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LETTER TO THE EDITOR

Letter to the editor regarding the article: ''Inflammation and Ischemic heart disease: the next therapeutic target?''

Carta ao editor relativa ao artigo: *Inflamação e doença cardíaca isquémica: o próximo alvo terapêutico*?

To the Editor:

''One (General) can know how to win (a war), but never get the opportunity to win...''
Sun Tzu, in The Art of War

We are glad that this Journal has published yet another article on vascular inflammation.[1] Some other groups have also used this Journal as the stage for presenting their work,[2,3] attempting to bridge the translational gap between inflammation and clinical application, precisely in ischemic heart disease. Over the years, many more have tried to do the same. The problem with vascular inflammation amounts to exactly this: The failure to bridge the translational gap from basic science to clinical use. In other words, despite the ever-growing wealth of pathological and biochemical data, all adding to creating a strong relation with atherosclerosis proper, there is a paucity in the actual, down-to-earth, clinical/practical use of this compelling evidence in the vast arena of the cardiovascular pandemic. Therefore, the question posed in the title placing vascular inflammation as the''next therapeutic target'' is correct, but this has been true for the latest 20 years.

In a simple way, in vascular inflammation there are three areas of interest: (1) Inflammation as the pathophysiological drive for atherosclerosis; (2) Inflammation as a potential supplier of cardiovascular risk markers and, lastly, (3) Inflammation as a supplier of therapeutic targets. Ultimately, the latter could provide the pathway to the holy grail of vascular medicine – a perspective for the cure/prevention for atherosclerosis.

On the first point, the important pathophysiological mechanisms necessary for the clinician to understand vascular inflammation are complex and were not the focus for this paper. Nevertheless, since the pioneering explanation presented by Russel Ross in 1999,[4] the evidence of inflammation in arterial disease is ever mounting and clear, relating inflammation to the molecular biology of atherosclerosis.[5,6]

As to the second point, the use of inflammatory markers as useful clinical risk markers, unfortunately, the role of high sensitivity C-reactive protein (hs-CRP) and other inflammatory markers is still undefined. In reality, a few studies in real life patients in Europe have proven the added benefit of inflammatory biomarkers to be modest.[7] Some authors believe that the complexity of an acute coronary event makes prediction difficult.[8] We tend to agree and so do the European guidelines.

There are other confounding factors for the general clinical use of hs-CRP, such as the molecule's unspecific nature and some reports of genetic variance among CRP, therefore allowing hs-CRP elevation to be disconnected from ischemic heart disease.[9,10]

For the third point – the focus of this paper – inflammation as a therapeutic target, some disclosure and common sense are needed. Since inflammation has failed clinically as the producer of reliable risk markers, most of the groups interested in this area have tried to focus on the therapeutic opportunities presented by this vast knowledge. The first reports about the use of anti-inflammatory therapy in ischemic heart disease refer to low dose aspirin,[11] raising the unconfirmed suspicion that this drug's anti-inflammatory properties could be relevant. Then comes the JUPITER Trial, testing the pleiotropic (anti-inflammatory effects) of statins, through mevalonate inhibition. The results were very good for all major cardiovascular endpoints, so the study was interrupted early. However, despite the excellent results, JUPITER was arguably the most criticized randomized trial in modern cardiovascular history.[12,13] The criticism stems from the fact that statins are beneficial even in people with lipid levels within the guidelines, such as the patients studied in this trial. Therefore, for many, the inflammatory proprieties of statins were deemed unproven.

Understandably, inflammation was drowning as a clinical therapeutic tool, so a proof-of-concept trial was needed. This is where CANTOS (using Canakinumab an anti-inflammatory agent devoid of modifying lipid properties), largely filling the shoes necessary for the validation of the vascular inflammation therapeutics theory enters the story. [14] The importance of colchicine, an old and cheap anti-inflammatory agent, as a modulator of vascular inflammation[15] is relatively recent, as the authors

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presented. However, this drug is not devoid of side effects, as many old clinicians and gout patients might remind us. Further evidence seems mandatory.

We strongly feel that this review on inflammation therapeutics falls short by focusing exclusively on drugs as inflammation modulators, obliterating the immunological advances (in this immune disease). Unlike the authors, we believe that the actual resolution of the ''residual risk for ischemic heart disease'' might come through immune modulation,[16–18] irrespective of the use of anti-inflammatory drugs. Proving it, in the foreseeable future, is the new gateway to vaccination for atherogenic lipoproteins.[19]

We are, therefore, far less optimistic than the authors on the general use of anti-inflammatory drugs in vascular inflammation. Like the citation above, wisely written many centuries ago by Sun Tzu, we do know a lot about vascular inflammation, but it is still uncertain if we will be able to get a real life opportunity to use it...

Conflicts of interest

The author has no conflicts of interest to declare.

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Luís Bronze[a,b]

[a] *Universidade da Beira Interior, Covilhã, Portugal*
[b] *Serviço de Cardiologia, Hospital das Forças Armadas, Pólo de Lisboa, Lisboa, Portugal*
E-mail address: luis.bronze@fcsaude.ubi.pt