Endocrinol Diabetes Nutr. 2017;64(10):515–516

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

EDITORIAL

Blockage of inflammation: New arsenal against arteriosclerosis☆

Bloqueo de la inflamación: nuevo arsenal contra la arteriosclerosis

Miguel Ruiz-Canela[a,b], **Miguel A. Martínez-González**[a,b,c,*]

[a] *Departamento de Medicina Preventiva y Salud Pública, Universidad de Navarra – IdiSNA, Pamplona, Spain*
[b] *CIBER Fisiopatología de la Obesidad y Nutrición (CIBER Obn), Instituto de Salud Carlos III, Madrid, Spain*
[c] *Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, United States*

In 1999, Ross described atherosclerosis as an inflammatory disease.[1] This hypothesis represented a change in our understanding of the origin of the atherosclerotic process beyond extracellular lipid accumulation. Mechanisms related to the role of vascular inflammation in the start and progression of atherosclerotic plaque were subsequently reported. Inflammatory markers emerged as potential therapeutic targets, and anti-inflammatory drugs were postulated as potential cardiovascular drugs.[2]

The recent Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) was designed to assess the inflammatory hypothesis of atherosclerosis (a proof-of-concept trial).[3] CANTOS assessed the efficacy and safety of canakinumab in major cardiovascular disease, including acute myocardial infarction, stroke, and cardiovascular death. Canakinumab is a monoclonal antibody that inhibits the conversion of interleukin-1β to interleukin-6, both precursors of C-reactive protein (CRP). This action mechanism decreases CRP levels, but has no influence on plasma lipid levels. The cardiovascular effect of canakinumab, therefore, can only be attributable to its anti-inflammatory action, thus confirming the hypothesis formulated by Ross two decades ago.

The CANTOS trial was an international multicenter study sponsored by Novartis. Starting in 2011, 10,061 participants were enrolled into the study and followed up for 3.7 years. All the patients had previously sustained myocardial infarction and had a mean age of 61 years, multiple cardiovascular risk factors (43% of prevalent diabetes), and a frequent history of revascularization, and were receiving multiple drugs (90% were taking statins). They had baseline hs-CRP levels of at least 2 mg/L. The patients were randomized to increasing doses of subcutaneous canakinumab (50 mg, 150 mg or 300 mg every 3 months) or placebo. After 48 months of follow-up, all three doses of canakinumab decreased hs-CRP by 26%, 37%, and 41% respectively as compared to placebo, but lipid levels did not change. The main finding was that canakinumab 150 mg achieved a 15% relative reduction (95% confidence interval, 26% to 2%) in the risk of a major cardiovascular event compared to placebo.

CANTOS represented a pioneering trial in promoting clinical research on cardiovascular anti-inflammatory treatment.[4] However, some aspects of this trial raise doubts as to the convenience of using anti-inflammatory therapy in standard clinical practice. First of all, the absolute cardiovascular risk reduction was small: in the placebo group, the cardiovascular event rate was 4.50 cases per 100 patient-years, as compared to the 3.86 events seen in participants treated with canakinumab 150 mg. This represented an

☆ Please cite this article as: Ruiz-Canela M, Martínez-González MA. Bloqueo de la inflamación: nuevo arsenal contra la arteriosclerosis. Endocrinol Nutr. 2017;64:515–516.

* Corresponding author.
E-mail address: mamartinez@unav.es (M.A. Martínez-González).

http://dx.doi.org/10.1016/j.endien.2017.11.014

absolute risk reduction of 0.64 per 100 patient-years. Second, the patients treated with canakinumab were found to be at greater risk of infection-related mortality. Finally, it has been estimated that the annual cost of treatment with canakinumab in the United States is 200,000 dollars,[4] which is unacceptably high from the public health perspective because of the number of patients needing to be treated.[5] In conclusion, the CANTOS trial provides proof of concept and opens up a new perspective for treatment, but there is still a long way to go until other effective and safe, sustainable and efficient anti-inflammatory treatments for cardiovascular disease are available.

In addition to those potential future drugs, there are lifestyle and dietary interventions that may achieve an effective cardiometabolic anti-inflammatory effect.[6] There is evidence for this, especially in the field of nutrition.[7] Certain nutrients or foods mainly act through their action on inflammation.[8] This has made it possible to define the inflammatory capacity of an overall dietary pattern. Two indices that quantify the inflammatory potential of diet, the Dietary Inflammatory Index[9] and the Empirical Dietary Inflammatory Index, have been devised.[10] The inflammatory capacity of diet measured with these indices has repeatedly been associated with an increased risk of cardiovascular disease or other cardiometabolic diseases.[11] Thus, it has also been shown that diet may have a significant cardioprotective effect thanks to its anti-inflammatory action. The essential fact is that the whole population is exposed to one diet or another, and the promotion of an anti-inflammatory dietary pattern may be the most effective and efficient approach.

The Mediterranean diet is an effective intervention for cardiovascular prevention.[12] Part of its effect is explained by its anti-inflammatory action and through an improvement in endothelial capacity.[13] However, current results as regards the anti-inflammatory effect of the Mediterranean diet in cardiovascular secondary prevention are less convincing.[14] The results of CANTOS are highly valuable in supporting the validity of research relating inflammation to cardiometabolic disease. However, lifestyle interventions may have a greater impact on the primary and secondary prevention of cardiometabolic diseases at a significantly lower cost.[15]

References

1. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med. 1999;340(2):115–26.
2. Kaptoge S, di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375(9709):132–40.
3. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119–31.
4. Harrington RA. Targeting inflammation in coronary artery disease. N Engl J Med. 2017;377(12):1197–8.
5. De Irala, Martínez-González MA, Figueiras A. Medidas de asociación y de impacto potencial. In: de Irala J, Martińez-González MA, Segui-Gomez M, editors. Epidemiologiá aplicada. Barcelona: Ariel; 2008. p. 141–77.
6. Kantor ED, Lampe JW, Kratz M, White E. Lifestyle factors and inflammation: associations by body mass index. PLOS ONE. 2013;8(7):e67833.
7. Neale EP, Batterham MJ, Tapsell LC. Consumption of a healthy dietary pattern results in significant reductions in C-reactive protein levels in adults: a meta-analysis. Nutr Res. 2016;36(5):391–401.
8. Calder PC, Ahluwalia N, Albers R, Bosco N, Bourdet-Sicard R, Haller D, et al. A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. Br J Nutr. 2013;109 Suppl.:S1–34.
9. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2014;17(8):1689–96.
10. Tabung FK, Smith-Warner SA, Chavarro JE, Wu K, Fuchs CS, Hu FB, et al. Development and validation of an empirical dietary inflammatory index. J Nutr. 2016;146(8):1560–70.
11. Ruiz-Canela M, Bes-Rastrollo M, Martínez-González MAM. The role of dietary inflammatory index in cardiovascular disease, metabolic syndrome and mortality. Int J Mol Sci. 2016;17(8):E1265.
12. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368(14):1279–90.
13. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. Nutr Metab Cardiovasc Dis. 2014;24(9):929–39.
14. Mayr HL, Tierney AC, Thomas CJ, Ruiz-Canela M, Radcliffe J, Itsiopoulos C, et al. Mediterranean-type diets and inflammatory markers in patients with coronary heart disease: a systematic review and meta-analysis. Nutr Res. 2017, http://dx.doi.org/10.1016/j.nutres.2017.10.014.
15. Carlos S, de Irala J, Hanley M, Martínez-González MÁ. The use of expensive technologies instead of simple, sound and effective lifestyle interventions: a perpetual delusion. J Epidemiol Community Health. 2014;68(9):897–904.