Leukotriene Antagonist Use Is Associated With Less Albuminuria and Lower Systolic Blood Pressure in Adults

Jennifer M. Lai, Seth Furgeson, Petter Bjornstad, Zhiying You, Kalie L. Tommerdahl, Jessica Kendrick

University of Colorado Denver, Aurora CO

BACKGROUND

- Chronic kidney disease (CKD) is associated with significant morbidity and mortality.
- Leukotrienes are pro-inflammatory lipid mediators that cause endothelial dysfunction, increase glomerular permeability to albumin, and mediate cardiovascular disease.
- In animal studies, the use of montelukast, a cysteinyl leukotriene receptor antagonist ($CystLT_1R$), is shown to significantly reduce renal fibrosis and improve renal function.
- We tested the hypothesis that the use of $CystLT_1R$ antagonists (montelukast/zafirlukast) in adults would associate with less albuminuria and lower systolic blood pressure (SBP).

METHODS

Study Population

- We examined the use of $CystLT_1R$ with albuminuria and SBP using data from 51,111 adults from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2018
- In NHANES, urine albumin and creatinine were measured in a single spot urine sample and were reported as urine albumin to creatinine ratio (ACR) in mg/g.
- Resting SBP was measured in mmHg by trained staff at mobile examination centers and during home examinations.
- Demographic data was collected via participants' responses to questionnaires.
- We defined chronic kidney disease as urine ACR >30 mg/g or eGFR <60 mL/min/1.73m^2.

Statistical Analysis

- Linear regression was used to evaluate the association between montelukast use and the primary outcomes of continuous variables, and odds ratio was used for categorical variables.
- Potential effect modifiers, such as age, sex, race, diabetes, hypertension, and body mass index (BMI) were adjusted in the models.

RESULTS

Table 1. Baseline Characteristics of Study Population

Characteristics	Montelukast/Zafirlukast Use N = 434	No Montelukast/Zafirlukast Use N = 50,677
Age	55.0 ± 17.0	47.1 ± 19.1
Female N (%)	281 (64.7)	26,082 (51.5)
Race White N (%)	235 (54.1)	21,863 (43.1)
Diabetes N (%)	108 (24.9)	6479 (12.8)
Hypertension N (%)	231 (53.2)	16,151 (31.9)
Body mass index (kg/m^2)	31.5 ± 7.8	28.7 ± 6.8
eGFR (ml/min/1.73m^2)	87.9 ± 21.9	96.6 ± 23.2
Urine ACR (mg/g)	32.1 ± 211.8	46.8 ± 352.7

GFR = estimated glomerular filtration rate; ACR = albumin to creatinine ratio

Table 2. Association of Montelukast/Zafirlukast Use with Albuminuria, Blood Pressure, and Kidney Disease

Montelukast/Zafirlukast Use vs. No Use	β-Estimate (95% CI)	P-value
Urine ACR*	-0.13 (-0.22 to -0.04)	0.005
eGFR**	-0.50 (-2.1 to 1.05)	0.51
SBP***	-1.98 (-3.82 to -0.11)	0.038
	Odds Ratio (95% CI)	**P-value**
CKD**	0.89 (0.66 to 1.21)	0.45

*Adjusted for age, sex, race, diabetes status, hypertension, body mass index, eGFR, and use of ACE inhibitor or angiotensin receptor blocker.
** Adjusted for age, sex, race, diabetes status, hypertension, body mass index, and use of ACE inhibitor or angiotensin receptor blocker.
*** Adjusted for age, sex, race, diabetes status, hypertension, body mass index, eGFR, urine ACR, and use of anti-hypertensive medications.

RESULTS CONTINUED

- Of the 51,111 study participants in NHANES, 434 were on montelukast/zafirlukast.
- Patients on montelukast/zafirlukast were older and had a lower baseline eGFR than participants who were not using the medication. They also had a higher prevalence of diabetes, hypertension, and obesity than participants not on montelukast/zafirlukast.
- After adjustment, montelukast/zafirlukast use was associated with a lower urine albumin-to-creatinine ratio (ACR).
- After adjustment, there was no association between montelukast/zafirlukast use and eGFR or CKD.
- After adjustment, montelukast/zafirlukast use was also associated with lower SBP.

DISCUSSION

- Elevated levels of leukotrienes in animal models have been demonstrated to be a potent chemoattractant for neutrophils, which leads to the release of lysosomal enzymes and reactive oxygen species that increase tissue damage in the kidneys.
- In a recent study, children with minimal change disease using montelukast for 12 months had a significant reduction in relapse rate during montelukast therapy and post-therapy.
- Animal studies have shown that montelukast improves vascular endothelial cell function and myocardial remodeling.
- More recently, an observational study of asthmatic adults has shown a significant relationship between montelukast use and the reduction of major ischemic cardiovascular events, such as myocardial infarction or ischemic stroke.

CONCLUSIONS

- Participants using montelukast/zafirlukast had significantly lower albuminuria and SBP than participants not using montelukast.
- Inhibition of leukotriene may represent a novel therapeutic target for patients with kidney disease and provide CVD protection.
- Further studies are needed to examine the relationship between montelukast/zafirlukast use and kidney and cardiovascular disease.