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Emerging Role of Ziltivekimab in Residual Inflammatory Cardiovascular Risk: A Comprehensive Narrative Review

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Absract:
The cardiovascular disease (CVD) continues to be one of the leading causes of mortality in the world in spite of the major advancements in the development of lipid-lowering therapies, as well as preventative cardiology. Accumulating scientific data support the notion that the persistence of vascular inflammation represents a substantial factor contributing to the residual cardiovascular risk of an individual even in the presence of his or her lipids in the target range. Being a pro-inflammatory cytokine, the interleukin-6 (IL-6) is regarded as an important factor influencing all aspects of CVD pathogenesis, including endothelial dysfunction, atherosclerosis, and thrombosis. Therefore, a novel monoclonal antibody ziltivekimab was developed to inhibit the action of the IL-6 ligand in order to diminish inflammation-induced damage. Ziltivekimab was found to result in a marked decrease in inflammatory bio-markers (hsCRP, fibrinogen, serum amyloid A). Moreover, ziltivekimab was proven to be well-tolerated in patients suffering from chronic kidney disease and thus prone to inflammation. In our presentation, we will review the information on disease and its causes; the pharmacological properties and mechanisms; pharmacological effects and side effects of ziltivekimab observed in clinical trials, and its potential future role in the treatment of CVD.

1. INTRODUCTION

The CVDs can be characterized as chronic diseases of a multifactorial nature, which cause morbidity and mortality all over the world. Traditional treatment approaches were based on the reduction of LDL-C levels by means of statins, ezetimibe, and PCSK9 inhibitors. In spite of the impressive results obtained by such methods in terms of cardiovascular events reduction, some patients continue to suffer from myocardial infarctions, strokes, and vascular re-events regardless of their proper lipid level control. Such a phenomenon is called residual cardiovascular risk.1There is a growing number

of scientific papers highlighting the crucial role of chronic inflammation in triggering atherosclerosis, independently of hyperlipidaemia.

Among many inflammatory mediators, one of the cytokines – IL-6 – is paid much attention due to its impact on the inflammation of vessels and plaque destabilization. The high levels of IL-6 and hsCRP determine high risks of morbidity and mortality in case of CVDs.2The result was the emergence of an innovative approach to the treatment of CVDs, namely anti-inflammatory therapy approach. Ziltivekimab is a new biological drug targeting IL-6 ligand.**Error! Reference source not found.**

1.1. *Overview of Atherosclerotic cardiovascular disease*

Atherosclerotic cardiovascular disease (ASCVD) is a form of chronic inflammatory disease and refers to a continuing progressive condition associated with arterial constriction and stiffening caused by lipid and inflammatory cells deposits within the arteries. Atherosclerosis usually results in conditions such as coronary artery disease, myocardial infarction, ischemic stroke, and peripheral arterial disease.4The pathogenesis of ASCVD starts with endothelial dysfunction resulting in lipid deposition and vascular inflammation. Inflammation in turn results in unstable and ruptured arterial walls as well as clot formation and blockages. It has been observed that even after effective lipid lowering treatment, inflammation is still present in patients, suggesting the existence of separate inflammation contribution to cardiovascular diseases.1

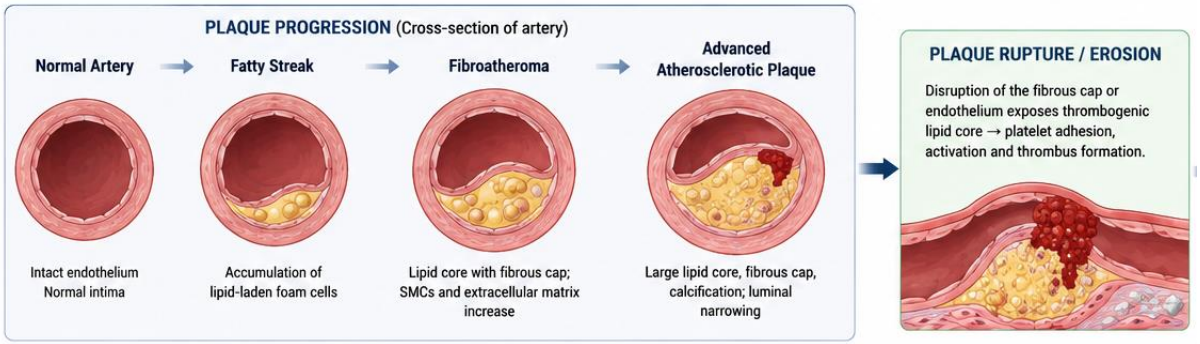


Figure 1. Overview of the pathophysiological mechanism of atherosclerotic cardiovascular disease (ASCVD).

1.2. *Major risk factors of ASCVD*

Atherosclerosis-induced CVDs result from interaction of several underlying genetic, metabolic, environmental, and inflammatory causes. The major risk factors associated with atherosclerosis are high cholesterol levels, high blood pressure, diabetes mellitus, obesity, smoking, low physical exercise, renal diseases, and old age. These predisposing factors all play an integral part in the development of endothelium damage and inflammatory response within the blood vessel.5There is production of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 by activated macrophages, endothelial cells,and T-lymphocytes. However, IL-6 has shown to significantly contribute to the process of inflammation in that it promotes the production of proteins like hsCRP and fibrinogen by the liver. This results into oxidative stress, proliferation of smooth muscles, and thrombosis. Patients with chronic renal disease have very serious inflammatory complication.6

2. DRUG PROFILE

2.1. *What is Ziltivekimab?*

Ziltivekimab is a fully human monoclonal antibody that is designed to block specifically the IL-6 ligand, a key cytokine responsible for chronic inflammation. It is an example of a biological anti-inflammatory agent that can be used as a promising treatment to reduce the inflammatory cardiovascular residual risk among patients with persistent high levels of inflammatory biomarkers despite adequate lipid lowering treatment. As opposed to traditional anti-inflammatory treatments, ziltivekimab blocks specifically the free IL-6 before it binds to the receptor in order to inhibit classical as well as trans-signalling and maintain intact receptors. Ziltivekimab is prescribed as a monthly subcutaneous treatment because of the drug's long half-life. Early clinical trials have shown predictable pharmacokinetics, inflammation biomarker suppression, and a favourable pharmacology.7

2.2. *Mechanism of Ziltivekimab.*

Interleukin-6 is an essential cytokine in the initiation and propagation of vascular inflammation, endothelial dysfunction, and atherosclerosis. Increased concentrations of IL-6 activate the JAK/STAT signaling pathway leading to stimulation of the production of acute phase proteins like high-sensitivity C-reactive protein (hsCRP), fibrinogen, and serum amyloid A by the liver. The activation of this pathway causes endothelial damage, oxidative stress, leukocyte recruitment, plaque rupture, and thrombosis, which ultimately increases the likelihood of developing cardiovascular diseases. Ziltivekimab binds to circulating IL-6 ligand and inhibits the interaction between the IL-6 ligand and the receptor on cell membranes or in soluble form. This inhibition leads to suppression of downstream inflammation. signalling causing significant reduction in systemic and vascular inflammation without influencing lipid levels. The benefits of this drug, therefore, are due to its anti-inflammatory effects but not cholesterol reduction.8

2.3. *Clinical Evidence of Ziltivekimab*

The clinical effectiveness of ziltivekimab has been assessed in patients with chronic kidney disease and elevated hsCRP levels, who remain at increased risk of cardiovascular disease despite undergoing conventional lipid-lowering therapy. Favourable pharmacokinetics and dose-dependent inhibition of inflammatory markers have been demonstrated in early Phase I trials. Later Phase II trials, especially the RESCUE trial, have provided strong evidence in support of its anti-inflammatory effects.

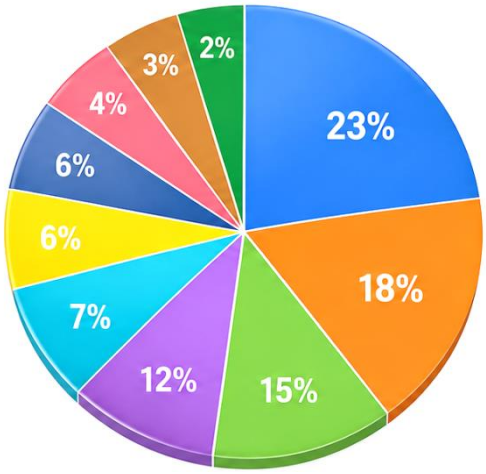
Figure 2.**Clinical trials demonstrate significant reduction in inflammatory biomarkers with ziltivekimab.**

Repeated doses of ziltivekimab resulted in dose-dependent reductions of hsCRP from 77% to 92%, along with substantial decreases in fibrinogen, serum amyloid A, haptoglobin, lipoprotein (a), and neutrophil to lymphocyte ratio. Most importantly, no alterations were observed in the levels of LDL and HDL cholesterol, thus proving that the therapeutic benefits of this drug are achieved via selective targeting of inflammation only. This evidence supports the possibility of reducing the residual inflammation-related risk of cardiovascular disease without affecting the lipid levels. Further Phase III outcome trials will confirm whether the observed reductions in biomarkers result in a reduction of

myocardial infarctions, strokes, cardiovascular death, and other major adverse cardiovascular events.1,**Error! Reference source not found.**,4

2.3. *Safe and Adverse effect of Ziltivekimab.*

Clinical trials have shown that ziltivekimab has a good safety and tolerability profile. The most frequently occurring adverse reactions are mild injection site reactions such as pain, erythema, swelling, and tenderness, which can usually resolve themselves without requiring discontinuation of the therapy. Mild upper respiratory infections such as nasopharyngitis have been reported probably as a result of partial suppression of IL-6 mediated immune responses. Decreased neutrophil levels have been observed in some patients due to IL-6 involvement in neutrophil maturation and mobilization, but clinically relevant neutropenia and severe infections have not been common. Increased levels of hepatic transaminases (AST and ALT) have also been reported in the absence of clinical evidence for any liver damage. Other side effects associated with the use of ziltivekimab are headache, fatigue, nausea, abdominal pain, and weakness. Although inhibition of IL-6 on the long term may lead to immunosuppression and opportunistic infections, there is currently no evidence indicating the presence of significant risk of these complications in relation to the use of ziltivekimab.



Adverse Event	Incidence (%)	Description
Injection Site Reactions	23%	Redness, pain, tenderness, or swelling at the injection site
Upper Respiratory Tract Infections	18%	Includes common cold, sore throat, and other mild infections
Nasopharyngitis	15%	Inflammation of the nasal passages and throat
Neutropenia	12%	Reduction in neutrophil count in blood
Elevated Liver Enzymes	7%	Increase in AST/ALT levels
Headache	6%	Includes mild to moderate headache
Fatigue	6%	Feeling of tiredness or lack of energy
Nausea	4%	Feeling of sickness or uneasiness
Diarrhea	3%	Loose or watery bowel movements
Serious Infections	2%	Includes severe bacterial or opportunistic infections

Figure 3. Adverse Events Observed in Clinical Trials of Ziltivekimab

3. FUTURE DIRECTIONS AND RESEARCH NEEDS

The invention of ziltivekimab can be seen as an innovation in inflammation-oriented cardiovascular treatment; nevertheless, many scientific gaps still exist. Although some existing trials have shown impressive decreases in inflammatory biomarkers, it still remains to be proven whether there is a decrease in cardiovascular morbidity and mortality in the long term. Whether ziltivekimab can decrease myocardial infarction, stroke, heart failure, and cardiovascular mortality will be established through current Phase III outcomes trials. More research is needed to evaluate its long-term safety issues, such as those related to chronic immunosuppression, infections, liver safety, and hematological effects.9 Further research should consider the effectiveness of ziltivekimab in various populations, such as diabetics, heart failure patients, obese patients, people with autoimmune diseases, and chronic kidney disease. Comparisons with other anti-inflammatory medications and the economic efficacy of

ziltivekimab can further define its place in managing cardiovascular risks. Predictive biomarkers should be studied to select suitable candidates for treatment.[10]

4. DISCUSSION

Vascular inflammation has been revealed as an important factor in remaining cardiovascular risks despite advances in lowering lipids. It is increasingly clear that the two factors (inflammation and dyslipidaemia) are complementary but distinct players in atherogenesis. Successes with other anti-inflammatory interventions have underscored the idea that modulating specific inflammatory pathways could lower cardiovascular risk. In this regard, IL-6 presents an ideal target owing to its importance in the regulation of inflammatory signalling and acute-phase protein production.[11]Ziltivekimab provides a new means to achieve selectivity towards IL-6 in that it specifically targets the IL-6 ligand in contrast to inhibiting the receptor; this allows for the effective inhibition of inflammation while preserving an excellent safety profile. The clinical evidence shows significant decreases in inflammatory markers without any impact on lipid metabolism, making it a good addition to the usual cardiovascular therapy. Despite this biological effectiveness shown by strong evidence, a larger, randomized trial is required to verify its effect on the heart before. [12]

5. CONCLUSION

Ziltivekimab represents a highly prospective biological agent that specifically blocks IL-6 ligand and helps manage the remaining inflammatory cardiovascular risk due to potent inflammation suppression. Modern evidence base reveals a considerable decrease in the levels of hsCRP and other markers of inflammation along with good safety and tolerance properties. In contrast to classical cholesterol-lowering medications, ziltivekimab acts on the pathways of inflammation involved in atherogenesis and provides complementary approach to cardiovascular risk reduction. However, reliable information about the cardiovascular outcomes, proper patient selection, and long-term safety of this drug is still missing. The results of further Phase III clinical trials will help to define its place in therapeutics and show whether biomarker changes lead to decreased rates of cardiovascular events. [13]

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