Atherosclerosis 284 (2019) 216–217

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Editorial

PCSK9 in HIV infection: New opportunity or red herring?

ARTICLE INFO

Keywords:
HIV infection
PCSK9

While modern drug therapy has improved survival of patients with immune deficiency virus (HIV) infection, the rate of myocardial infarction among affected individuals has increased by 50% [1]. This is not explicable by conventional cardiovascular (CV) risk factors and could relate to HIV infection itself or to specific drug treatments [2].

In this issue of *Atherosclerosis*, Gencer et al. [3] aimed at evaluating PCSK9 as a risk determinant of atherosclerotic CV risk in HIV$^+$ patients taking into account that among these subjects, unhealthy lifestyles, *e.g.* use of marijuana, may have further raised risk [4]. In this cross-sectional study including 239 HIV$^+$ patients of the Swiss HIV Cohort Study, the authors found that the potential predictors linked to variation in plasma PCSK9 levels were daily marijuana consumption and low CD4 counts (< 200 cell/μL) [3]. Considering that the mechanisms underlying HIV-associated atherosclerosis and the ability to predict which individual is at higher risk are still unclear, the present findings highlight some important points worthy of consideration, *i.e.* does the reported association with PCSK9 afford a new therapeutic opportunity or is it a red herring?

In the conclusion, Gencer et al. advocate to plan a randomized controlled trial assessing PCSK9 inhibitors in HIV$^+$ patients to improve control of dyslipidemia [3]. Indeed, if we follow the axioma that (i) in the present study higher PCSK9 levels correspond to higher levels of total and LDL-cholesterolemia and (ii) in previous findings, risk estimating pooled cohort equations performed better than data-derived models incorporating HIV-specific variables [5], LDL-C lowering may be considered a valid therapeutic approach to be pursued. A retrospective cohort study recently showed that in HIV$^+$ patients statin initiation led to a lower than expected LDL-C reduction, highlighting an unmet need for atherosclerotic cardiovascular disease risk reduction [6].

Although PCSK9 inhibition has been associated to an indisputable CV benefit in non-HIV$^+$ subjects, it should be considered that, besides dyslipidemia, inflammation may play a key role in the atherosclerotic process in people living with HIV [7]. Compared with people without HIV and C-reactive protein (CRP) levels in the normal range, the odds ratio was found to be 2-fold higher in those with increased CRP and HIV infection [8].

At present, the lack of efficacy of PCSK9 inhibitors on CRP [9] does not indicate a prominent role for these agents in the HIV setting, although data on RCTs evaluating efficacy on LDL-C of evolocumab in HIV$^+$ subjects with hyperlipidemia and/or mixed dyslipidemia (NCT02833844) are eagerly awaited. A different primary endpoint is that of the EPIC-HIV (effect of PCSK9 inhibition on CV Risk in treated HIV Infection) study with alirocumab evaluating PCSK9 inhibition on vascular inflammation, endothelial function, and non-calcified plaque (NCT03207945). It should be noted that in HIV$^+$ patients inhibition of IL-1 β by canakinumab has led to a reduction of arterial inflammation [10]. Indeed, Subramanian et al. demonstrated that individuals with HIV but without known coronary artery disease had an increased arterial inflammation [11]. For this reason, evaluation of lipoprotein (a) [Lp(a)] levels, a marker of arterial wall inflammation and CV risk [12], would have strengthened the conclusions raised by Gencer et al. [3]. Lp (a) levels are raised by antiretroviral therapy contributing to promote atherosclerotic CV disease risk in HIV$^+$ individuals [13].

In the still debated scenario of HIV and elevated CV risk factors, identifying nontraditional risk factors, *e.g.* PCSK9 levels, is another hint. In the present manuscript, PCSK9 levels, in the same range of those in non-HIV infected people, do not seem related to high CV risk, as assessed by the Framingham risk score [3]. The clinical relevance of measuring PCSK9 plasma levels may be hindered by the complexity of PCSK9 biology at the transcriptional and translational levels being lipid lowering therapies, *e.g.* statins, and inflammation, *i.e.* HCV co-infection, possible triggers [14]. All of these confounders were taken into consideration by the authors who chose a statin naïve cohort with 1% of HIV/HCV co-infections. Indeed, in a previous report, Kohli et al. showed that HIV$^+$ patients on statin therapy and co-infected with HCV had higher PCSK9 levels *vs* HIV-monoinfected individuals [15]. Moreover, the Authors did not find any association between PCSK9 levels and the use of abacavir, a protease inhibitor previously associated with an increased risk of MI [16], independent of dyslipidemia [17].

Finally, although in the general population the effect of marijuana on CV risk factors and outcomes, including stroke and myocardial

DOI of original article: https://doi.org/10.1016/j.atherosclerosis.2019.02.015

https://doi.org/10.1016/j.atherosclerosis.2019.03.002
Received 4 March 2019; Accepted 6 March 2019
Available online 09 March 2019

infarction, is unclear [18], marijuana use *per se* represents a CVD risk factor in HIV-infected individuals, independent of tobacco smoking and traditional risk factors [19]. In this scenario, the findings by Gencer et al., reporting daily marijuana consumption as a potential predictor of raised PCSK9 levels, may put PCSK9 at the crossroad between marijuana consumption and the detrimental effects on atherosclerosis. However, the lack of any pathophysiological mechanism beyond this assumption along with the concept that low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice [20], leave this point open.

The conclusion by Gencer et al. is that the use of PCSK9 inhibitors to improve the control of dyslipidemia in HIV^+ patients should be encouraged. However, two open questions remain: the long-term safety of these agents and the cost-effectiveness, this last possibly restraining patients' access to the drug and the impact on long-term adherence [21]. Moreover, it should be considered that HIV^+ patients often display hypertriglyceridemia with reduced HDL-C, particularly in cases of onset at a young age [22], frequently of difficult drug handling in daily practice. Dysfunctional HDL from HIV^+ individuals has been also found to have an enhanced ability to promote foam cell formation *ex vivo*, as well as to have a reduced antioxidant function [23]. Reports on triglyceride lowering/HDL raising drugs (*e.g.* fenofibrate or EM niacin), despite raising HDL-C, failed to show benefit on endothelial function or inflammatory markers in patients with well controlled HIV infection [24]. Since a possible renal risk of fibrates [25], may be feared in HIV patients, the use of n-3 PUFAs, proven to be effective in HIV associated hypertriglyceridemia [26], is worthy of evaluation, after the positive outcome of the secondary CV prevention REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial) study using high dose purified icosapent ethyl [27].

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflicts of interest with respect to this manuscript.

References

[1] M.S. Freiberg, C.C. Chang, L.H. Kuller, et al., HIV infection and the risk of acute myocardial infarction, JAMA Intern. Med. 173 (2013) 614–622.
[2] P.Y. Hsue, D.D. Waters, Time to recognize HIV infection as a major cardiovascular risk factor, Circulation 138 (2018) 1113–1115.
[3] B. Gencer, S. Pagano, N. Vuilleumier, et al., Clinical, behavioral and biomarker predictors of pcsk9 levels in hiv-infected patients naïve of statin therapy: a cross-sectional analysis from the swiss hiv cohort, Atherosclerosis (2019) 253–259.
[4] S. Raposeiras-Roubin, E. Abu-Assi, A. Iniguez-Romo, Tobacco, illicit drugs use and risk of cardiovascular disease in patients living with HIV, Curr. Opin. HIV AIDS 12 (2017) 523–527.
[5] M.J. Feinstein, R.M. Nance, D.R. Drozd, et al., Assessing and refining myocardial infarction risk estimation among patients with human immunodeficiency virus: a study by the centers for AIDS research network of integrated clinical systems, JAMA Cardiol. 2 (2017) 155–162.
[6] G.A. Burkholder, P. Muntner, H. Zhao, et al., Low-density lipoprotein cholesterol response after statin initiation among persons living with human immunodeficiency virus, J. Clin Lipidol. 12 (2018) 988–998 e985.
[7] J.H. Stein, P.Y. Hsue, Inflammation, immune activation, and CVD risk in individuals with HIV infection, J. Am. Med. Assoc. 308 (2012) 405–406.
[8] V.A. Triant, J.B. Meigs, S.K. Grinspoon, Association of C-reactive protein and HIV infection with acute myocardial infarction, J. Acquir. Immune Defic. Syndr. 51 (2009) 268–273.
[9] M. Ruscica, N. Ferri, A. Corsini, et al., PCSK9 antagonists and inflammation, Atherosclerosis 268 (2018) 235–236.
[10] P.Y. Hsue, D. Li, Y. Ma, et al., IL-1beta inhibition reduces atherosclerotic inflammation in HIV infection, J. Am. Coll. Cardiol. 72 (2018) 2809–2811.
[11] S. Subramanian, A. Tawakol, T.H. Burdo, et al., Arterial inflammation in patients with HIV, J. Am. Med. Assoc. 308 (2012) 379–386.
[12] S. Tsimikas, A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies, J. Am. Coll. Cardiol. 69 (2017) 692–711.
[13] B. Enkhmaa, E. Anuurad, W. Zhang, et al., Effect of antiretroviral therapy on allele-associated Lp(a) level in women with HIV in the Women's Interagency HIV Study, J. Lipid Res. 59 (2018) 1967–1976.
[14] C. Macchi, M. Banach, A. Corsini, et al., Changes in circulating pro-protein convertase subtilisin/kexin type 9 levels - experimental and clinical approaches with lipid-lowering agents, Eur. J. Prev. Cardiol. (2019) 2047487319831500.
[15] P. Kohli, P. Ganz, Y. Ma, et al., HIV and hepatitis C-coinfected patients have lower low-density lipoprotein cholesterol despite higher proprotein convertase subtilisin kexin 9 (PCSK9): an apparent "PCSK9-lipid paradox, J. Am. Heart Assoc. 5 (2016).
[16] G. Guaraldi, P. Raggi, Antiretroviral therapies and cardiovascular risk: true or false? Atherosclerosis 263 (2017) 313–314.
[17] P. Maggi, C. Bellacosa, A. Leone, et al., Cardiovascular risk in advanced naive HIV-infected patients starting antiretroviral therapy: comparison of three different regimens - PREVALEAT II cohort, Atherosclerosis 263 (2017) 398–404.
[18] D. Ravi, M. Ghasemiesfe, D. Korenstein, et al., Associations between marijuana use and cardiovascular risk factors and outcomes: a systematic review, Ann. Intern. Med. 168 (2018) 187–194.
[19] D.R. Lorenz, A. Dutta, S.S. Mukerji, et al., Marijuana use impacts midlife cardiovascular Events in HIV-infected men, Clin. Infect. Dis. 65 (2017) 626–635.
[20] S. Steffens, N.R. Veillard, C. Arnaud, et al., Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice, Nature 434 (2005) 782–786.
[21] N.C. Ward, M.M. Page, G.F. Watts, PCSK9 inhibition 2018: riding a new wave of coronary prevention, Clin. Sci. (Lond.) 133 (2019) 205–224.
[22] E. Arrive, J.P. Viard, B. Salanave, et al., Metabolic risk factors in young adults infected with HIV since childhood compared with the general population, PLoS One 13 (2018) e0206745.
[23] T.A. Angelovich, A.C. Hearps, M.N. Oda, et al., Dysfunctional high-density lipoprotein from HIV+ individuals promotes monocyte-derived foam cell formation in vitro, AIDS 31 (2017) 2331–2336.
[24] M.P. Dube, L. Komarow, C.J. Fichtenbaum, et al., Extended-release niacin versus fenofibrate in HIV-infected participants with low high-density lipoprotein cholesterol: effects on endothelial function, lipoproteins, and inflammation, Clin. Infect. Dis. 61 (2015) 840–849.
[25] R.L. Attridge, W.D. Linn, L. Ryan, et al., Evaluation of the incidence and risk factors for development of fenofibrate-associated nephrotoxicity, J. Clin Lipidol. 6 (2012) 19–26.
[26] N. Amador-Licona, T.A. Diaz-Murillo, G. Gabriel-Ortiz, et al., Omega 3 fatty acids supplementation and oxidative stress in HIV-seropositive patients. A Clinical Trial, PLoS One 11 (2016) e0151637.
[27] D.L. Bhatt, P.G. Steg, M. Miller, et al., Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia, N. Engl. J. Med. 380 (2019) 11–22.

Massimiliano Ruscica*
Department of Pharmacological and Biomolecular Sciences, Università Degli Studi di Milano, Milan, Italy
E-mail address: massimiliano.ruscica@unimi.it.

Gerald F. Watts
School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Australia
Lipid Disorders Clinic, Cardiometabolic Services, Department of Cardiology, Royal Perth Hospital, Perth, Australia
Familial Hypercholesterolaemia Australia Network, Australia

Cesare R. Sirtori
Centro Dislipidemie, A.S.S.T. Grande Ospedale Metropolitano Niguarda, Milan, Italy

* Corresponding author. Department of Pharmacological and Biomolecular Sciences, Via Balzaretti 9, 20133, Milano, Italy. Tel.: 00390250318220; fax: 00390250318297.