

Association of Interleukin 6 Inhibition With Ziltivekimab and the Neutrophil-Lymphocyte Ratio

A Secondary Analysis of the RESCUE Clinical Trial

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 Supplemental content

IMPORTANCE The neutrophil-lymphocyte ratio (NLR) independently predicts atherosclerotic events and is a potential biomarker for residual inflammatory risk. Interleukin (IL) 1 β inhibition reduces the NLR, but whether inhibition of IL-6, a cytokine downstream of IL-1, also lowers the NLR is uncertain.

OBJECTIVE To evaluate whether ziltivekimab, a therapeutic monoclonal antibody targeting the IL-6 ligand, associates with a lower NLR compared with placebo.

DESIGN, SETTING, AND PARTICIPANTS This was an exploratory post hoc analysis of Trial to Evaluate Reduction in Inflammation in Patients With Advanced Chronic Renal Disease Utilizing Antibody Mediated IL-6 Inhibition (RESCUE), a double-blind, randomized, placebo-controlled, phase 2 trial conducted from June 17, 2019, to January 14, 2020, with 24 weeks of follow-up. Participants were enrolled at 40 sites in the US and included adults aged 18 or older with moderate to severe chronic kidney disease and high-sensitivity C-reactive protein levels of 2 mg/L or greater. Data were analyzed from September 28, 2021, to October 2, 2022.

INTERVENTIONS Participants were randomly assigned equally to placebo or ziltivekimab, 7.5 mg, 15 mg, or 30 mg, subcutaneously every 4 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was the change in the NLR at 12 weeks.

RESULTS A total of 264 participants (median [IQR] age, 68 [60-75] years; 135 men [51%]; 129 women [49%]) were enrolled, of which 187 (71%) had diabetes, and 126 (48%) had known atherosclerosis. The median (IQR) change in the NLR at 12 weeks was 1.56% (IQR, -15.7% to 20.0%), -13.5% (IQR, -31.6% to 3.20%), -14.3% (IQR, -26.9% to 4.62%), and -22.4% (IQR, -33.3% to -4.27%) in the placebo, 7.5-mg, 15-mg, and 30-mg groups, respectively. The estimated treatment difference compared with placebo was -14.6% (95% CI, -24.8% to -4.81%; $P = .004$), -15.3% (95% CI, -25.2% to -5.10%; $P = .004$), and -23.6% (95% CI, -33.2% to -14.2%; $P < .001$) in the 7.5-mg, 15-mg, and 30-mg groups, respectively. A similar reduction in the absolute neutrophil count was observed.

CONCLUSIONS AND RELEVANCE Results of this post hoc analysis of the RESCUE trial show that IL-6 ligand inhibition with ziltivekimab associates with a lower NLR, suggesting that it may disrupt multiple atherogenic inflammatory pathways, including those mediated by the myeloid cell compartment. The NLR may have use in monitoring ziltivekimab's efficacy should it be introduced into clinical practice.

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Following guideline-directed therapies, residual inflammatory risk and residual cholesterol risk jointly contribute to atherosclerotic disease progression. Both inflammation inhibition and lipid lowering are now proven to reduce vascular event rates.¹⁻³ Although high-sensitivity C-reactive protein (hsCRP) is an established test for atherosclerotic inflammatory risk, the neutrophil-lymphocyte ratio (NLR) has emerged as an inexpensive biomarker that may reflect pathologic bone marrow activity and assess residual inflammatory risk.

Confirming data from prior small studies, we recently evaluated the NLR as a predictor of cardiovascular (CV) risk in over 60 000 patients from 5 contemporary clinical trials.⁴ In all 5 trials, baseline NLR significantly predicted CV events. More recent studies have linked the NLR to adverse outcomes in an expanding list of clinical scenarios, including heart failure and ischemic stroke.^{5,6}

Anti-inflammatory therapy with the interleukin (IL) 1 β inhibitor canakinumab, which reduces CV risk,¹ lowered the NLR.⁴ This observation suggests that the NLR may have additional utility in monitoring anti-inflammatory therapies. Despite canakinumab's overall benefit, participants with elevated on-treatment IL-6—the cytokine downstream from IL-1 β in the NLRP3 inflammasome pathway—did not respond, indicating residual risk attributable to unaddressed IL-6 activity.⁷ Furthermore, mendelian randomization studies have supported a causal role for IL-6 and its receptor in atherothrombosis.⁸

Attention has thus turned to drugs targeting IL-6.⁸ For example, in the randomized trial Assessing the Effect of Anti-IL-6 Treatment in Myocardial Infarction (ASSAIL-MI), reductions in the absolute neutrophil count (ANC) and NLR from IL-6 receptor blockade were associated with higher myocardial salvage indices.⁹

Ziltivekimab is a novel therapeutic monoclonal antibody targeting the IL-6 ligand. The Trial to Evaluate Reduction in Inflammation in Patients With Advanced Chronic Renal Disease Utilizing Antibody Mediated IL-6 Inhibition (RESCUE) evaluated the effect of ziltivekimab on inflammatory biomarkers in patients with chronic kidney disease (CKD) and elevated hsCRP level, a population at high atherosclerotic risk.¹⁰ Within RESCUE, ziltivekimab allocation resulted in dose-dependent reductions in hsCRP, fibrinogen, serum amyloid A, haptoglobin, secretory phospholipase A2, and lipoprotein(a) levels. Here, we address whether ziltivekimab also associated with changes in 3 cell-based inflammatory biomarkers—the NLR, ANC, and absolute lymphocyte count (ALC).

Methods

RESCUE was a double-blind, randomized, placebo-controlled, phase 2 trial conducted at 40 sites in the US. The study protocol was approved by the independent ethics committee of the institutional review board for each center.¹⁰ Written informed consent was obtained from participants before participation.

Adults with stage 3 to 5 CKD and hsCRP level of 2 mg/L or greater (to convert to milligram per deciliter, divide by 10) were

Key Points

Question Does interleukin 6 ligand inhibition with ziltivekimab associate with changes in the neutrophil-lymphocyte ratio (NLR)?

Findings In Trial to Evaluate Reduction in Inflammation in Patients With Advanced Chronic Renal Disease Utilizing Antibody Mediated IL-6 Inhibition (RESCUE), a double-blind, randomized, placebo-controlled, phase 2 clinical trial of 264 participants assessing the effects of ziltivekimab on surrogate inflammatory markers, targeted interleukin 6 ligand inhibition dose-dependently associated with a lower NLR at week 12.

Meaning Results of this study suggest that ziltivekimab may be associated with multiple proatherogenic inflammatory pathways, including those mediated by the myeloid cell compartment.

randomly assigned equally to placebo or ziltivekimab, 7.5 mg, 15 mg, or 30 mg, subcutaneously every 4 weeks, up to 24 weeks. A major exclusion criterion included an ANC of less than $2.0 \times 10^9/L$ (to convert to cells per microliter, divide by 0.001). Full enrollment criteria are published separately.¹⁰ Complete blood and differential counts were collected at each visit. Participants from the following race and ethnic groups were included: Asian, Black, Native Hawaiian/Pacific Islander, White, and other. There were both Hispanic and non-Hispanic ethnicities included. Race and ethnicity were identified via self-reporting. Data on race and ethnicity were collected to identify population-specific signals, to ensure that participants reflected the demographics of clinically relevant populations, and to align with the US Food and Drug Administration recommendations. Collecting data on race and ethnicity was not a requirement of the funder.

Using parallel methods as those used in RESCUE for its prespecified primary end point of change in hsCRP level, we evaluated associations between ziltivekimab and changes in the NLR. The change in NLR compared with baseline was computed for each participant. The primary outcome was the change in the NLR at 12 weeks after beginning treatment. The assay for serum IL-6 cannot discriminate between bound and unbound ligand; therefore, it could not be used as a surrogate for drug efficacy. Secondary outcomes included the changes in the ANC and ALC at week 12. The change in NLR was also computed for various subgroups. Because the ANC, ALC, and NLR have nonnormal distributions,⁴ nonparametric statistical methods were used. The Hodges-Lehmann estimator determined the location shift between each ziltivekimab group and placebo and the associated 95% CI. The Wilcoxon 2-sample *t* test compared the changes in the active groups to placebo. The incidence of infections and serious infections were computed for participants with a 12-week ANC above/below the median.

Spearman correlation coefficients were used to quantify the associations between baseline NLR and other biomarkers, as well as the changes in NLR and other biomarkers at week 12. All reported *P* values are 2-sided with a level of .05 indicating statistical significance. All analyses were performed using SAS, version 9.4 (SAS Institute). Data were analyzed from September 28, 2021, to October 2, 2022.

Results

A total of 264 participants (median [IQR] age, 68 [60-75] years; 135 men [51%]; 129 women [49%]) were enrolled, with 66 randomly assigned to each group. A total of 215 participants had a week 12 visit. Due to the COVID-19 pandemic, the trial was terminated prematurely, leading to balanced missing values across groups.¹⁰

Baseline characteristics were evenly distributed (eTable 1 in the Supplement). Participants from the following race and ethnic groups were included: 3 Asian (1.1%), 60 Black (22.7%), 1 Native Hawaiian/Pacific Islander (0.4%), 199 White (75.4%), and 1 other race (0.4%). A total of 71 participants (26.9%) identified as Hispanic, 192 participants (72.7%) identified as non-Hispanic, and 1 participant (0.4%) had unknown ethnicity. A total of 187 participants (71%) had diabetes, and 126 participants (48%) had known atherosclerosis.

The median (IQR) change in the NLR at 12 weeks was 1.56% (IQR, -15.7% to 20.0%), -13.5% (IQR, -31.6% to 3.20%), -14.3% (IQR, -26.9% to 4.62%), and -22.4% (IQR, -33.3% to -4.27%) in the placebo, 7.5-mg, 15-mg, and 30-mg groups, respectively (Figure and Table 1). The estimated treatment difference compared with placebo was -14.6% (95% CI, -24.8% to -4.81%; $P = .004$), -15.3% (95% CI, -25.2% to -5.10%; $P = .004$), and -23.6% (95% CI, -33.2% to -14.2%; $P < .001$) in the 7.5-mg, 15-mg, and 30-mg groups, respectively. Associations of ziltivekimab with lower NLR were also observed at week 1 (Table 1). Ziltivekimab was associated with lower NLR in all analyzed subgroups (eTable 2 in the Supplement).

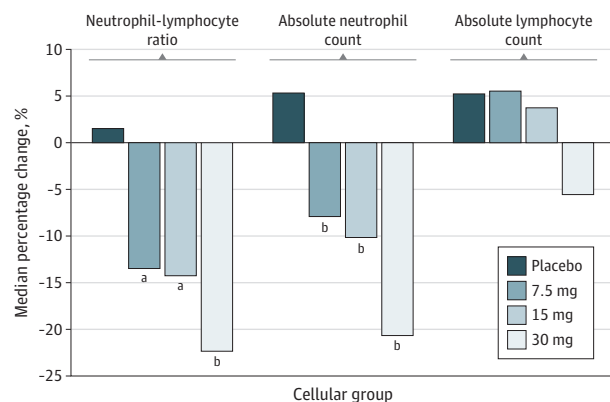
Ziltivekimab was associated with similar reductions in the ANC level. The median change in the ANC level at 12 weeks was 5.41% (IQR, -10.0% to 23.8%), -7.92% (IQR, -26.8% to 5.56%), -10.2% (IQR, -21.6% to 6.07%), and -20.7% (IQR, -36.0% to -10.7%) in the placebo, 7.5-mg, 15-mg, and 30-mg groups, respectively (Figure and eTable 3 in the Supplement). Ziltivekimab did not associate with changes in the ALC level (Figure and eTable 4 in the Supplement).

Baseline NLR correlated modestly with IL-6 (Spearman $\rho = 0.18$; $P = .01$) (eTable 5 in the Supplement). The change in NLR at 12 weeks correlated modestly with changes in hsCRP level (Spearman $\rho = 0.26$; $P < .001$), fibrinogen level (Spearman $\rho = 0.18$; $P = .02$), haptoglobin level (Spearman $\rho = 0.17$; $P = .03$), and Lp(a) level (Spearman $\rho = 0.22$; $P = .004$) (Table 2). A full correlation matrix is provided in the supplement (eTable 6 in the Supplement). Infections were not more common in participants with an ANC level below the median at 12 weeks (eTable 7 in the Supplement).

Discussion

Results of this study suggest that ziltivekimab, a therapeutic monoclonal antibody targeting the IL-6 ligand that substantially lowered hsCRP level in RESCUE,¹⁰ was also associated with a dose-dependent reduction in the NLR by lowering the ANC. These changes were observed from week 1 through week

Figure. Associations of Ziltivekimab With the Neutrophil-Lymphocyte Ratio, Absolute Neutrophil Count, and Absolute Lymphocyte Count



Median percentage change in the neutrophil-lymphocyte ratio, absolute neutrophil count, and absolute lymphocyte count at 12 weeks for those randomly allocated to placebo or to ziltivekimab, 7.5 mg, 15 mg, or 30 mg.

^a $P < .01$ when compared with placebo.

^b $P < .001$ when compared with placebo.

12. The change in NLR correlated modestly with changes in hsCRP level, suggesting that the participants with the greatest reductions in hsCRP level were not necessarily the same as those with greater reductions in the NLR. Ziltivekimab was well tolerated, and despite these reductions in the NLR, only 6 participants across all 4 groups developed grade 1 to 2 neutropenia (1000 to <2000 cells/mm³). There were no cases of grade 3 to 4 neutropenia. The ANC reduction was not associated with higher infectious risk.

The associations between IL-6, myelopoiesis, and atherosclerosis have been explored in mechanistic studies. In mice, atherosclerosis of the bone marrow microvasculature leads to IL-6 expression by endothelial cells, which augments leukopoiesis yielding increased circulating proatherogenic leukocytes.¹¹ In humans, the metabolic syndrome associates with augmented granulocyte—but not lymphocyte—numbers in peripheral blood.¹² In these ways, the association between the NLR and atherosclerotic events may be bidirectional, enabling a positive feedback loop that can ultimately provoke atherothrombosis.

One of the goals of addressing residual inflammatory risk might be to disrupt these bidirectional pathways between the bone marrow and the vasculature. There is strong evidence in favor of IL-1 and IL-6 inhibition in achieving this goal. Canakinumab, which reduced the NLR by a similar degree as ziltivekimab, reduced major adverse CV events.^{1,4} IL-1 β inhibition influences bone marrow activity and the behavior of circulating leukocytes.¹³ IL-6 receptor blockade with tocilizumab not only led to rapid reduction in the ANC and NLR after ST-elevation myocardial infarction, but also changes in the gene expression related to neutrophil function.¹⁴

The observation that ziltivekimab associates with a lower NLR has potential clinical significance because of the associations between NLR and atherosclerotic risk.⁴ There are

Table 1. Association of Ziltivekimab With the Neutrophil-Lymphocyte Ratio (NLR)^a

Treatment	Week 1					P value	Week 12				
	Baseline, NLR	NLR	Change	% Change	Treatment difference, % (95% CI)		NLR	Change	% Change	Treatment difference, % (95% CI)	P value
Placebo, median (IQR)	3.00 (2.40 to 3.33)	2.93 (2.15 to 4.06)	0 (-0.46 to 0.50)	0 (-14.9 to 21.6)	NA		3.05 (2.37 to 4.00)	0.04 (-0.54 to 0.62)	1.56 (-15.7 to 20.0)	NA	
7.5 mg, median (IQR)	2.98 (2.29 to 3.94)	2.39 (1.72 to 3.22)	-0.54 (-1.32 to -0.02)	-20.9 (-38.2 to -9.96)	-21.6 (-31.9 to -12.5)	<.001	2.60 (2.08 to 3.60)	-0.31 (-0.98 to 0.13)	-13.5 (-31.6 to 3.20)	-14.6 (-24.8 to -4.81)	.004
15 mg, median (IQR)	2.78 (2.29 to 3.71)	2.11 (1.57 to 2.55)	-0.60 (-1.25 to -0.31)	-24.5 (-42.5 to -12.2)	-27.6 (-35.9 to -19.4)	<.001	2.57 (1.93 to 3.22)	-0.23 (-0.71 to 0.13)	-14.3 (-26.9 to 4.62)	-15.3 (-25.2 to -5.10)	.004
30 mg, median (IQR)	2.86 (2.09 to 3.91)	2.06 (1.44 to 2.80)	-0.69 (-1.40 to -0.31)	-28.0 (-41.2 to -13.1)	-30.2 (-39.2 to -21.9)	<.001	2.13 (1.73 to 3.00)	-0.51 (-1.02 to -0.10)	-22.4 (-33.3 to -4.27)	-23.6 (-33.2 to -14.2)	<.001

Abbreviation: NA, not applicable.

^a Estimated treatment differences (%) in NLR compared with placebo provided with corresponding 95% CI and P value.

Table 2. Correlations Between Change in Neutrophil-Lymphocyte Ratio (NLR) and Changes in Other Biomarkers

Parameter change	No.	Correlation with change in NLR ^a	P value
SAA	168	0.15	.05
ApoA1	170	-0.06	.44
ApoB	170	-0.01	.87
ApoB/ApoA1	170	-0.03	.70
hsCRP	170	0.26	<.001
Fibrinogen	166	0.18	.02
Haptoglobin	168	0.17	.03
HDL	170	-0.04	.59
LDL	159	-0.02	.85
Lp(a)	170	0.22	.004
sPLA2	170	0.08	.31
Trig	170	-0.03	.68

Abbreviations: Apo, apolipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); SAA, serum amyloid A; sPLA2, secretory phospholipase A2; Trig, triglyceride.

^a Spearman correlation coefficients comparing change in NLR to change in other biomarkers at 12 weeks.

multiple hypotheses for causality: neutrophils localize near atherosclerotic plaques where they enhance monocyte transmigration, contribute to endothelial dysfunction, promote superficial plaque erosion, and influence fibrous cap rupture.¹² Lymphocytes have both atherogenic and atheroprotective subtypes,¹⁵ overall predicting decreased CV risk.⁴ In the ASSAIL-MI trial, reductions in the ANC and NLR from IL-6 receptor blockade were associated with higher myocardial salvage indices.¹⁴ These mechanistic and epidemiologic observations justify a favorable interpretation of our findings regarding ziltivekimab’s potential clinical efficacy.

Limitations

This study has limitations. First, the sample size is modest. Second, the change in NLR at 12 weeks was not a prespecified end point in RESCUE; therefore, these post hoc analyses should be viewed as exploratory. Finally, the brief follow-up period and small sample size did not allow for assessment of clinical outcomes or evaluation of the incremental risk discrimination of the NLR over usual risk factors.

Conclusions

Results of this post hoc analysis of the RESCUE trial suggest that ziltivekimab, which lowered hsCRP level in RESCUE, was associated with reductions in the NLR, a parameter readily available from routine blood cell counts. The NLR may therefore have use in monitoring ziltivekimab’s efficacy should it be introduced into clinical practice. Moreover, our findings suggest that ziltivekimab may disrupt multiple atherogenic inflammatory pathways, including those mediated by the myeloid cell compartment. The CV outcomes trial Effects of Ziltivekimab vs Placebo on Cardiovascular Outcomes in Participants With Established Atherosclerotic Cardiovascular Disease, Chronic Kidney Disease, and Systemic Inflammation (ZEUS), in which 6000 patients with atherosclerosis, CKD, and elevated hsCRP level are being randomly assigned to ziltivekimab, 15 mg, monthly or placebo, will determine whether these effects on surrogate inflammatory markers correspond to reduced major adverse CV events and progression of kidney dysfunction.⁸

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Author Contributions: Drs Adamstein and Ridker had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Adamstein, Ridker.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Adamstein.

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Conflict of Interest Disclosures: Dr Adamstein reported receiving grants from Novo Nordisk for conference expenses during the conduct of the study. Dr Cornel reported receiving advisory board fees from Amgen, AstraZeneca, and Novo Nordisk outside the submitted work. Dr Davidson reported being founder and chief science officer of Corvidia Therapeutics and receiving payments from Novo Nordisk outside the submitted work. Dr Libby reported being an unpaid consultant for Amgen, AstraZeneca, Beren Therapeutics, Baim Institute Esperion Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Medimmune, Merck, Norvo Nordisk, Novartis, Pfizer, Sanofi-Regeneron, Dewpoint, DalCor Pharmaceuticals, Olatec Therapeutics, XBiotech Inc, Caristo Diagnostics, Cartesian Therapeutics, CSL Behring, PlaqueTec, TenSixteen Bio, Soley Therapeutics, and Eulicid Bioimaging; having patents pending for Use of Canakinumab (20200239564) and Treatment of Brain Ischemia-Reperfusion Injury (5409-0001); receiving research funding from Novartis; being on

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Dr de Remigis reported being an employee of Novo Nordisk outside the submitted work. Ms Jensen reported being an employee of Novo Nordisk outside the submitted work. Dr Ekström reported being an employee of Novo Nordisk outside the submitted work. Dr Ridker reported receiving grant support from Novartis, Kowa, Amarin, Pfizer, Esperion, and the National Heart, Lung, and Blood Institute; serving as a consultant to Novartis, Flame, Agepha, AstraZeneca, Janssen, Civi Biopharm, GlaxoSmithKline, SOCAR, Novo Nordisk, Uptton, Omecios, Health Outlook, Montai Health, New Amsterdam, Boehringer Ingelheim, Angiowave, RTI, Horizon Therapeutics, and Cardio Therapeutics; and receiving compensation for service on the Peter Munk Advisory Board (University of Toronto), the Leducq Foundation, Paris, France, and the Baim Institute (Boston, Massachusetts). No other disclosures were reported.

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