

NNRTI, Efavirenz and nevirapine, induce leukocyte-endothelial cell interactions in the microvasculature

Mario M. Andrade ^{1,2}, Francesc Baixauli¹, Ana Blas-García¹, Juan V. Esplugues^{1,3}, Ángeles Álvarez^{1,3}.

¹ Department of Pharmacology, Faculty of Medicine, University of Valencia (Spain)

² Foundation BANCAJA and Foundation Juan Esplugues (Spain)

³Ciberehd, Faculty of Medicine, University of Valencia (Spain)

INTRODUCTION

Combined antiretroviral therapy has had a dramatic effect improving prognosis and quality of life of people infected with Human Immunodeficiency Virus (HIV). Once the survival issue is solved, the long-term toxicities become important. In particular, metabolic abnormalities including dyslipidemia, insulin resistance, redistribution of body fat and cardiovascular diseases.

It has been describe a higher risk of developing cardiovascular diseases in antiretroviral drug-treated patients compared to untreated (Frisi-Moller et al, 2003; Currier et al, 2003).

Since patients receive various drugs simultaneously, it has been difficult to determine the role of each particular antiretroviral group or specific agent in these side effects (The DAD study group, 2007).

AIM

To analyze the acute effects of widely used antiretroviral agents from different pharmacological groups:

- NNRTIs (Non Nucleoside Reverse Transcriptase Inhibitors): Efavirenz and Nevirapine
- NRTIs (Nucleoside Reverse Transcriptase Inhibitors): Lamivudine and Zidovudine

- PIs (Protease Inhibitors): Atazanavir and Lopinavir* on leukocyte recruitment as one of the first steps in the pathogenesis of atherosclerosis.

* Strengthen by Ritonavir like in clinical protocols.

REFERENCES

• Frisi-Moller et al. Combination antiretroviral therapy and the risk of myocardial infarction. N. Engl. J. Med. 349: 1993-2003, 2003.

• Currier JS et al. Coronary heart disease in HIV-infected individuals. J. Acquir. Immune Defic. Syndr. 33: 506-512, 2003.

• The DAD study group. Class of antiretroviral drugs and the risk of myocardial infarction. N. Engl. J. Med. 356: 1723-1735, 2007.

METHODS

•Pentobarbital **anaesthetised SD rats** (65 mg/kg, i.p.) were used

•**Intravital video microscopy** studies were made in mesenteric postcapillary venules superfused with warmed bicarbonate buffer saline

•**Experimental protocol:**



Experiments were performed in groups of n≥4 animals

Antiretroviral administrations:

Efavirenz (NNRTI): 25, 50, 85 or 160 mg/kg, p.o.

Nevirapine (NNRTI): 50, 100, 150, 300 mg/kg, p.o.

Lamivudine (NRTI): 3, 30, 60, 100 mg/kg, p.o.

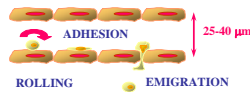
Zidovudine (NRTI): 1.5, 5 mg/kg, p.o.

Atazanavir (PI): 25, 50 or 100 mg/kg, p.o.

Lopinavir/Ritonavir (PI): 53, 106 mg/kg, p.o./13, 26 mg/kg, p.o.

Doses were chosen according to the literature in order to mimic plasma levels clinically present in humans (3-30 μM).

Parameters determined:



Leukocyte:

- Leukocyte rolling flux: cells/min
- Leukocyte adhesion: cells/100 μm venule
- Leukocyte emigration: cells/field

Haemodynamic parameters:

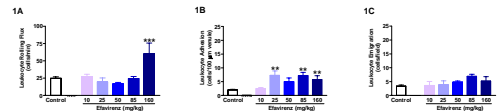
Venular diameter (μm), mean arterial blood pressure (mmHg) and Shear rate (s⁻¹) were not affected by any of the treatments.

•**Statistical analysis:**

All data are expressed as mean±SEM. Data were analyzed using an analysis of variance (one-way-ANOVA) with a Newman-Keuls correction for multiple comparisons. Significance was set at p<0.05.

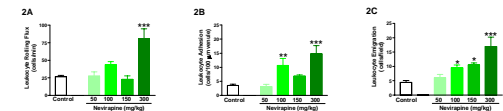
RESULTS

Figure 1: Actions of efavirenz (NNRTI) on leukocyte responses on rat mesenteric venules



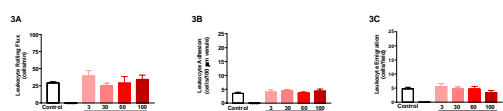
Efavirenz induces a significant increase on leukocyte rolling flux and adhesion, however it does not have effect on leukocyte emigration.

Figure 2: Actions of nevirapine (NNRTI) on leukocyte responses on rat mesenteric venules



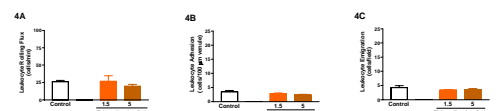
Nevirapine causes a significant increase on leukocyte rolling flux, adhesion and emigration.

Figure 3: Actions of lamivudine (NRTI) on leukocyte responses on rat mesenteric venules



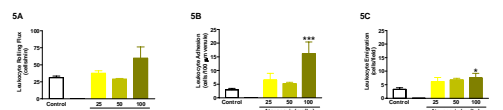
Lamivudine does not promote any effect on leukocyte parameters.

Figure 4: Actions of zidovudine (NRTI) on leukocyte responses on rat mesenteric venules



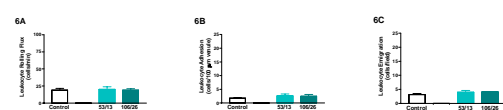
Zidovudine does not induce any change on leukocyte parameters.

Figure 5: Actions of atazanavir (PI) on leukocyte responses on rat mesenteric venules



Atazanavir promotes a significant increase on leukocyte adhesion and emigration, but it does not have effect on leukocyte rolling flux.

Figure 6: Actions of lopinavir (PI) on leukocyte responses on rat mesenteric venules



Lopinavir (strengthen by ritonavir) does not cause any effect on leukocyte rolling flux, adhesion or emigration.

CONCLUSION

Our results indicate that acute exposure to clinic concentrations of NNRTI (efavirenz and nevirapine) and the PI (atazanavir) but not lopinavir or NRTI (lamivudine and zidovudine), induces leukocyte recruitment. This suggest that these drugs can be implicated in the preliminary events that lead to the cardiovascular complications observed in HIV-infected patients on combined antiretroviral therapy.