Atherosclerosis 291 (2019) 122–123

Contents lists available at ScienceDirect

Atherosclerosis

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

Editorial

sCD40L: An overestimated marker for cardiovascular risk prediction?

ARTICLE INFO

Keywords:
sCD40L
Cardiovascular risk
Vascular inflammation

Vascular inflammation was suggested as an important contributor to atherosclerosis half a century ago [1]. Lately, and finally, in the CANTOS Trial [2], the application of 150 mg canakinumab, a monoclonal antibody targeting interleukin-1β, resulted in a 15% relative risk reduction, independent of lipid lowering. Thus, the last remaining doubters of the inflammation hypothesis in general were silenced. In addition, plaques in the artery wall were demonstrated to rupture more likely when inflammation is present; and plaque rupture is a common cause for myocardial infarction and cardiovascular death [2,3]. Over the years, multiple players in the conundrum of inflammation, atherosclerosis development and progression, as well as associated events, have been identified; however, which strategies beside the inhibition of interleukin-1β will be successful remains to be elucidated.

In this issue of *Atherosclerosis*, Gergei et al. [5] investigated the potential role of soluble CD40L as a marker of cardiovascular and all-cause mortality. The well-defined study was embedded in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. 2759 patients were enrolled between 1997 and 2000 and followed for roughly 10 years. 111 of those patients died within one year, 819 died within the observation period. The majority of deaths was attributed to a cardiovascular cause (80 after one year and 517 after roughly 10 years).

At one year, there was a significant increase in all-cause mortality in patients with high sCD40L levels overall (Hazard Ratio (HR): 1.65 (1.03–2.63), $p = 0.04$), which disappeared after full adjustment for age, sex, smoking, systolic blood pressure, diastolic blood pressure, low density lipoprotein cholesterol, high density lipoprotein cholesterol, coronary artery disease status, eGFR, and C-reactive.

However, the authors identified significant associations of one-year all-cause mortality and sCD40L in three subgroups: hypertension (HR: 2.33 (1.20–4.53), $p = 0.01$), established coronary artery disease (CAD; HR: 2.47 (1.32–4.62), $p = 0.01$), and heart failure with preserved ejection fraction (HFpEF, HR: 5.62 (1.51–20.87), $p = 0.01$).

No associations between one-year cardiovascular mortality and sDC40L levels were found. A significant association between sCD40L levels and cardiovascular mortality could only be shown in subgroup analyses for patients with coronary artery disease (HR: 2.25 (1.08–4.70), $p = 0.03$) and HFpEF (HR: 7.39 (1.52–35.91), $p = 0.01$).

Strikingly, there was no significant association between long term all-cause or cardiovascular mortality overall or in subgroup analyses apart from a significantly lower cardiovascular mortality rate in the second sCD40L tertile (0.81 (0.66–1.00), $p = 0.05$).

Although the associations between sCD40L and outcome are limited, there are some noteworthy exceptions: while initially significant associations between sCD40L and CAD/HFpEF could be explained, the lack of significance at a later time is much more difficult to grasp. Indeed, sCD40L has been described as a prognostic marker for one-year survival in liver transplantion [6], and previous cardiovascular studies have described significant associations in short term settings and during acute cardiovascular events [7]. Regarding the non-significance of long-term mortality, the authors suggest possible fluctuations of sCD40L levels over time as a limitation. In addition, just recently, a study demonstrated that blood pressure affects sCD40L levels [8]. Thus, variable blood pressure control over a long observation period time, could confound an association between sCD40L and mortality. Furthermore, “classic” cardiovascular medications such as platelet aggregation inhibitors, statins, angiotensin-converting enzyme inhibitors, as well as many others, were demonstrated to reduce both sCD40L and cardiovascular risk [9].

Thus, another kind of study would be needed to allow competing risk analysis for the effect of the diverse drugs on sCD40L as well as on mortality, and then to investigate whether sCD40L independently from all drugs applied still exhibited an influence on outcome.

If such a study because of so many insecurities is considered unreasonable, a Phase 1–3 intervention study program might be an easier choice.

Summarizing, sCD40L might still play a role as an outcome marker and might have the potential as a future therapeutic target in an acute to short-term setting. The data of Gergei et al. [5], however, would argue against a long-term cardiovascular outcome trial.

DOI of original article: https://doi.org/10.1016/j.atherosclerosis.2019.09.004

https://doi.org/10.1016/j.atherosclerosis.2019.10.006
Received 3 October 2019; Accepted 9 October 2019
Available online 16 October 2019
0021-9150/

Declaration of competing interest

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

References

[1] R.N. Poston, D.F. Davies, Immunity and inflammation in the pathogenesis of atherosclerosis. A review, Atherosclerosis 19 (1974) 353–367.
[2] P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, R.J. Glynn, CANTOS Trial Group, Antiinflammatory therapy with canakinumab for atherosclerotic disease, N. Engl. J. Med. 377 (2017) 1119–1131.
[3] A.C. van der Wal, A.E. Becker, C.M. van der Loos, et al., Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology, Circulation 89 (1994) 36–44.
[5] I. Gergei, T. Kalsch, H. Scharnagl, et al., Association of soluble CD40L with short-term and long-term cardiovascular and all-cause mortality: the Ludwigshafen risk and cardiovascular health, (LURIC) study, Atherosclerosis 291 (2019) 127–131. Atherosclerosis.
[6] L. Lorente, S.T. Rodriguez, P. Sanz, et al., High serum soluble CD40L levels previously to liver transplantation in patients with hepatocellular carcinoma are associated with mortality at one year, J. Crit. Care 43 (2018) 316–320.
[7] H. Pusuroglu, O. Akgul, M. Erturk, et al., Predictive value of elevated soluble CD40 ligand in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction, Coron. Artery Dis. 25 (2014) 558–564.
[8] M. Guzel, M.T. Dogru, V. Simsek, et al., Influence of circadian blood pressure alterations on serum SCUBE-1 and soluble CD40 ligand levels in patients with essential hypertension, Am. J. Cardiovasc. Dis. 9 (2019) 42–48.
[9] C. Antoniades, C. Bakogiannis, D. Tousoulis, et al., The CD40/CD40 ligand system: linking inflammation with atherothrombosis, J. Am. Coll. Cardiol. 54 (2009) 669–677.

Gerfried Pesau, Gerit-Holger Schernthaner*
Division of Angiology, Department of Medicine II, Medical University of Vienna, Austria
E-mail address:
gerit.schernthaner@meduniwien.ac.at (G.-H. Schernthaner).

* Corresponding author. Division of Angiology, Department of Internal Medicine II, Medical University of Vienna, Waehringer Guertel 18-20, A-1090, Vienna, Austria.