KI REPORTS
KIReports.org
RESEARCH LETTER

Leukotriene Antagonist Use is Associated With Lower Systolic Blood Pressure in Adults

Jennifer Lai[1], Seth Furgeson[1], Petter Bjornstad[1,2], Zhiying You[1], Kalie L. Tommerdahl[2,3] and Jessica Kendrick[1]

[1]Division of Renal Disease and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA; [2]Department of Pediatrics, Section of Pediatric Endocrinology, Children's Hospital Colorado and University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA; and [3]Barbara Davis Center for Diabetes, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

Correspondence: Jessica Kendrick, Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, 12700 East, 19th Avenue, C281, Aurora, Colorado 80045, USA. E-mail: jessica.kendrick@cuanschutz.edu

Received 8 September 2022; revised 20 November 2022; accepted 22 November 2022; published online 25 November 2022

Kidney Int Rep (2023) **8,** 373–375; https://doi.org/10.1016/j.ekir.2022.11.013
KEYWORDS: albuminuria; blood pressure; leukotrienes; montelukast

INTRODUCTION

Chronic kidney disease (CKD) is an increasingly prevalent and progressive disorder that affects many adults in the United States. This disorder is associated with significant health care costs, morbidity, and mortality because CKD leads to kidney failure and increased cardiovascular risk. With most forms of CKD, inflammation plays a central role in the progression of kidney and cardiovascular disease (CVD).[1] The severity of CKD correlates with the number of kidney macrophages promoting the induction of chronic inflammation, tubular injury, and fibrosis.[2] Specifically, proinflammatory lipid mediators called leukotrienes produced through the 5-lipoxygenase pathway by macrophages and neutrophils cause endothelial dysfunction and increased glomerular permeability to albumin.[S1] In addition, leukotrienes mediate CVD, and increased expression of leukotrienes is found in human atherosclerotic lesions.[S2] In animal studies, inhibition of the 5-lipoxygenase pathway significantly reduces kidney fibrosis and improves kidney function.[3] Montelukast, a cysteinyl leukotriene receptor antagonist ($CystLT_1R$), also exhibits beneficial effects on vascular endothelial cell function in animal models.[4] Even though $CystLT_1R$ antagonists have been used extensively for the treatment of asthma and other diseases for decades, relatively little is known about their effects on kidney and cardiovascular outcomes in people with and without CKD. Using data from the National Health and Nutrition Examination Survey, we tested the hypothesis that the use of $CystLT_1R$ antagonists (montelukast/zafirlukast) in adults would associate with lower albuminuria and systolic blood pressure (SBP).

RESULTS

Among the 44,828 study participants from National Health and Nutrition Examination Survey, we identified 308 individuals that used montelukast or zafirlukast and propensity score matched them to 1232 individuals not using the medication (See Supplementary Methods). The characteristics of the study participants stratified by montelukast/zafirlukast prescription status are summarized in Table 1. Study participants were well matched. The mean age for all participants was 56.8 ± 18.0 years and the mean estimated glomerular filtration rate (eGFR) was 87.3 ± 23.5 ml/min per 1.73 m^2. The mean body mass index was in the obese range (31.4 ± 8.0 kg/m^2). Table 2 shows the association of montelukast or zafirlukast use with kidney and cardiovascular outcomes. After adjusting for age, sex, race, diabetes status, hypertension, body mass index, eGFR, use of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and serum C-reactive protein there was no association between montelukast/zafirlukast use and urine albumin-to-creatinine ratio (ACR), eGFR or CKD status (Table 2). Montelukast or zafirlukast use was associated with lower SBP after adjustment for age, sex, race, diabetes status, hypertension, body mass index, eGFR, urine ACR, use of antihypertensive medications and serum C-reactive protein (β [95% confidence interval]: −2.50 [−4.79, −0.20]).

Table 1. Baseline characteristics of study participants

	Montelukast/Zafirlukast Use	
Characteristic	**Yes ($N = 308$)**	**No ($N = 1232$)**
Age (yr)	55.7 ± 17.0	57.0 ± 17.7
Female (N, %)	199 (64.7)	796 (64.6)
Race		
Non-Hispanic White (N, %)	168 (54.5)	703 (57.1)
Diabetes (N, %)	68 (22.1)	244 (19.8)
Hypertension (N, %)	163 (52.9)	675 (54.8)
Body mass index ≥ 30 (kg/m^2)	155 (50.3)	616 (50.0)
eGFR (ml/min/1.73 m^2)	87.7 ± 21.8	86.8 ± 23.5
Urine ACR (mg/g)	0.50 ± 5.4	0.66 ± 4.9

ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.
Data are presented as mean ± SD.

DISCUSSION

The results of this analysis suggest that among a nationally representative sample, the use of montelukast or zafirlukast was related to SBP. We did not find an association between montelukast or zafirlukast use and eGFR, urine ACR or CKD status. Treatments that attenuate SBP are important, especially in individuals with chronic diseases such as diabetes and hypertension that can progress to kidney failure. Our findings suggest that CystLT$_1$R antagonists may be protective against kidney and CVD and warrant further testing.

The essential role of leukotrienes in promoting inflammation and recruiting neutrophils suggests that the use of CystLT$_1$R antagonists has protective benefits for kidney function. In some animal studies, elevated concentrations of leukotrienes such as leukotriene B$_4$ are a potent chemoattractant for neutrophils, which subsequently leads to the release of lysosomal enzymes and reactive oxygen species that increase tissue damage in the kidneys.[5] Infusion of leukotrienes in animal models provoked vasoconstriction that led to a significant reduction in renal blood flow and attenuated GFR.[6] Inhibition of leukotrienes also significantly reduces renal fibrosis in animal models.[3] In a small study, children with minimal change disease using montelukast for 12 months showed a significant reduction in relapse rate during montelukast therapy and posttherapy.[7] Thus, inhibition of leukotrienes using CystLT$_1$R antagonists may inhibit kidney damage and prevent development of CKD.

In addition to having kidney protective benefits, CystLT$_1$R antagonists have been implicated to have cardiovascular benefits as well. Elevated concentrations of leukotrienes, specifically leukotriene B$_4$ and cysteinyl leukotrienes, are associated with a greater degree of atherosclerosis.[8] Animal studies have shown that montelukast improves vascular endothelial cell function and myocardial remodeling.[4] More recently, an observational study of adults with asthma demonstrated a significant relationship between montelukast use and a reduction in major ischemic cardiovascular events, including myocardial infarction and ischemic stroke.[9] Therefore, montelukast may target leukotriene-driven inflammation and have important benefits in reducing CVD.

Our study has limitations worth discussing. First, because this is an observational study, we are unable to imply causality. Second, we do not have information about adherence to the montelukast or zafirlukast prescription, which could have confounded our findings. Although we were able to adjust for C-reactive protein, we were not able to adjust for additional inflammatory markers because they were not available. In addition, albuminuria was based on a single random measure of ACR. We did not find any association with urine ACR, CKD, or eGFR in the current study. This may be due to a relative preservation of GFR throughout the participants and a very low prevalence of CKD overall. Finally, urine ACR was very low in the entire cohort. Accordingly, further study is needed in a population with a higher prevalence of CKD.

In summary, we found in National Health and Nutrition Examination Survey that participants using montelukast or zafirlukast had significantly lower SBP than participants not using montelukast or zafirlukast. Inhibiting leukotriene effects may prevent generalized inflammation that contributes to the advancement of both CKD and CVD. As a result, our analysis suggests that leukotriene inhibition may represent a novel therapeutic target for people with kidney disease and provide cardiovascular protection. Future investigations are needed to evaluate larger-scale cohorts, assess different populations, and further examine the relationship between montelukast use and kidney and CVD in mechanistic trials.

Table 2. Association of montelukast/zafirlukast use with albuminuria, blood pressure, and kidney disease

Montelukast use vs. no use	**β-estimate (95% CI)**	***P*-value**
Urine ACR[a]	−0.10 (−0.21, 0.03)	0.14
eGFR[b]	0.53 (−1.50, 2.54)	0.60
SBP[c]	−2.50 (−4.79, −0.20)	0.033
	Odds ratio (95% CI)	***P*-value**
CKD[b]	0.80 (0.47, 1.34)	0.38

ACE, angiotensin converting enzyme; ACR, albumin-to-creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
[a]Adjusted for age, sex, race, diabetes status, hypertension, body mass index, eGFR, and use of ACE inhibitor or angiotensin receptor blocker and CRP.
[b]Adjusted for age, sex, race, diabetes status, hypertension, body mass index, and use of ACE inhibitor or angiotensin receptor blocker and CRP.
[c]Adjusted for age, sex, race, diabetes status, hypertension, body mass index, eGFR, urine ACR, and use of antihypertensive medications and CRP.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

JK receives salary and research support from NIH/NIDDK R01DK130255 and NIH/NIA AG068657. KLT receives salary and research support from the NIH/NHLBI (K23 HL159292), Children's Hospital Colorado Research Institute Research Scholar Award, NIH/NIDDK (P30 DK116073), Ludeman Family Center for Women's Health Research at the University of Colorado, ISPAD-JDRF Research Fellowship, and the Department of Pediatrics, Section of Endocrinology and Barbara Davis Center for Diabetes at University of Colorado School of Medicine. PB receives salary and research support from NIDDK (R01 DK129211, R01 DK132399, R21 DK129720, K23 DK116720, UC2 DK114886), NHLBI (R01HL165433), JDRF (3-SRA-2022-1097-M-B, 3-SRA-2022-1243-M-B, 3-SRA-2022-1230-M-B), Boettcher Foundation, American Heart Association (20IPA35260142), Ludeman Family Center for Women's Health Research at the University of Colorado, the Department of Pediatrics, Section of Endocrinology and Barbara Davis Center for Diabetes at University of Colorado School of Medicine. Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

AUTHOR CONTRIBUTIONS

JL, JK, and SF contributed to the study conception and design. All authors contributed to data acquisition and interpretation. All authors contributed to the drafting, revising and final approval of the version to be published. All authors are in agreement to be accountable for all aspects of the work prepublication and postpublication.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

REFERENCES

1. Akchurin OM, Kaskel F. Update on inflammation in chronic kidney disease. *Blood Purif*. 2015;39:84–92. https://doi.org/10.1159/000368940
2. Tang PM, Nikolic-Paterson DJ, Lan HY. Macrophages: versatile players in renal inflammation and fibrosis. *Nat Rev Nephrol*. 2019;15:144–158. https://doi.org/10.1038/s41581-019-0110-2
3. Montford JR, Bauer C, Dobrinskikh E, et al. Inhibition of 5-lipoxygenase decreases renal fibrosis and progression of chronic kidney disease. *Am J Physiol Ren Physiol*. 2019;316:F732–F742. https://doi.org/10.1152/ajprenal.00262.2018
4. Hoxha M, Rovati GE, Cavanillas AB. The leukotriene receptor antagonist montelukast and its possible role in the cardiovascular field. *Eur J Clin Pharmacol*. 2017;73:799–809. https://doi.org/10.1007/s00228-017-2242-2
5. Noiri E, Yokomizo T, Nakao A, et al. An in vivo approach showing the chemotactic activity of leukotriene B(4) in acute renal ischemic-reperfusion injury. *Proc Natl Acad Sci U S A*. 2000;97:823–828. https://doi.org/10.1073/pnas.97.2.823
6. Badr KF, Baylis C, Pfeffer JM, et al. Renal and systemic hemodynamic responses to intravenous infusion of leukotriene C4 in the rat. *Circ Res*. 1984;54:492–499. https://doi.org/10.1161/01.res.54.5.492
7. Abeyagunawardena S, Jayaweera H, Abeyagunawardena AS. The effect of montelukast sodium on the reduction of relapse rates in children with steroid dependent nephrotic syndrome. *Arch Nephrol Urol*. 2021;4:009–017.
8. Colazzo F, Gelosa P, Tremoli E, Sironi L, Castiglioni L. Role of the cysteinyl leukotrienes in the pathogenesis and progression of cardiovascular diseases. *Mediators Inflammm*. 2017;2017:2432958. https://doi.org/10.1155/2017/2432958
9. Hoxha M, Tedesco CC, Quaglin S, et al. Montelukast use decreases cardiovascular events in asthmatics. *Front Pharmacol*. 2020;11:611561. https://doi.org/10.3389/fphar.2020.611561