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Modulation of Inflammation in Heart Failure: The Role of Ziltivekimab and Canakinumab

Łukasz Wołowiec[1*], Walery Żukow[2], Julia Anna Pęcherz[1], Daria Czaplińska[1], Albert Jaśniak[1], Grzegorz Grześk[1]

[1]Department of Cardiology and Clinical Pharmacology, Faculty of Health Sciences, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Torun, Poland

[2] Nicolaus Copernicus University, Toruń, Poland

Corresponding author*: Łukasz Wołowiec, lukaswolowiec111@gmail.com

ABSTRACT

This article examines the role of inflammation in heart failure pathogenesis and explores novel therapeutic strategies targeting inflammatory pathways. The increasing

prevalence of heart failure, particularly those with preserved ejection fraction (HFpEF), highlights the urgent demand for effective treatments. Canakinumab, a monoclonal antibody targeting interleukin-1β, has shown promise in reducing cardiovascular events by modulating inflammation, while Ziltivekimab, a newer monoclonal antibody targeting interleukin-6, demonstrates potential in heart failure patients with elevated inflammatory markers. The article reviews clinical trials, including CANTOS and RESCUE, providing evidence of the efficacy of patient outcomes. The findings underscore the importance of personalized treatment strategies on heart failure, with a focus on inflammation-driven pathways, positioning anti-inflammatory therapies as a significant advancement in cardiovascular disease management. Future research will determine the broader clinical applicability of these therapies in managing heart failure, its complications, and fostering more favorable outcomes.

Key words: ziltivekimab, canakinumab, heart failure

INTRODUCTION

Heart failure is a critical and escalating public health issue, currently affecting more than 64 million patients worldwide [1]. It is the primary cause of hospitalization among the elderly, particularly those over 65 years of age [1]. Despite advancements in the management of heart failure, the disease continues to be associated with high morbidity and mortality rates [1]. This persistent burden is largely due to the heterogeneous nature of heart failure, with varying phenotypes that complicate treatment. Among these, heart failure with HFpEF has seen a marked increase in incidence, further complicating therapeutic strategies.

Systemic inflammation is an integral component of the pathogenesis of both acute and chronic heart failure [2]. Inflammation has been linked to the onset, progression, and complications of the disease, underscoring the necessity for a deeper understanding of its mechanisms to develop effective treatments [2]. Patients with heart failure have been observed to have elevated levels of inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-2 (IL-2) [3–5]. Moreover, inflammation promotes atherothrombosis and acute myocardial infarction, both of which are closely linked to the development of heart failure [6]. It is worth addressing that atherosclerotic cardiovascular disease (ASCVD), associated with high - sensitivity C-reactive protein (hsCRP)

levels, is one of the leading causes of death worldwide [7]. C-reactive protein (CRP) is commonly elevated in heart failure, and its level is strongly associated with patient prognosis, as higher concentrations correlate with increased mortality [8,9]. These findings have shifted the focus toward developing novel therapeutic approaches that target these inflammatory pathways, which are now recognized as key contributors to the onset and progression of heart failure. Immunomodulatory therapies, particularly monoclonal antibodies like canakinumab (targeting IL-1β) and ziltivekimab (targeting IL-6), are showing promising potential in reducing inflammation and improving outcomes in patients with heart failure [10,11].

Canakinumab (ACZ885, Ilaris) is a human anti-interleukin-1β monoclonal antibody that specifically neutralizes interleukin-1β without any cross-reactivity with interleukin-1α [11] . The beneficial effects of canakinumab have demonstrated clinical utility in the treatment of autoinflammatory diseases and it is currently being used to treat Still's disease, certain periodic fever syndromes, and gout flares [12–14].

Ziltivekimab is one of the latest fully human monoclonal antibodies developed against IL-6 , which is a key mediator of inflammation in the body [15]. IL-6 influences the increase in CRP levels, lipoprotein(a) and other inflammatory markers, which play a critical role in cardiovascular diseases such as atherosclerosis and HFpEF [16–19]. Ziltivekimab works by blocking the IL-6 pathway, offering hope for its use in treating these conditions [10]. Given the promising results from clinical trials discussed later in this article, we believe that ziltivekimab therapy, aimed at inhibiting the IL-6 pathway, has great potential in treating and improving the prognosis of individuals suffering from heart failure.

This article aims to provide a comprehensive review of the emerging role of inflammation in heart failure and the potential therapeutic benefits of targeting inflammatory pathways. It explores the basics of heart failure-related inflammation, as well as key clinical trials evaluating the efficacy of canakinumab and ziltivekimab.

The main research problems addressed are.

1. How does systemic inflammation contribute to the development and progression of heart failure?

2a. How effective are canakinumab (targeting IL-1β) and ziltivekimab (targeting IL-6) in reducing inflammation and improving outcomes in heart failure patients?

2b. What are the mechanisms by which these therapies modulate inflammation in heart failure?

3. Can patient selection based on inflammatory biomarkers improve outcomes with anti-inflammatory therapies in heart failure?

4. What is the safety profile of canakinumab and ziltivekimab when used to treat heart failure?

5. Are anti-inflammatory therapies like canakinumab cost-effective for treating heart failure compared to standard care?

6. How do anti-inflammatory therapies perform in heart failure with preserved ejection fraction (HFpEF) versus reduced ejection fraction (HFrEF)?

7. What are the long-term impacts of IL-6 inhibition with ziltivekimab on cardiovascular events and kidney disease progression?

Based on the research problems presented in the article, here are appropriate research hypotheses and potential methods/materials to investigate and verify them.

1. Hypothesis. Elevated levels of inflammatory markers (e.g. IL-1β, IL-6, CRP) are associated with increased incidence and severity of heart failure. Methods. Prospective cohort study measuring inflammatory biomarkers in patients with and without heart failure. Animal models of heart failure with genetic or pharmacological manipulation of inflammatory pathways. Tissue analysis of inflammatory cell infiltration and cytokine expression in heart failure samples

2a. Hypothesis. Treatment with canakinumab or ziltivekimab reduces inflammatory biomarkers and improves clinical outcomes in heart failure patients compared to placebo.

Methods. Randomized controlled trials comparing canakinumab/ziltivekimab to placebo in heart failure patients. Measurement of inflammatory biomarkers (e.g. CRP, IL-6) before and after treatment. Assessment of clinical endpoints like hospitalization rates, mortality, and quality of life scores.

2b. Hypothesis. Canakinumab and ziltivekimab reduce myocardial inflammation and fibrosis by inhibiting IL-1β and IL-6 signaling pathways respectively. Methods. In vitro studies on cardiomyocytes and cardiac fibroblasts treated with canakinumab/ziltivekimab. Animal models of heart failure treated with these drugs, analyzing tissue inflammation and fibrosis. Proteomic and transcriptomic analysis of heart tissue before and after treatment.

3. Hypothesis. Heart failure patients with elevated baseline inflammatory markers show greater benefit from anti-inflammatory therapies compared to those with lower inflammatory

markers. Methods. Subgroup analysis of clinical trial data stratifying patients by baseline inflammatory marker levels. Prospective study targeting patients with high inflammatory markers for anti-inflammatory therapy. Development and validation of a risk score incorporating inflammatory biomarkers to guide patient selection.

4. Hypothesis. Canakinumab and ziltivekimab have acceptable safety profiles in heart failure patients, with manageable adverse events compared to standard care. Methods. Comprehensive safety analysis from clinical trials, including adverse event reporting. Long-term follow-up studies to assess potential late-onset side effects. Pharmacovigilance data analysis from post-marketing surveillance.

5. Hypothesis. Despite higher upfront costs, canakinumab is cost-effective for treating heart failure due to reduced hospitalizations and improved quality of life. Methods. Cost-effectiveness analysis using data from clinical trials and healthcare system costs. Markov modeling to project long-term costs and outcomes. Sensitivity analyses to account for variations in drug pricing and healthcare costs.

6. Hypothesis. Anti-inflammatory therapies show greater efficacy in HFpEF compared to HFrEF due to the more prominent role of inflammation in HFpEF pathophysiology. Methods. Stratified analysis of clinical trial data comparing outcomes in HFpEF vs HFrEF patients. Separate randomized controlled trials for HFpEF and HFrEF populations. Mechanistic studies comparing inflammatory pathways in HFpEF and HFrEF tissue samples.

7. Hypothesis. Long-term IL-6 inhibition with ziltivekimab reduces cardiovascular events and slows kidney disease progression in patients with chronic kidney disease and elevated inflammatory markers. Methods. Large-scale, long-term randomized controlled trial (e.g. ZEUS study) with cardiovascular and renal outcomes. Regular assessment of cardiovascular events, kidney function (eGFR, albuminuria), and inflammatory markers. Subgroup analyses based on baseline kidney function and cardiovascular risk factors.

These hypotheses and methods provide a framework for addressing the research problems outlined in the article, allowing for comprehensive investigation of the role of inflammation in heart failure and the potential of anti-inflammatory therapies.

THE ROLE OF IL-1 IN HEART FAILURE

The nucleotide-binding domain like receptor 3 (NLRP3) inflammasome is a key factor in inflammation as it promotes the production of IL-1 [20]. IL-1 family consists of 11 cytokine members, including IL-1β, the most extensively researched one [20,21]. Data collected from various experimental models of heart failure, including myocardial infarction (MI), left ventricular pressure overload, transgenic overexpression of calcineurin, and diabetic cardiomyopathy, have shown elevated levels of IL-1, underscoring its undeniable role in the pathogenesis of cardiac dysfunction [21]. IL-1 is produced and activated in heart failure by a variety of cell types including immune cells, fibroblasts, vascular cells, and cardiomyocytes [21]. IL-1 plays a significant role in heart failure by affecting both systolic and diastolic function through multiple pathways [22]. Enhanced IL-1 activity contributes to impaired systolic function by inhibiting L-type calcium channels and uncoupling adenylyl cyclase from β-adrenergic receptors [22]. Diastolic dysfunction arises from transcriptional and posttranslational changes in phospholamban and sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA)[22]. IL-1 increases the expression of nitric oxide synthase (NOS), leading to elevated production of nitric oxide (NO), which triggers mitochondrial dysfunction and reduces the heart's contractile reserve [22]. IL-1β contributes to cardiac fibrosis by enhancing the infiltration of inflammatory cells into the myocardium and inducing matrix-degrading phenotype in cardiac fibroblasts [23]. IL-1β promotes apoptosis of cardiomyocytes [23]. IL-1β is involved in the pyroptosis pathway, which is defined as a programmed cell death linked to inflammation and has been identified as a driving factor behind cardiac remodeling [24]. Additionally, IL-1 elevates arterial stiffness and promotes microvascular inflammation, both of which are contributing to HFpEF [21].

THE ROLE OF IL-6 IN HEART FAILURE

IL-6 is an interleukin that stimulates the production of CRP and is produced throughout the body by many types of cells, including macrophages and monocytes, as well as fibroblasts and endothelial cells, typically following IL-1 stimulation [10]. IL-6 cellular signaling can occur in three ways [10]. The classical variant involves the binding of secreted IL-6 to the membrane-bound IL-6R receptor, which on its own, without activation by IL-6, does not exhibit signaling capability [10]. The complex formed by this binding then interacts with the membrane protein gp130, which is present in all cells, triggering intracellular signaling activation [10]. Even though the IL-6R receptor is not found on all cells, there is another mechanism for activating signaling, called trans-signaling [10]. This process is mediated by sIL-

6R, the soluble counterpart of the membrane-bound IL-6R [10]. When sIL-6R binds to IL-6, forming the sIL-6R/IL-6 complex, it can interact with gp130, thus activating intracellular signaling in cells where the IL-6R receptor is not present [10]. A third form of IL-6 signaling, known as trans-presentation, has also been described [10]. This requires an additional interaction between dendritic cells and the recipient T cell [10]. Each of these pathways ultimately converges at the gp130 membrane receptor subunit, which then activates the intracellular JAK-STAT pathway (Janus kinase signal transducer and activator of transcription) [10]. This leads to the regulation of specific genes [10]. High IL-6 levels are strictly related to development of HFpEF [25]. IL-6 has been shown to induce a negative inotropic effect and contribute to hypertrophy via activation of the gp130/STAT3 signaling pathway [21]. IL-6 promotes extracellular matrix synthesis and induces fibroblast proliferation. IL-6 has been associated with fibrosis and increased myocardial stiffness [21]. Moreover, high IL-6 concentration has been associated with decline in kidney function and peripheral edema [25].

CLINICAL TRIALS FOR CANAKINUMAB

Canakinumab was proven to significantly decrease levels of CRP, interleukin-6, and fibrinogen without significantly affecting HbA1c, glucose, insulin, or lipid concentrations [26]. The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) was a phase III, double-blind, randomized trial that enrolled 10,061 participants worldwide[27]. It was designed to evaluate whether canakinumab could prevent recurrent vascular events in patients with a prior MI and elevated hsCRP levels [27]. The trial assessed three different doses of canakinumab (50 mg, 150 mg, and 300 mg), administered subcutaneously every 3 months, compared to a placebo [27]. All doses of canakinumab lowered hsCRP concentrations more effectively than the placebo [27]. Patients receiving the 150-mg dose had a significantly reduced probability of developing MI, stroke, or cardiovascular death after a median follow-up of 3.7 years, compared to those on placebo [27]. The study demonstrated that targeting inflammation by blocking IL-1 could prevent cardiovascular events and underscored the role of IL-1 in the pathogenesis of heart failure [27].

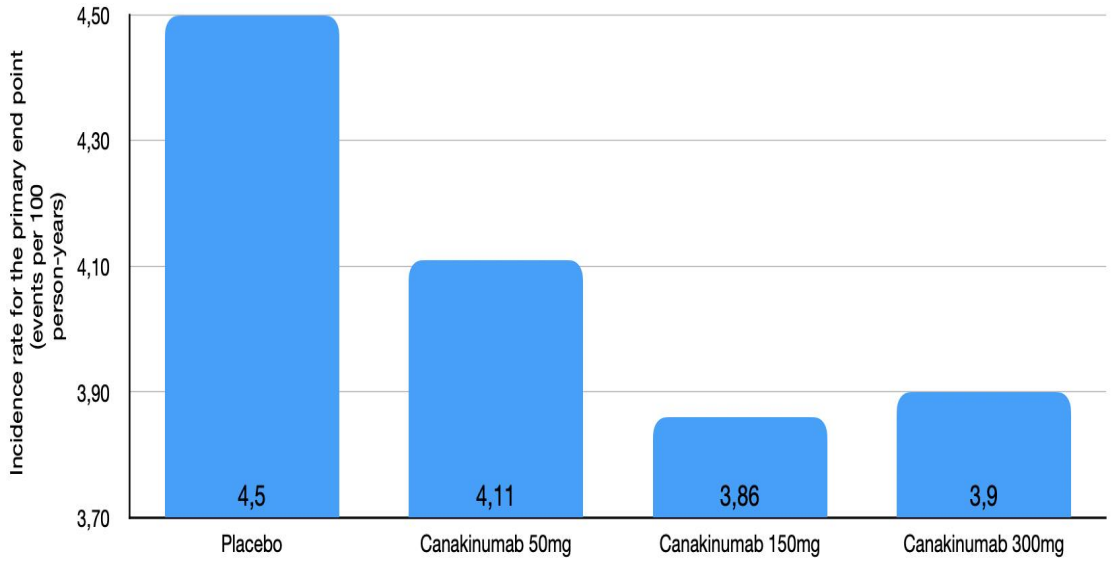

Fig. 1. The incidence rate of the primary endpoint (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) at a median follow-up period of 3.7 years from CANTOS study[10,1].

Furthermore, the long-term results of canakinumab therapy were directly linked to the extent of hsCRP reduction achieved after administering a single dose of the drug[28]. Patients who reached hsCRP concentrations below 2 mg/L within three months experienced a 25% reduction in major adverse cardiovascular events [28]. In contrast, those with hsCRP levels above 2 mg/L showed no significant cardiovascular benefit from canakinumab treatment, suggesting that hsCRP concentration could serve as a marker of treatment effectiveness [28].

Inhibition of the IL-1β–NLRP3 inflammasome appears to be particularly crucial for patients with clonal hematopoiesis of indeterminate potential (CHIP), a condition commonly observed in healthy elderly individuals and associated with TET2 and DNMT3A mutations [29]. In studies on rodent models, TET2-mediated clonal hematopoiesis deficiency was shown to increase IL-1β expression, leading to impaired cardiac function, thereby linking CHIP to an elevated risk of developing heart failure [30]. A genomic substudy of the CANTOS trial revealed that individuals with CHIP and TET2 mutations achieved better outcomes with canakinumab treatment compared to the overall cohort [31]. Both genetic testing and hsCRP concentration could potentially be used in the future to identify patients more likely to respond to canakinumab, supporting its role in personalized medicine and targeted cardiovascular therapies.

A recent study on individuals with human immunodeficiency virus (HIV) revealed that the administration of canakinumab was associated with decreased bone marrow metabolic activity and a shift in the monocyte population toward an anti-inflammatory phenotype [32]. These findings underscore the necessity for a deeper understanding of the underlying mechanisms of action of canakinumab.

ZILTIVEKIMAB - A NEW DRUG IN HEART FAILURE

Ziltivekimab is a monoclonal antibody targeting the IL-6 ligand, specifically developed with atherosclerosis in mind. By substituting three amino acids in the Fc domain, its half-life was extended [10]. The hypothesis suggests that ziltivekimab could be safer with fewer side effects related to lipid levels, hematological markers, and liver function compared to other IL-6 inhibitors [33]. This is because ziltivekimab can be administered in lower doses, as it targets the IL-6 ligand directly, rather than its receptor [34]. Its development primarily focused on a subgroup of patients from the CANTOS trial, particularly those with chronic kidney disease (CKD) and elevated hsCRP [10]. Given the success of canakinumab, the potential of ziltivekimab also appeared promising [10]. Ziltivekimab has proven effective in reducing hsCRP and other inflammatory and thrombosis markers in high-risk atherosclerotic cardiovascular disease (ASCVD) patients [35].

The IL-6 signaling pathway in cardiovascular diseases has recently become a primary focus of research in patients with heart failure, both as a potential pathogenetic and therapeutic mediator [19]. The development of HFpEF has been linked to increased IL-6 levels [19]. Given the associations of HFpEF with coronary artery disease, ventricular hypertrophy, and inflammation, drugs targeting IL-6, such as ziltivekimab, may play a particularly important role for patients suffering from HFpEF [19].

As a result of these findings, a study was conducted focusing on patients admitted to hospitals with a primary diagnosis of decompensated heart failure in three hospitals in eastern Scotland[19]. Initially, it included heart failure patients (as defined by the European Society of Cardiology criteria) regardless of LVEF [19]. However, to align the data with recent large clinical trials on HFpEF, an LVEF cutoff of >40% was adopted [19]. This also ensured consistency with inflammatory marker cutoffs previously analyzed [19]. Patients with a primary myocardial infarction or coexisting systemic disease, which could significantly shorten life expectancy, were excluded from the study [19].

The conclusion of the study confirmed that IL-6 levels are an independent prognostic factor for overall mortality, including cardiovascular-related deaths, as well as for the need for rehospitalization in heart failure patients previously hospitalized for decompensated HFpEF [19]. Consequently, drugs like ziltivekimab, which target IL-6, hold particular importance for HFpEF patients due to the negative impact of inflammation on prognosis, as highlighted by the above findings [19].

ZILTEVIKIMAB IN HEART FAILURE-RELATED DISEASES

Since kidney function is closely linked to heart function, an acute or chronic impairment of one of these organs can disrupt the functioning of the other. Heart failure can develop in patients with CKD, primarily because CKD is very often associated with a chronic inflammatory process, which is measured by the level of hsCRP and leads to metabolic disorders that contribute to conditions like atherosclerosis and hypervolemia, which in turn promote hypertension and left ventricular hypertrophy [36–38]. Therefore, the following studies play a significant role in gathering information that could be important for the treatment of heart failure with ziltivekimab.

The second phase of the RESCUE trial (Reduction in Inflammation in Patients With Advanced Chronic Renal Disease Utilizing Antibody Mediated IL-6 Inhibition) was recently completed[10]. This study also involved patients with moderate to severe CKD and hsCRP levels above 2 mg/L[10]. A total of 264 patients received ziltivekimab or placebo subcutaneously in doses of 7.5, 15, or 30 mg at 4-week intervals for 24 weeks [10]. While the median hsCRP level was reduced by only 4% in the placebo group, ziltivekimab reduced it by 77%, 88%, and 92% across the dose range [10]. Additionally, depending on the dose, reductions were observed in levels of haptoglobin, fibrinogen, lipoprotein(a), secretory phospholipase A2, and serum amyloid A[10]. The data from this study showed that IL-6 inhibition and subsequent hsCRP reduction through ziltivekimab were highly effective in almost all participants compared to placebo[10]. Notably, the reduction in hsCRP with ziltivekimab (77%-92%) was nearly double that of canakinumab (35%-40%) in the CANTOS study [15].

In addition to the highly effective inhibition of IL-6 and the reduction of hsCRP compared to placebo, ziltivekimab, as studied in the RESCUE trial in individuals without clinically overt systemic inflammatory disorders, demonstrated no significant injection site reactions [10]. It also did not cause prolonged neutropenia or thrombocytopenia, and had no

impact on the ratio of total cholesterol to high-density lipoprotein cholesterol, which significantly distinguishes it from other available IL-6 inhibitors [10] .

Further insights gained from the analysis of the RESCUE trial revealed that the neutrophil-to-lymphocyte ratio (NLR), which can independently predict atherosclerotic events and has potential as a biomarker of inflammatory risk, also decreases when IL-6 ligand is inhibited with ziltivekimab [39]. Should ziltivekimab eventually be introduced into clinical practice, NLR has the potential to be used as a marker to monitor its effectiveness [39].

It is also worth noting that during the RESCUE analysis, it was observed that ziltivekimab improved iron homeostasis and anemia markers in patients with CKD and accompanying inflammation, suggesting the possibility of using ziltivekimab for the treatment of anemia [40].

The results of the RESCUE study were further validated through the RESCUE 2 study, conducted on a Japanese population of patients with non-dialysis CKD who had systemic inflammation associated with atherosclerosis. This study aimed to evaluate the efficacy and safety of ziltivekimab, using doses of 15 mg and 30 mg. As in the original study, ziltivekimab led to a significant reduction in inflammatory biomarkers compared to placebo. In light of these results, combined with a favorable safety profile similar to placebo, it can be concluded that ziltivekimab holds significant potential for inhibiting inflammatory pathways, consequently reducing the risk of atherosclerosis and improving cardiovascular outcomes in patients with ASCVD. This is particularly important for both physicians and patients, as it underscores the need not only to treat traditional ASCVD risk factors but also to engage in secondary prevention by monitoring and reducing inflammation-related risks [33,40].

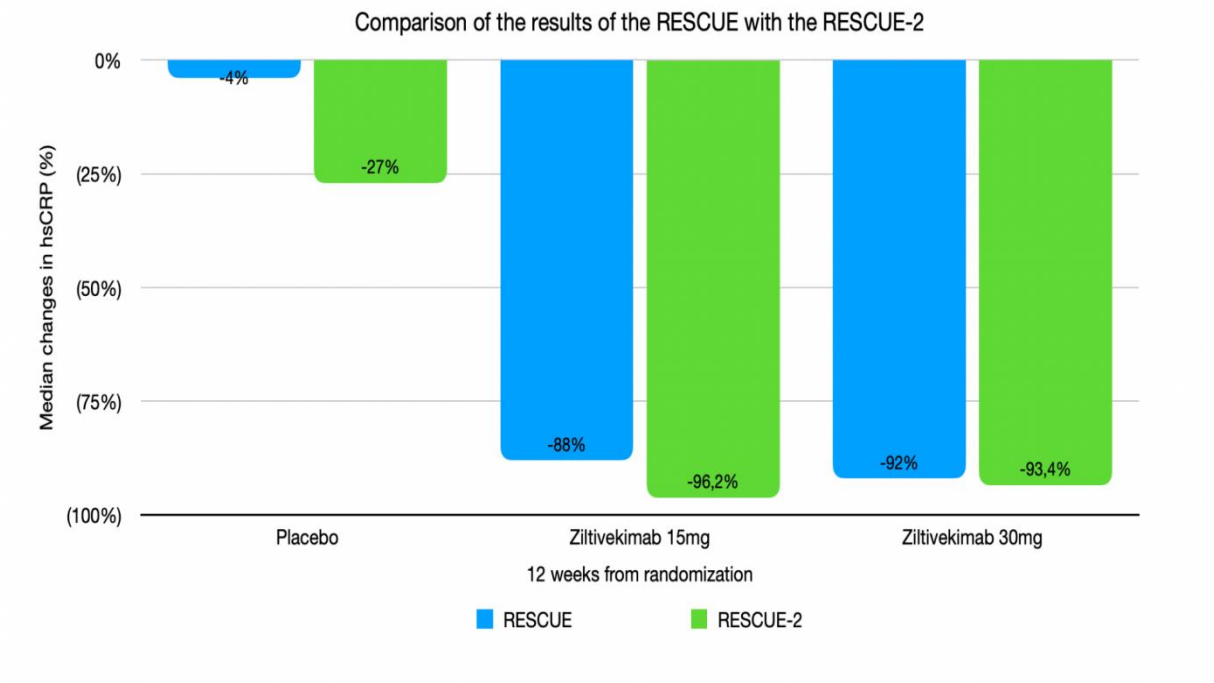

Fig. 2. Results from the RESCUE-2 study in Japan confirmed the effectiveness of ziltivekimab in reducing hsCRP levels and were consistent with data obtained from the earlier RESCUE trial [33,40].

Given these promising results, another clinical trial, known as ZEUS (Ziltivekimab Cardiovascular Outcomes Study), was initiated and is currently in phase III [19]. The study is designed to compare the effects of ziltivekimab to placebo and to evaluate the impact of IL-6 inhibition on cardiovascular outcomes in a cohort of approximately 6,000 patients with CKD and elevated hsCRP. The primary outcomes include baseline and serial assessments of LVEF and heart failure events. Baseline LVEF will be determined through echocardiography, aiming to classify patients based on the presence of heart failure and whether their ejection fraction is preserved or reduced. During treatment, serial LVEF measurements will be taken to evaluate the potential of IL-6 inhibition to improve systolic function [10,41].

Additionally, as a secondary objective, the ZEUS study will assess the impact of chronic IL-6 inhibition with ziltivekimab on slowing the progression of kidney disease. To establish this, data on clinical renal events and changes in glomerular filtration rate (GFR) as well as the urine albumin-to-creatinine ratio over time will be analyzed [10].

The information provided by the research conducted so far on the reduction of inflammatory biomarkers encourages further studies on the specific inhibition of the inflammatory cascade by ziltivekimab [42].

NEWEST CLINICAL TRIALS FOR ZILTIVEKIMAB

As all of these studies wich where discussed focus on the elevated inflammation associated with atherosclerosis, it is worth addressing the latest research that has recently begun. One of the consequences of atherosclerosis is acute myocardial infarction (AMI), which is preceded by a chronic inflammatory state that subsequently leads to excessive acute inflammation superimposed on chronic inflammation (AoCI). Common complications resulting from AMI, such as the formation of intracardiac thrombi, arrhythmias, and acute heart failure (AHF), can further exacerbate the inflammation already caused by AoCI. AHF following AMI is associated with higher mortality rates and an increased rate of rehospitalization. Elevated biomarkers seen in AHF, such as IL-6 and NLR, lead to poor prognosis for patients [43].

ATHENA (NCT06200207) and HERMES (NCT05636176) are recently initiated studies that, based on the above observations, are investigating the effects of ziltivekimab in patients with heart failure [43]. HERMES started in 2023 and is expected to last up to 4 years. Participants in the study will need to visit the clinic 20 times and record and report all information related to drug injections, which will be administered once a month in the form of a prefilled syringe, injected into the skin fold, or via an auto-injector pen to inject the drug into flat skin [44]. ATHENA, on the other hand, began in 2024 and is expected to last 1 year and 4 months. It also focuses on patients suffering from heart failure with present inflammation and aims to investigate the potential for treating these patients with ziltivekimab. In this study, the drug will also be administered subcutaneously once a month. In both studies, patients will not know whether they are receiving ziltivekimab or a placebo [43].

Considering previous studies, there is great hope for ziltivekimab and the expectation of positive results, but we will have to wait for the conclusions from these trials. It is worth noting that CANTOS provided the first promising data on the use of anti-inflammatory therapy in the late phase after myocardial infarction, resulting in a reduction in hospitalizations related to heart failure. Another area requiring research is the effect of introducing anti-inflammatory therapy in the early phase after a myocardial infarction complicated by AHF [43].

FUTURE PERSPECTIVES

Canakinumab is mentioned in the 2024 European Society of Cardiology Guidelines, where it is identified as a promising new pharmacological therapy for peripheral arterial and aortic diseases [4]. Immunomodulatory drugs have the potential to reshape the treatment landscape for cardiovascular diseases. Further research on targeting IL-1 and IL-6 is needed to bring immunomodulatory therapies to clinical practice and drive change in current treatment standards. Unfortunately, there is a concern that the high costs associated with immunomodulatory therapies may limit their clinical utility. It was decided to conduct an analysis regarding the base costs and utility of canakinumab from the perspective of the publicly funded Canadian healthcare system. The research horizon was set for the patient's entire lifetime, and the dosing data was based on the CANTOS study. The cost of canakinumab is USD 16,000 per 150 mg vial, which, when calculated per patient and their annual requirement for the drug, amounts to USD 64,000. These are very high amounts, which, when compared to standard care, make canakinumab, at its current price, not a cost-effective strategy, regardless of its relative efficacy as shown in the CANTOS study [45].

After analyzing the article and its sources, We can present the following verification of the hypotheses.

1. The hypothesis regarding the role of elevated inflammatory markers in heart failure has been confirmed. The article indicates a strong association between elevated levels of inflammatory markers (e.g., IL-1β, IL-6, CRP) and increased incidence and severity of heart failure.

2a. The hypothesis about the effectiveness of canakinumab and ziltivekimab in reducing inflammatory markers and improving clinical outcomes has been partially confirmed. The CANTOS study for canakinumab and the RESCUE trial for ziltivekimab demonstrated significant reductions in hsCRP and other inflammatory biomarkers. A full assessment of the impact on clinical outcomes requires further studies, especially for ziltivekimab (ongoing ZEUS study).

2b. The hypothesis concerning the mechanisms of action of these drugs has been confirmed. The article details how canakinumab and ziltivekimab work by inhibiting the IL-1β and IL-6 pathways respectively, leading to reduced inflammation and potentially improved heart function.

3. The hypothesis that patients with baseline elevated inflammatory markers would benefit more from anti-inflammatory therapy has been partially confirmed. Analysis of the CANTOS study showed that patients who achieved lower hsCRP levels benefited more from canakinumab treatment.

4. The safety profile hypothesis has been partially confirmed. Studies have shown an acceptable safety profile for both drugs, but full assessment requires longer observations and larger patient groups.

5. The hypothesis about the cost-effectiveness of canakinumab was not confirmed. Cost analysis showed that at its current price, canakinumab is not cost-effective compared to standard care.

6. The hypothesis about greater efficacy of anti-inflammatory therapy in HFpEF compared to HFrEF has neither been conclusively confirmed nor rejected. The article indicates potential benefits in HFpEF, but direct comparisons between these two types of heart failure are lacking.

7. The hypothesis regarding the long-term impact of IL-6 inhibition on cardiovascular events and kidney disease progression cannot be fully verified based on the presented data. The ongoing ZEUS study is expected to provide more information on this.

Most hypotheses have been partially confirmed, but some require further research for full verification. The article emphasizes the promising potential of anti-inflammatory therapies in treating heart failure, while also indicating the need for further clinical trials and economic analyses.

CONCLUSIONS

Anti-inflammatory drugs such as canakinumab and ziltivekimab show promise as alternative treatments for patients with cardiovascular diseases, including heart failure. The approach of targeting specific phenotypes within the heart failure syndrome by selecting patients who are predisposed to better treatment outcomes represents a major step towards personalized medicine. Continued research into immunomodulatory therapies for heart failure is essential to validate and expand upon these findings. Additionally, a deeper analysis of the inflammatory pathways involved in heart failure may be crucial to unlocking new therapeutic opportunities.

Based on the verification of hypotheses, here are the conclusions emphasizing their applicability.

1. Inflammatory Markers in Heart Failure. The confirmation of the role of elevated inflammatory markers in heart failure suggests that routine monitoring of these markers (e.g., IL-1β, IL-6, CRP) could be valuable in clinical practice. This could aid in early identification of patients at higher risk of developing or experiencing worsening heart failure, allowing for more proactive management strategies.

2. Efficacy of Anti-inflammatory Therapies. The partial confirmation of the effectiveness of canakinumab and ziltivekimab in reducing inflammatory markers supports their potential use in heart failure management. However, the translation of these biomarker reductions into meaningful clinical outcomes requires further investigation. Clinicians should consider these therapies as promising but not yet fully established options, particularly for patients with persistently elevated inflammatory markers despite standard treatment.

3. Patient Selection for Anti-inflammatory Therapy. The finding that patients with higher baseline inflammatory markers may benefit more from these therapies suggests a potential for personalized medicine approaches. Clinicians could use inflammatory marker levels to guide treatment decisions, potentially offering anti-inflammatory therapies to those most likely to benefit.

4. Safety Considerations. The partially confirmed safety profile of canakinumab and ziltivekimab is encouraging but calls for cautious application in clinical practice. Long-term safety monitoring should be implemented when using these therapies, and clinicians should remain vigilant for potential adverse effects.

5. Cost-Effectiveness. The lack of cost-effectiveness for canakinumab at its current price point is a significant barrier to widespread adoption. This finding underscores the need for either price adjustments or more targeted use in high-risk patients where the benefits might outweigh the costs. Health systems and policymakers should consider these economic factors when making decisions about including these therapies in treatment guidelines or formularies.

6. Heart Failure with Preserved Ejection Fraction (HFpEF). The potential benefits of anti-inflammatory therapies in HFpEF, a condition with limited treatment options, warrant further exploration. Clinicians should consider enrolling HFpEF patients in clinical trials of these therapies where available, and researchers should prioritize studies specifically targeting this patient population.

7. Long-term Outcomes and Kidney Disease. The ongoing research into long-term cardiovascular outcomes and kidney disease progression highlights the need for comprehensive patient monitoring. Clinicians using these therapies should track not only cardiac function but also renal outcomes, contributing to a better understanding of their overall impact on patient health.

Applicability of Conclusions. 1. Clinical Practice. These findings support the integration of inflammatory marker testing into routine heart failure management. They also suggest a more personalized approach to treatment, considering a patient's inflammatory status when making therapeutic decisions. 2. Research Direction. The conclusions highlight key areas for future research, including long-term efficacy studies, direct comparisons between different types of heart failure, and further investigation into the broader health impacts of these therapies. 3. Health Policy. The cost-effectiveness findings have implications for drug pricing and reimbursement policies. They suggest a need for either price adjustments or more selective use of these therapies to ensure their economic viability in healthcare systems. 4. Patient Care. The potential for improved outcomes in difficult-to-treat conditions like HFpEF offers hope for patients and clinicians alike. However, the conclusions also emphasize the need for careful patient selection and monitoring when using these novel therapies. 5. Interdisciplinary Approach. The impact of these therapies on both cardiac and renal outcomes underscores the importance of a holistic, interdisciplinary approach to patient care in heart failure management.

Anti-inflammatory therapies show promise in heart failure management, their application in clinical practice should be carefully considered, taking into account individual patient characteristics, potential benefits, safety considerations, and economic factors. Ongoing research and real-world evidence will be crucial in refining the role of these therapies in heart failure treatment paradigms.

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