CROI 2014 - Conference on Retroviruses and Opportunistic Infections, 3-6 March 2014, Boston, MA, USA

How to Characterize Post-Treatment Controllers in Patients Treated During Primary HIV Infection?

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Background

- Post-treatment control (PTC) has been described in HIV-infected patients treated during primary HIV-infection (ANRS Visconti cohort[1]). Characteristics of these patients differ from elite controllers. Markers associated with PTC were normal CD4 cell counts at the time of treatment interruption, normal CD4+/CD8+ ratio, low levels of immune activation and low cell-associated HIV-DNA levels.
- We evaluated the respective parameters in patients of the New Era Study, an ongoing, prospective 7-year clinical trial initiated in 2009 using 5-drug HAART in patients with primary HIV infection (PHI, ≤2 Western blot bands) and in patients with chronic HIV-infection on suppressive PI-based HAART for ≥3 years without prior virologic failure (CHR).
- The primary objectives of the study were to halt residual viral replication in plasma and to achieve depletion of cell-associated HIV-DNA ('proviral DNA') as a step towards (functional) HIV cure which should be proven by treatment interruption.

Methods

Target sample size and major study eligibility criteria

- All patients (N=40) : CD4 nadir >200/µl, no history of AIDS, CCR5 tropism
- PHI group (N=20) : Detectable plasma HIV-RNA, ≤2 Western blot bands
- CHR group (N=20) : Suppressive PI-based HAART for ≥3 years without history of virologic failure

Study intervention

- PHI group : 2 NRTI + 1 PI + MVC (Maraviroc) + RAL (Raltegravir)
- CHR group : Intensification of stable PI-based HAART with MVC + RAL

Objective

Here we describe immunologic and virologic outcomes at month 24, i.e. cell-associated HIV-DNA copies per 10^6 peripheral blood mononuclear cells (PBMC) ('proviral HIV-DNA') and CD8+CD38+ T cell counts for PHI and CHR patients stratified by CD4+ T cell count ≥900/µL and CD4+/CD8+ ratio ≥1.

Analysis population

All patients with a follow-up visit at week 24.

Statistical Analyses

For comparing median values between groups, the Mann-Whitney U test was used. For comparing frequencies, the Fisher´s Exact test was used. The level of significance was p ≤0.05 (n.s. = not significant).

Results

In total, 20 CHR and 22 PHI patients were enrolled. Treatment initiation in PHI patients was within 2.6 weeks after HIV diagnosis. By month 24, there were two study discontinuations in the PHI group. Reasons for discontinuation were 'patient´s wish' (n=1) and 'virological failure' (n=1), i.e. confirmed HIV-RNA >200 cp/mL after month 6, which was not attributed to a switch of viral tropism or the detection of resistance associated mutations.

Study population (analysis population)

Table 1: Baseline characteristics of patients with 24 week follow-up

	Units	CHR group (N=20)	PHI group (N=20)
Female gender	N; %	6; 30.0	1; 4.6
		Median (range)	
Age	years	43.3 (28.0 – 61.2)	39.5 (18.8 – 50.1)
HIV-1 RNA	cp/mL	0.2 (0.1 – 12) single-copy assay	6.1 log (4.5 –7.6) standard assay
Proviral HIV-DNA	log cp/10^6 PBMC	2.5 (1.8 – 3.0)	3.6 (2.8 – 4.1)
CD4+ T cell count	cells/µL	763 (400 – 1370)	485 (302 – 766)
CD4+/CD8+ ratio	---	0.9 (0.4 – 2.0)	0.5 (0.1 – 1.0)
CD8+ CD38+ T cell count	%	14 (2 – 33)	89 (57 – 98)

Antiretroviral combination partners in addition to study drugs RAL + MVC continued in CHR patients or initiated in PHI patients were TDF+FTC+LPV/r (4 and 11), TDF+FTC+DRV/r (2 and 6), TDF+FTC+ATV/r (4 and 2), TDF+FTC+FPV/r (3 and 0), and other NRTI/PI combination partners (7 and 1).

Immunologic markers and cell-associated HIV-DNA at month 24

- Median proviral DNA levels were significantly lower in PHI than in CHR patients (2.1 vs 2.6 log cp/ 10^6 PBMC, p=0.0002).
- Significantly more PHI patients had a CD4+/CD8+ ratio ≥1: 90% (18/20) vs 30% (6/20) (p<0.001).
- CD4 count was ≥900/µL in 55% of PHI (11/20) and 40% of CHR patients (8/20) (p=n.s.).
- 50% of PHI (10/20) and 20% of CHR (4/20) patients fulfilled both criteria regarding CD4+/CD8+ ratio and CD4+ T cell count (p=0.096).
- Proviral DNA levels and CD8+CD38+ cell activation are shown in Table 2.

Table 2: Virologic and immunologic outcomes at month 24

	Units	CHR group		PHI group	
		CD4+ ≥900/µL AND CD4+/CD8+ ratio ≥1	Others	CD4+ ≥900/µL AND CD4+/CD8+ ratio ≥1	Others
n/N; %		4/20; 20%*	16/20; 80%	10/20; 50%*	10/20; 50%
		Median (range)			
Cell-associated HIV-DNA	log cp/10^6 PBMC	2.7 (2.3 – 3.1)	2.6 (1.6 – 3.6)	1. 9 (1.3 – 2.6)	2.3 (1.8 – 2.5)
Cell-ass. HIV-DNA <2 log cp/10^6 PBMC	n; %	0/4; 0%	2/16; 12.5%	6/10†; 60%	1/10†; 10%
Absolute CD8+ CD38+ T cell count	cells/µL	125 (85 – 366)	135 (20 – 366)	75 (8 – 487)	71 (6 – 244)
Relative CD8+ CD38+ T cell count	%	9 (3 – 15)	13 (1 – 23)	9 (1 – 24)	14 (2 – 20)
For PHI: Western blot negative	n; %	---	---	6/10; 60%	4/10; 40%
HIV-1 RNA level ‡					
'target not detected'	n; %	3/4; 75%	6/16; 38%	6/10; 60%	5/8°; 63%
<50 cp/mL		1/4; 25%	9/16; 56%	4/10; 40%	2/8°; 25%
≥50 cp/mL		0/4; 0%	1/16; 6%	0/10; 0%	1/8°; 13%

** p=0.096; † p=0.057; ‡based on site specific standard assays (Roche CAP/Cobas TaqMan HIV-1 Test v2.0 or Abbott RealTime HIV-1 assay m2000/2000rt); ° 2 measurements were excluded because only quantitative branched DNA results were available (both <50 cp/mL)*

Patient safety

Based on the annual study reports including a list of all serious adverse events (SAEs), clinical adverse events (AEs) and laboratory AEs of grades 3 or 4, the independent Data Safety Monitoring Board (DSMB) did not raise concerns about the safety of the study.

Conclusions

- In both groups, early treated PHI patients and selective control patients continuously on suppressive HAART, patients with a CD4 cell count ≥900/µL and a CD4+/CD8+ ratio ≥1 were found. Only for PHI patients, cell-associated HIV-DNA levels were lower in case of normal CD4 count and normal CD4+/CD8+ ratio supporting the hypothesis that preservation of immune functions during PHI and/or early immune reconstitution are associated with a lower HIV reservoir size and potentially higher rates of post treatment controllers.
- There is a worldwide unmet need for effective laboratory markers to predict later post-treatment controlling.

References

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Acknowledgement

Financial support and/or drug supply : AbbVie Deutschland GmbH Co. KG, MSD SHARP & DOHME GMBH, and Pfizer Inc./ViiV Healthcare Ltd.

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ICH Study Center (PD Dr. C. Hoffmann, Dr. K. Schewe, Prof. Dr. H.J. Stellbrink, et al.), Hamburg; Isarpraxis - Private practice Dr. W. Becker, Dr. R. Pauli, Munich; Private Practice for Internal Medicine, Hematology and Oncology (Dr. J. Brust, Prof. Dr. M. Hensel, Dr. C. Ploeger, Dr. D. Schuster) Mannheim; Private Practice for Hematology, Oncology and Infectious Diseases (Dr. F. Mosthaf, Dr. M. Procaccianti, Dr. K. Zutavern-Bechthold, Dr. J. Hagemeyer), Karlsruhe; Private practice Dr. L. Schneider, Fuerth, Germany, Private practice Dr. A. Ulmer, Dr. B. Frietsch, Dr. M. Mueller, Stuttgart; University Hospital Munich, Dept. of Infectious Diseases (PD Dr. U. Seybold, Prof. Dr. J. Bogner), Munich; and MVZ Karlsplatz - HIV Research and Clinical Care Centre (A. Eberhard, Dr. Dr. C. Oldenbuettel, Dr. E. Jaegel-Guedes, Dr. H. Jaeger), Munich, all Germany.

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