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Cardiovascular Diseases Associated Inflammatory Biomarker Levels in A Small Cohort of HIV-1 Infected Patients Deintensificated from Abacavir/Lamivudine/Dolutegravir to Lamivudine Plus Dolutegravir

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1. Introduction

Following the successful introduction of combined antiretroviral therapy (cART), a dramatic decrease in viral burden and opportunistic infections along with a consistent increase in life expectancy has been observed in human immunodeficiency virus (HIV) infected patients [1]. This deep change in the HIV disease evolution has determined that HIV positive subjects were effectively monitored for several alterations of many tissue and organs due to HIV chronic disease and antiretroviral treatment for example, cardiovascular system, bone, adipose tissues, kidney and central nervous system represent the major target of these structural and functional damages during HIV infection.

In particular, cardiovascular diseases (CVD) were considered important clinical complications in the HIV patient and represent a leading cause of death among HIV-positive patients, accounting for approximately 11% of the total deaths in this population [2]; the risk of CVD is higher in HIV positive individuals compared with HIV negative people, and particularly the reported myocardial infarction (MI) incidence in cohort study ranges from 3 to 11 cases per 1000 patients a year in HIV- positive individuals against 2 to 7 cases per 1000 patients-years in HIV-negative population [3, 4].

Although initial studies indicated a higher prevalence of traditional CVD risk factors in HIV infected population [5, 6] as a possible cause, the molecular mechanisms of increased CVD risk in HIV still remain incompletely defined and should be probably attributable to a combination of multiple factors, including both direct and indirect effects of HIV infection on metabolism. Evidence from experimental and observational studies [7, 8] in recent years suggested a more important role of HIV itself in contributing to CVD.

Endothelial dysfunction due to gp120, Tat and Nef proteins have been identified as a critical link between infection, inflammation, immune activation, atherosclerosis and cardiovascular system. Moreover, ART may play a role in the exacerbation of risk factors for CVD [9]; since the presentation of findings from the Data Collection on Adverse Events of Anti-HIV Drugs (D: A: D) study in 2008 demonstrating a 90% increased risk of MI in HIV- positive individuals receiving ART regimens including abacavir (ABC), subsequent studies, conducted by FDA [10], GlaxoSmithKline [11] and independent researchers [12], to investigate this risk have yielded conflicting results.

Although more recent studies have shown an effective increased risk of CVD associated with use of ABC, many results did not reach statistical significance [13-16]. The absence of a demonstrated underlying biological mechanism for such a risk added interest and confusion about the question, as well as the higher prevalence of risk factors for CVD, such as renal impairment and substance abuse among abacavir

recipients; in addition, a recent meta-analysis suggests that relative risk (RR) for MI is increased within a 6 months' exposure to ABC (RR=1.61; 95% confidence interval: 1.48–1.75) and in cART-naive population [18].

While the published evidence remains conflicting and a plausible biological mechanism for this potential association has not yet been identified, in the following study we have tried to verify whether, after introduction of ABC and its discontinuation in the contest of HAART deintensification, common metabolic markers CVD related such as glucose, LDL, HDL, total cholesterol and triglycerides and inflammatory biomarkers such as IL-6 and D-dimer could change in a small cohort of HIV-1 infected patients.

2. Materials and Methods

As described in a previous article [21], from March to December 2016 we enrolled 20 HIV-1 infected patients. 17 patients were still in follow-up (12 men and 5 women) in August 2020, and all were taking lamivudine plus dolutegravir. HIV-1 infected patients were not co-infected with hepatitis B and/or hepatitis C viruses. All the enrolled subjects gave informed consent to all procedures in accordance with the Helsinki Declaration.

Blood samples were collected at HIV-1 infection diagnosis before starting a three-drugs regimen consisting in ABC/3TC/ DTG (T0), at 12 months (T2) and 12 months (T3) after therapy deintensification to lamivudine plus DTG (DITT; deintensification treatment time).

Inclusion criteria included: I) naive to ART patients affected by HIV chronic infection, II) undetectable HIV-RNA levels (< 50 copies/ml) for over 12 months with a three-drugs ART treatment consisting in ABC/3TC/DGT at T2, III) undetectable HIV-RNA levels (< 50 copies/ml) for over 12 months with a dual ART regimen consisting in lamivudine plus DGT at T3, iv) absence of adverse drug reactions with the proposed regimens, v) no use of statins and lipid-lowering therapy at the enrolling time and at DITT.

Blood samples were collected by venipuncture during the follow up, 30 days before the DITT (T2) and 12 months after the DITT (T3). Every blood sample collected consisted in quantitative plasmatic determination of glucose, IL6, D-Dimer and plasmatic lipids such as triglycerides, LDL, HDL and total cholesterol.

Biomarkers plasmatic levels were evaluated with specific commercial kits. For IL-6 we used Human IL-6 high sensitivity ELISA kit (Diaclone, Besancon, France); for D-dimer RayBio Human D-dimer ELISA Kit (RayBiotech, Norcross, GA, USA). Values of different samples were evaluated between the different time groups (T1, T2 and T3 groups) with statistical non-parametric procedures such as Wilcoxon test and Friedmann test using GraphPad Prism 7 software. Data were considered significant with p value <0.05.

3. Results

We analyzed a cohort of 17 HIV-1 infected patients (12 men and 5 women, aged from 24 to 70 years, average 41.35 years old) infected by HIV-1 B subtypes. All mean and median values for each group are reported in (Table 1), together with normal reference values. Cytokine IL-6 did not show any significant amount of variation among the three groups of samples (Group 1 vs 2 p=0.83; Group 1 vs 3 p=0.65; Group 2 vs 3 p= 0.97 Wilcoxon test). The statistical analysis of the three groups confirmed these data (p=0.645; Friedmann test). Similarly, D-dimer did not significantly change its levels in serum (Group 1 vs 2 p=0.32; Group 1 vs 3 p=0.38; Group 2 vs 3 p= 0.69 Wilcoxon test; p=0.53 Friedmann test).

Table 1: All mean and median values for each group compared with normal reference values

Group 1	Mean	Median	Normal values
IL-6	0.80±0.37 pg/ml	0.77 pg/ml	0-4.72 pg/ml
D-Dimer	209.3±33.4 ng/ml	221 mg/dl	<500 ng/ml
Total cholesterol	168.2±31.82 mg/dl	173 mg/dl	<200 mg/dl
HDL	51.56±18.69 mg/l	47.5 mg/dl	>48 mg/dl
LDL	104.8±21.11 mg/l	107.5 mg/dl	<130 mg/dl
Triglycerides	99.63±39.56 mg/dl	91.5 mg/dl	<150 mg/dl
Glycemia	85.65±8.95 mg/dl	84 mg/dl	63-99 mg/dl
Group 2	Mean	Median	Normal values
IL-6	0.96±0.82 pg/ml	0.675 pg/ml	0-4.72 pg/ml
D-Dimer	217.8±34.9 ng/ml	232.5 mg/dl	<500 ng/ml
Total cholesterol	174.1±44.35 mg/dl	181.5 mg/dl	<200 mg/dl
HDL	49.19±11.49 mg/dl	47.5 mg/dl	>48 mg/dl
LDL	113.5±27.18 mg/dl	109 mg/dl	<130 mg/dl
Triglycerides	112.3±55.37 mg/dl	102 mg/dl	<150 mg/dl
Glycemia	86.12±9.61 mg/dl	82 mg/dl	63-99 mg/dl
Group 3	Average	Mean	Normal values
IL-6	0.90±0.69 pg/ml	0.84 pg/ml	0-4.72 pg/ml
D-Dimer	220.7±20.64 pg/ml	229 mg/dl	<500 ng/ml
Total cholesterol	180.2±39.85 mg/dl	173 mg/dl	<200 mg/dl
HDL	48.44±14.38 mg/dl	48 mg/dl	>48 mg/dl
LDL	109.9±29.46 mg/dl	107.5 mg/dl	<130 mg/dl
Triglycerides	104.6±44.95 mg/dl	95 mg/dl	<150 mg/dl
Glycemia	84.76±11.26 mg/dl	84 mg/dl	63-99 mg/dl

The analysis of serum glucose(Group 1 vs 2 p=0.94; Group 1 vs 3 p=0.97; Group 2 vs 3 p= 0.88 Wilcoxon test; p=0.67 Friedmann test), total cholesterol (Group 1 vs 2 p=0.07; Group 1 vs 3 p=0.65; Group 2 vs 3 p= 0.41 Wilcoxon test; p=0.21 Friedmann test), cholesterol HDL (Group 1 vs 2 p=0.92; Group 1 vs 3 p=0.89; Group 2 vs 3 p= 0.58 Wilcoxon test; p=0.82 Friedmann test), cholesterol LDL (Group 1 vs 2 p=0.09; Group 1 vs 3 p=0.88; Group 2 vs 3 p= 0.36 Wilcoxon test; p=0.71 Friedmann test) and triglycerides (Group 1 vs 2 p=0.58; Group 1 vs 3 p=0.93; Group 2 vs 3 p= 0.39 Wilcoxon

test; p=0.67 Friedmann test) did not demonstrate significant level variations.

4. Discussion

Since the publication of the D: A: D study, a number of possible mechanisms have emerged as potential mediators of the abacavir effect. In ACTG 5202, participants receiving abacavir in the low viral load stratum (<100 000 copies/ml) had higher rates of cholesterol elevations compared with controls. In addition, abacavir has been related to several processes, which may lead to accelerated vascular disease such as platelet activation [26], hyperlipidemia [27], T-lymphocyte activation, abnormal endothelial function and vascular inflammation [23, 28]. Hypersensitivity reaction and concomitant inflammatory processes may affect platelet and endothelial function. Of note, HLAB5701 testing to prevent abacavir hypersensitivity reactions was not the standard of care during the conduct of this study. Therefore, it is possible that the risk of CVD may be lower in contemporarily treated patients who are unlikely to experience abacavir hypersensitivity reactions, but more investigations are necessary to elucidate this point.

Moreover, D: A: D study results showing a reversal of risk of CVD within 6 months of discontinuation of abacavir prompted investigators to search for a relatively rapidly acting underlying biological mechanism able to correlate CVD with abacavir exposure. A possible role of inflammatory biomarkers such as high sensitivity c-reactive protein (hsCRP) and interleukin-6 (IL-6) in association with CVD among abacavir users was proposed by the SMART/INSIGHT study [28], while other studies focused on IL-6, selectin P and E, D-dimer, vascular adhesion molecule-1, intercellular adhesion molecule-1, and tumor necrosis factor alpha; all of these studies showed no increased levels in the setting of abacavir exposure [29, 30]. While the association between lipid metabolism, flogosis and CVD are widely described in scientific literature, proving causation for any particular biomarker of inflammation has been difficult.

IL-6 signals a downstream proinflammatory response by activating membrane-bound IL-6 receptors (IL-6R) on the cell surface. IL-6 and IL-6R are demonstrated to have a direct and dose-dependent role directly causing higher blood levels on CRP responsible for proinflammatory settings linked to CVD onset.

Moreover, D-dimer has been identified as a pro-atherogenic factor, being hypercoagulability a recognized risk factor for CVD; because of that, this study included monitoring these two biomarkers blood levels on a total of 24-months

Many studies estimated abacavir's role in causing endothelial dysfunction, reporting that ABC would affect lower brachial artery flow mediated vasodilation, a measure of endothelial dysfunction, as an independent prediction factor [8, 27]; switching from ABC to tenofovir was also associated to a Framingham risk score improvement [31].

In a recent RCT, anyway, no evidence of endothelial dysfunction from abacavir use as compared to tenofovir was found [32].

Platelet aggregation and reactivity, potentially leading to thrombosis phenomena, have also been associated by ABC's exposure in vitro and in vivo (33,34); particularly, various platelet agonists, increased in plasma after ABC assumption (e.g. adenosine diphosphate, collagen, epinephrine, and thrombin receptor-activating peptide) [33], this observation being due to a documented decreased production of cyclic guanosine monophosphate, an inhibitor of platelet aggregation and secretion [33, 34], but more further studies are needed to confirm these data.

Existing literature on plausible underlying biological mechanisms are summarized in a recent systematic review, collecting in vivo and in vitro results [17]: ABC 's structural likeness to endogenous purines possessing pro-inflammatory and pro-thrombotic potential may finally explain its role as a vascular inflammation inducer via leukocyte–endothelial cell interactions, causing cardiovascular implications , but how such acute and reversible mechanisms may correlate with recent clinical findings of CVD risk from cumulative exposure beyond 6 months is still unclear [35, 36].

With the literature demonstrating such controversial results, the search for plausible biological explanations goes on. Recent ABC assumption is associated with 60% increased risk of CVD not attenuated after adjusting for substance use, renal dysfunction, and several other potential confounders. The finding of an increased risk of CVD associated with abacavir use among ART-naive individuals may be more suggestive of a causal relationship; many of the studies concerning ABC potential risk were observational, whose results may be confounded by unmeasured risk factors.

While this risk appears to be reversible upon discontinuation of abacavir, further research is necessary to confirm this in view of recent studies that showed evidence of increased risk from cumulative exposure beyond 6 months. Our data showed, after ABC introduction and discontinuation in antiretroviral therapy based on the association of ABC/3TC/ DTG, the absence of significant variations in the serum levels of different inflammatory and metabolic markers. In fact, glycemia, triglycerides, HDL, LDL, Il-6 and total cholesterol showed negligible quantitative change at all three tested time points.

Finally about a possible role of inflammatory biomarkers (e.g.D-dimer and interleukin-6 IL-6) in association with CVD among abacavir users, our results, even though in a small cohort of HIV-infected patients, would confirm the results of other studies showing that IL-6 and D-dimer are not elevated in the setting of abacavir exposure

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