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Inflammation and Atherosclerosis: A Dynamic Connection

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Description

The development of atherosclerosis, which is the primary characteristic of many cardiovascular diseases like myocardial infarction and ischemic stroke, has been a subject of debate for several decades regarding its underlying causes and triggers. The initial indications pointing towards inflammation as a potential cause of atherosclerosis emerged from the groundbreaking research conducted by Russell Ross and his team. Their work, extensively discussed and summarized in reference [1], shed light on the pathogenic mechanism of atherosclerosis as an initial vascular response to endothelial injury. This injury, in turn, sets off a persistent local inflammatory reaction [1-3].

Subsequent investigations have provided further evidence supporting the role of inflammation in atherosclerosis, involving various immune cells and mediators, as a crucial factor in the progression of the disease and the vulnerability of plaques to rupture. This understanding is supported by references [4-7]. It is worth noting that while the majority of cardiovascular disease (CVD) patients with a history of atherosclerosis exhibit significant signs of inflammation, not all individuals show the same degree of inflammatory imprinting, as mentioned in reference [8].

The JUPITER trial findings offer valuable insights into this context. The study demonstrated that among individuals with elevated levels of high-sensitivity C-reactive protein (CRP), a nonspecific inflammatory marker, the use of high-dose statins resulted in a lower risk of cardiovascular events compared to the control group [9]. However, it should be noted that the reduction in cardiovascular events cannot be solely attributed to the alteration of the inflammatory milieu, as the statin treatment also led to a decrease in low-density lipoprotein (LDL) cholesterol levels from baseline. Consequently, it has been challenging for the scientific community to establish a definitive link between the presence of elevated CRP and other inflammatory markers and the implementation of new treatment approaches aimed at reducing adverse cardiovascular events. Recent groundbreaking research has demonstrated the efficacy of a specific anti-inflammatory molecule in protecting heart attack survivors who are still at risk of further vascular events, despite having well-controlled lipid levels. This molecule is an antibody called canakinumab, which specifically binds to interleukin-1β (IL-1β). The results of the CANTOS trial, involving over 10,000 patients and published in the New England journal of medicine, revealed that canakinumab reduced the incidence of heart attacks, strokes, and death by 15% compared to a placebo. Canakinumab exhibited a dose-dependent effect on lowering high-sensitivity C-reactive protein (CRP) levels within a few months, which remained consistent throughout the duration of the treatment period. Notably, this reduction in CRP levels occurred without any significant impact on low-density lipoprotein (LDL) cholesterol levels [10]. By targeting IL-1β, which is the primary circulating form of interleukin-1, canakinumab effectively blocks a crucial mediator of inflammation [11]. IL-1β is produced when cholesterol crystals activate the NLRP3 inflammasome and when locally produced oxidized LDL is present, likely in conjunction with other pathological mechanisms. IL-1β, in turn, triggers a cascade of pro-inflammatory molecules, including IL-6. IL-6 is a cytokine known to induce the production of CRP and has direct implications in the development of atherosclerosis and plaque rupture [12]. This study represents a significant milestone in atherosclerosis and cardiovascular disease research. It provides conclusive evidence supporting the inflammatory hypothesis in the pathogenesis and natural progression of atherosclerosis within a clinical context. This finding has the potential to usher in a new era of clinical research that can significantly impact the outcomes of these still life-threatening diseases. It is important to acknowledge that measuring IL-1β activity is challenging, and the use of CRP as a biomarker for IL-1β activity is not perfect. While changes in CRP levels can serve as a marker of response, baseline levels may not accurately predict individual responses. This consideration has implications for the design and stratification of future studies, emphasizing the need for careful interpretation of CRP as a biomarker. Secondly, in terms of the effectiveness of this novel treatment, it is worth noting that the reduction in cardiovascular risk observed in the CANTOS trial aligns with the benefits achieved using PCSK9 inhibitors. This highlights the significance of targeting inflammatory pathways to control cardiovascular risk, with IL-1β being just one of several pro-inflammatory molecules implicated in determining this risk. Thirdly, the cost of such a therapy needs to be taken into consideration. Canakinumab is an expensive medication that has been approved for rare autoimmune diseases, and a single injection costs over $16,000 USD (150 mg in 1 ml of subcutaneous solution is priced at $16,770 US. In the CANTOS trial, it was administered every three months, amounting to approximately $67,000 USD for a year of treatment. To make it a viable option as a preventive cardiovascular drug, the manufacturer may need to lower the price, considering the larger market potential in the cardiovascular setting. Lastly, it is important to highlight the current high costs associated with canakinumab treatment and the slightly increased risk of infection observed in the treated population. These factors currently limit the suitability of canakinumab for use in a cardiovascular setting. However, this opens up possibilities for exploring alternative, less expensive drugs and generic options that could be tested in anti-inflammatory approaches. For example, methotrexate is one such drug that has shown promise in this context. Furthermore, it is noteworthy that the CANTOS trial demonstrated a significant reduction in cancer mortality among patients receiving canakinumab compared to those receiving a placebo. This reduction was particularly evident in terms

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of lung cancer incidence and mortality, providing support for the role of the inflammatory milieu, specifically the IL-1 pathway, in tumor biology and the development of human cancers.

Summary

In summary, additional research is necessary to further explore the role of canakinumab as an effective cardiovascular medication, as well as its potential implications in the fascinating field of clinical oncology. Nonetheless, the milestone achieved with the CANTOS trial holds great significance. It firmly establishes atherosclerosis as an inflammatory disease and introduces a proven mechanism that has the potential to revolutionize therapy guidelines and improve outcomes in the coming decades. This represents a notable innovation for both the scientific community and the patients affected by these conditions.

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