute University, Milan, Italy; [5]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy; [6]Azienda Ospedaliera San Paolo, Milan, Italy; [7]University of Perugia, Perugia, Italy, [8]Santa Maria Annunziata Hospital, Florence, Italy,; [9]University of Brescia, Brescia, Italy

BACKGROUND AND AIMS

Antiretroviral drug resistance has been, and continues to be, a major barrier to the successful treatment of HIV infection. One of the drugs available to prevent the virus from entering the cell is represented by Maraviroc (MVC) which had been approved for clinical use; but this CCR5 antagonist had multiple limitations, including need for tropism testing, moderate potency, drug interactions and CXCR4 tropism. PRO 140 is a novel humanized form of a mouse immunoglobulin G4 (IgG4) CCR5-directed monoclonal antibody (MoAb) with nanomolar potency against a broad range of CCR5-tropic isolates belonging to different HIV-1 subtypes (1,2).

The aim of this study was to analyze HIV-1 tropism and in vitro susceptibility to PRO 140 according to MVC exposure in a cohort of highly treatment-experienced (HTE) HIV-1-infected patients, harboring a documented 4-class drug-resistance to NRTIs, NNRTIs, PIs, InSTIs, enrolled in the Italian PRESTIGIO Registry.

METHODS

Plasma RNA (viremic patients) or PBMC DNA (non-viremic patients) was used for Sanger sequencing and Next Generation Sequencing (NGS, Illumina platform) of the gp120-V3 region followed by geno2pheno [coreceptor] interpretation. Viral tropism and susceptibility to PRO 140 were assessed through a home-made phenotypic assay based on pseudotyped viruses expressing patient derived Env protein and luciferase as reporter gene. Patients' demographics and laboratory data are described as median (Q1-Q3), mean (±SD) or frequency (%); comparisons by Mann-Whitney or chi-square/Fisher exact's tests.

RESULTS

Demographic, clinical and laboratory characteristics of the 25 HTE patients from the PRESTIGIO Registry included in the PRO-140 study are described in **Table 1**.

Table 1. Patients' characteristics

CHARACTERISTICS	Overall (n=25)
Age (years), median IQR	49.9 (43.6 – 52.7)
Male gender, N (%)	20 (80%)
Years since first HIV positive test, median IQR	22.6 (19.4 – 25.5)
Years since ART start, median IQR	20.1 (15.8 – 22.8)
Previous diagnosis of AIDS, N (%)	14 (56%)
Nadir CD4+T-cells (N/µL), median IQR	79 (9 - 165)
Zenith HIV-1 RNA (log_{10} copies/mL), median IQR	5.07 (4.40 – 5.60)
HIV-1 RNA (log_{10} copies/mL), median IQR	4.58 (4.02 – 5.11)
$CD4^+$T-cells (N/µL), median IQR	207 (73 - 326)
$CD8^+$T-cells (N/µL), median IQR	901 (615 - 1641)
$CD4^+/CD8^+$ ratio, median IQR	0.23 (0.12 – 0.39)

Table 2. HIV-1 tropism results in the overall sample

CHARACTERISTICS	Overall (n=25)
False positive rate (FPR) by g2p, median IQR	5.7 (0.2 – 51.0)
R5 (FPR >10)	**9/21 (43%)**
X4(FPR≤10)	12/21 (57%)
FPR by Sanger, median IQR	5.35 (0.5 – 50.2)
R5 (FPR >10)	**8/22 (36%)**
X4(FPR≤10)	14/22 (64%)
Percent of X4 variants by deep sequencing setting FPR at 3.5%, median IQR	27.1 (0.6 – 96.9)
R5 (≥2%)	**9/25 (36%)**
Non-R5(<2%)	16/25 (64%)
Phenotypic tropism, N (%)	
R5	9/25 (36%)
Non-R5	16/25 (64%)
X4	7 (28%)
D/M	9 (36%)
IC50 PRO-140, median IQR	0.40 (0.30 - 0.70)

CCR5-tropic virus was observed in 36%, 43% and 36% according to Sanger, NGS and the phenotipic assay, respectively. All 9 viruses with CCR5-tropic phenotype were susceptible *in vitro* to PRO 140, with median IC50 0.4 (0.3-0.7) nM, comparable to the IC50 of the reference wild-type CCR5-tropic AD8 virus (mean IC50 0.7±0.4 nM) (**Table 2**).

Table 3. HIV-1 tropism results according to previous exposure to MVC

CHARACTERISTICS	Previous exposure to MVC (n=8)	No previous exposure to MVC (n=17)	p-value
False positive rate (FPR) by g2p	13.1 (11.0-51.0)	1.4 (0.2-34.0)	0.247
R5 (FPR >10)	4/5 (80%)	5/16 (31%)	0.119
X4(FPR≤10)	1/5 (20%)	11/16 (69%)	
FPR by Sanger	8.3 (1.1-51.3)	4.7 (0.45-33.3)	0.605
R5 (FPR >10)	3/6 (50%)	5/16 (31%)	0.624
X4(FPR≤10)	3/6 (50%)	11/16 (69%)	
Percent of X4 variants by deep sequencing setting FPR at 3.5%	1.05 (0.05-70.5)	32.7 (3.1-96.9)	0.277
R5 (≥2%)	5/8 (63%)	4/17 (24%)	0.087
Non-R5(<2%)	3/8 (37%)	13/17 (76%)	
Phenotypic tropism			
R5	3/8 (38%)	6/17 (35%)	0.999
Non-R5	5/8 (62%)	11/17 (65%)	
R5	3/8 (38%)	6/17 (35%)	0.437
X4	1/8 (12%)	6/17 (35%)	
D/M	4/8 (50%)	5/17 (29%)	
IC50 PRO-140, median IQR	0.70 (0.50-1.2)	0.35 (0.30-0.40)	0.087

IC50 PRO-140 was marginally higher in MVC-naïve patients compared to MVC-exposed [p=0.087, **Table 3**]. Current exposure to MVC was not associated with different PRO 140 activity [current use of MVC: 0.35 (0.30-0.40) nM; no current use of MVC: 0.50 (0.30-0.80) nM; p=0.376].

CONCLUSIONS

In the HTE subjects with MDR virus, the CCR5-tropic strains were susceptible to PRO 140 and they were not significantly influenced by MVC exposure. While a substantial proportion of HTE subjects may harbor X4 or D/M viruses, PRO 140 can play a key role in subjects with very limited therapeutic options and CCR5-tropic virus.

REFERENCES **1.** Trkola A et al. Potent, broad-spectrum inhibition of human immunodeficiency virus type 1 by the CCR5 monoclonal antibody PRO 140. J Virol. 2001;75(2):579-588. **2.** Thompson MA. The return of PRO 140, a CCR5-directed mAb. Curr Opin HIV AIDS. 2018;13(4):346-353.