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A Review of the Role of Canakinumab - An Anti-Inflammatory Agent in CAD

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ABSTRACT

Coronary Artery Disease (CAD) is the leading cause of mortality and loss of disability-adjusted life years (DALYs) worldwide. Optimal medical therapy is the cornerstone of management for patients with CAD. However, patients on currently available medical therapy still have a residual risk of poor cardiovascular outcomes. Recent studies have underscored the role of inflammation in the development and progression of CAD and proposed that anti-inflammatories such as Canakinumab may significantly reduce the incidence of poor cardiovascular outcomes. This review explored the role of Canakinumab in CAD management and discovered that Canakinumab without the requirement of daily dosing, reduces the incidence of adverse cardiovascular outcomes in CAD patients. However, its high cost and limited knowledge concerning its long-term effects may limit its use for CAD patients

Keywords: *Canakinumab, Coronary artery disease, Inflammation. Anti-inflammatory, Cardiovascular management, pharmacology*

INTRODUCTION

Coronary Artery Disease (CAD) is the most prevalent cardiovascular disease globally, characterized by atherosclerotic plaque development in the coronary arteries [1-3]. It encompasses various conditions such as asymptomatic CAD, Stable Angina, Acute Coronary Heart Disease, and Ischemic Myocardial Infarction [1,3].

CAD is the leading cause of mortality and loss of disability-adjusted life years (DALYs) worldwide [4]. In 2021, CAD accounted for approximately 9.44 million deaths and 185 million DALYs, with a steady rise from 2015 when CAD accounted for 8.9 million deaths and 164.0 DALYs [1, 2, 4]. Despite advancements in diagnostic and therapeutic measures, the increasing mortality and morbidity from CAD underscore the importance of secondary prevention [1-4]. Current interventions for CAD include lifestyle changes, medical management, and surgical interventions [5]. Optimal medical therapy remains the cornerstone for all CAD patients, including those who have undergone surgery [5].

The role of anti-inflammatory medications, such as Canakinumab and Colchicine, has gained attention due to studies highlighting the connection between inflammation and atherosclerosis [6, 7]. Canakinumab, a monoclonal antibody targeting IL-1β, initially developed for immune disorders, shows potential as a treatment option for

CAD [8-11]. However, there is a limited body of literature exploring its role in CAD management.

This literature review aims to explore Canakinumab's role in CAD management by providing an overview of CAD pathology, the role of anti-inflammatory medications (especially Canakinumab), and the reasons for and implications of Canakinumab's use in CAD management.

PATHOPHYSIOLOGY OF CAD:

CAD is caused by atherosclerosis, a process characterized by the buildup of cholesterol plaques in blood vessels supplying the heart (CAD) [1]. Atherosclerosis is a chronic inflammatory condition affecting the inner lining (intima) of medium-sized arteries. While atherosclerosis is exacerbated by widely recognized risk factors such as high blood pressure, elevated cholesterol levels, smoking, diabetes, and genetic predisposition, inflammation has been proposed as a key promoter for atherosclerosis and its complications [1].

Alterations in the production and availability of endothelial-derived molecules by other factors, like nitric oxide (NO), prostacyclin, and endothelin, also contribute to a vasoconstrictive and procoagulant environment [3]. This process consequently results in the upregulation of proinflammatory cytokines, cell adhesion molecules, and chemokines [3].

IL-1β, a proinflammatory cytokine, plays multiple roles in the atherothrombotic process [6, 7]. When activated, IL-1β activates systemic and vascular inflammation. Furthermore, it up-regulates adhesion molecules on endothelial cells of vessels, consequently leading to the migration of other immune cells to the site of inflammation. Collectively, these mechanisms enhance the penetration of the middle lining of the vessels (media) by inflammatory cells, macrophages, and cholesterol, thereby initiating atherosclerosis [6, 7]. IL-1β and other cytokines also stimulate the proliferation of fibroblasts, and collagen contributes to the complex formation of a plaque with cholesterol crystals [7]. Additionally, these cholesterol crystals promote IL-1β's activation by the nucleotide-binding leucine-rich repeat-containing pyrin receptor 3 inflammasomes creating a vicious cycle [6, 7].

USE OF ANTI-INFLAMMATORIES IN CAD:

The Canakinumab anti-inflammatory thrombosis outcomes study (CANTOS) study highlighted the role of inflammation in CAD etiology, leading to further investigations into the use of anti-inflammatory medications for CAD management [11]. While nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with adverse outcomes in CAD patients [13], recent studies have discovered that anti-inflammatory medications focused on the action of IL-6 and IL1b may significantly decrease the incidence of cardiac events in CAD patients [11] In addition to Canakinumab, other anti-inflammatories like methotrexate and colchicine have shown potential in reducing cardiovascular events. However, safety concerns and limited evidence restrict their widespread use in clinical practice [11].

PHARMACOLOGY OF CANAKINUMAB:

Canakinumab is a monoclonal anti-human IL-1β that selectively neutralizes IL-1β, a proinflammatory cytokine that plays multiple roles in the atherothrombotic process [5]. It is an IgG1/k isotype and binds to IL-1β, preventing it from interacting with its receptors, and consequently reducing inflammation associated with the cytokine [16, 17].

Like most monoclonal antibodies, canakinumab is not metabolized by the cytochrome P450 system and undergoes intracellular catabolism. Its anti-inflammatory actions may indirectly restore the expression of cytochrome P450 (CYP) enzymes to normal levels [6,7]. Canakinumab is long-acting and administered intravenously or

subcutaneously, with a half-life of approximately 26 days [18].

While FDA-approved for inflammatory conditions like cryopyrin-associated periodic syndrome (CAPS), tumor necrosis factor receptor-associated periodic syndrome (TRAP), and familial Mediterranean fever (FMF), recent studies suggest that Canakinumab significantly reduces cardiovascular events in CAD patients [8 - 10]

CANAKINUMAB IN CAD:

Inflammatory markers such as high-sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6) have been identified as predictors of cardiovascular outcomes, and reducing their levels using medications like statins has been associated with favorable outcomes [12]. However, a residual risk of cardiovascular events continues to exist in CAD patients on statin-based medication [2]. Consequently, inflammation reduction further augments the benefits obtained from lipid-lowering therapies [11].

Canakinumab significantly reduces the rate of recurrent cardiovascular events. Its reduction in recurrent CV events is independent of cholesterol level and associated with a concomitant decrease in high-sensitive C-reactive protein (hs-CRP) and IL-6 [6, 12].

Previous studies suggest that Canakinumab may be administered once every three months for CAD instead of daily, like other CAD medications, making it an attractive option for CAD medical therapy [14,15]. However, its cost-effectiveness remains a concern, with doses for CAD management amounting to approximately $73,000 per year (15).

ADVERSE REACTIONS AND DRUG INTERACTIONS OF CANAKINUMAB:

Canakinumab has a low potential for drug-drug interactions, making it compatible with most medications [6]. However, its long-term effects are currently unknown, and like other anti-inflammatory agents proposed for CAD management, it has safety concerns regarding immune response interference [11, 14].

While Canakinumab generally exhibits mild adverse effects such as injection site reactions, abdominal pain, and low-grade infections in practice [1, 2], rare instances of severe adverse reactions have been reported, particularly related to infections [5]. For instance, in the CANTOS trial, patients receiving Canakinumab experienced increased neutropenia and sepsis-related deaths compared to the placebo group [14]. Previously reported infections associated with Canakinumab include respiratory tract infections, urinary tract infections, gastroenteritis, and viral infections, with no cases of opportunistic infections [4].

CONCLUSION

Coronary Artery Disease (CAD) remains a significant global health burden, leading to a substantial number of disability-adjusted life years and mortality. While optimal medical therapy forms the foundation of CAD management, there is still a residual risk of adverse cardiovascular outcomes for patients under current treatment regimens. Recent studies have highlighted the role of inflammation in CAD development and progression, opening avenues for exploring anti-inflammatory agents like Canakinumab as potential therapeutic options.

This literature review explored the role of Canakinumab in CAD management and found promising evidence supporting its efficacy in reducing the incidence of adverse cardiovascular outcomes. Notably, Canakinumab's mechanism of action in selectively neutralizing the proinflammatory cytokine IL-1β has been shown to significantly decrease the rate of recurrent cardiovascular events, independent of cholesterol levels. Furthermore, the possibility of administering Canakinumab once every three months, as opposed to daily dosing, adds to its appeal as a treatment option for CAD patients.

However, the use of Canakinumab in CAD management also presents challenges. The high cost of the medication may limit its

widespread use in clinical practice. Additionally, long-term safety concerns and the lack of sufficient evidence for its use in certain patient populations warrant further investigation.

Canakinumab shows promise as an anti-inflammatory agent for CAD management, offering the potential to address the residual risk of adverse cardiovascular outcomes. As researchers continue to explore its role in CAD therapy, more extensive studies are needed to assess its long-term safety, cost-effectiveness, and overall benefits compared to other treatment options. By expanding our understanding of Canakinumab's potential in CAD management, we may pave the way for more targeted and effective approaches to reducing the global burden of CAD.

Declaration by Authors

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