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Impact of aliskiren treatment on urinary aldosterone levels in patients with type 2 diabetes and nephropathy: an AVOID substudy

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Abstract

Introduction: Aldosterone blockade reduces albuminuria in diabetic patients with chronic kidney disease (CKD), and improves prognosis in chronic heart failure. This study assessed the effects of direct renin inhibition with aliskiren in combination with losartan and optimal antihypertensive therapy on urinary aldosterone, plasma renin activity (PRA) and plasma renin concentration (PRC).

Materials and methods: In the AVOID study, 599 patients with type 2 diabetes, hypertension and nephropathy received 6 months aliskiren (150 mg force titrated to 300 mg once daily after 3 months) or placebo added to losartan 100 mg and optimal antihypertensive therapy. Urinary aldosterone excretion, PRA and PRC were measured at baseline and after 24 weeks in a prespecified subset of 133 patients.

Results: Aliskiren added to losartan provided reductions from baseline in urinary aldosterone compared with adding placebo (−24% vs. −4%, $p = 0.017$) at week 24. There was no significant difference between the aliskiren and placebo groups in the proportion of patients with aldosterone breakthrough (aliskiren 35%, placebo 46%, $p = 0.199$). Aliskiren treatment reduced PRA by 90% at 24 weeks and increased PRC by 328%.

Conclusions: Adding aliskiren to recommended renoprotective treatment with losartan and optimal antihypertensive therapy provided significant reductions in urinary aldosterone excretion which may attenuate decline in kidney function.

Keywords

Albuminuria, aldosterone, aliskiren, diabetes, nephropathy, renin inhibition

Introduction

Aldosterone has well described deleterious effects in several key organs.[1] Treatment directed towards the aldosterone receptor has a potential for treating CKD.[2–4] After initiation of renin–angiotensin–aldosterone system (RAAS) blocking treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), plasma aldosterone levels normally decrease, but in 30–40% of patients, plasma aldosterone levels return to pretreatment levels or higher during ongoing treatment. This phenomenon, called 'aldosterone breakthrough',[5] is associated with a larger decline in renal function,[5,6] and may constitute a potential point of intervention with mineralocorticoid antagonists in patients otherwise treated with maximal renoprotective therapy.

Direct renin inhibition bears interesting possibilities as treatment with aliskiren, the first available drug in this class, blocks the RAAS at the first rate-limiting step resulting in very low levels of angiotensin II. Although plasma renin concentration rises accordingly, aliskiren effectively binds to renin and plasma renin activity is decreased.[7] The AVOID study[8] is the largest study so far with aliskiren in patients with type 2 diabetes and nephropathy. The main result showed that aliskiren 300 mg once daily added to recommended

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Table 1. Baseline characteristics of 133 patients included in the substudy of the AVOID study

Characteristic	Aliskiren (*n*=62)	Placebo (*n*=71)	*p*-value
Age, years	57.6±10.4	60.8±9.5	0.12
Male gender, *n*(%)	40(65%)	55(77%)	0.12
Race, *n*(%)			0.62
Caucasian	42(68%)	51(72%)	
Black	13(21%)	16(23%)	
Other	7(11%)	4(6%)	
Body mass index, kg/m^2	37.5±8.1	35.5±6.8	0.15
≥ 30 kg/m^2, *n*(%)	53(85%)	53(75%)	0.42
Baseline eGFR, *n*(%)			0.44
<60 mL/min/1.73 m^2	29(47%)	30(42%)	
≥60 mL/min/1.73 m^2	33(53%)	41(58%)	
SBP, mmHg	133.3±10.5	132.0±11.7	0.36
DBP, mmHg	76.0±7.3	74.8±8.8	0.53
UACR,[a] mg/g	492(392–615)	554(457–672)	0.56
UAER,[a] µg/min	757(584–980)	785(634–972)	0.87

Data are presented as mean±SD, unless otherwise stated. [a]Data are shown as geometric means (95% confidence interval). DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, UACR: urinary albumin creatinine ratio, UAER: urinary albumin excretion rate.

renoprotective treatment with the ARB losartan 100 mg once daily and optimal antihypertensive treatment reduced albuminuria by 20% compared with placebo over 6 months. Samples were taken from a prespecified subset of 133 patients, and were analysed for urinary aldosterone levels, plasma renin activity (PRA) and plasma renin concentration (PRC) to investigate the impact of combined RAAS blockade on urinary aldosterone and plasma renin levels.

Materials and methods

In a randomized, double blind, placebo-controlled study (AVOID), we evaluated the renoprotective effect of aliskiren in 599 hypertensive patients with type 2 diabetes and nephropathy. The methods have been described in detail in the main publication.[8]

In a subset of patients (n = 133) biomarkers were analysed. In plasma samples we measured PRC using CISbio Renin III kits (Bagnols/Cèze, France) and PRA using DiaSorin RIA kits (Minneapolis, USA). Urinary aldosterone was measured using Siemens RIA Coat-a-Count (Tarrytown, USA). Urinary aldosterone excretion over 24 hours was chosen over plasma aldosterone sampling, as the urinary analysis reflects the mean aldosterone level better than random plasma samples due to diurnal variation in plasma aldosterone levels.

Changes from baseline in log-transformed biomarkers were analysed using analysis of covariance (ANCOVA) models with baseline log-transformed biomarker as a covariate, and treatment, region and baseline albuminuria classification as factors. To assess the frequency of aldosterone breakthrough in the two treatment groups, responder analysis evaluated the proportion of patients with a reduction from baseline (i.e. >0% reduction) in urinary aldosterone; between-treatment comparisons were made by χ^2 test.

Results

Characteristics of the subset patients (Table 1) were not significantly different from patients in the original AVOID study, but the difference between the two groups was less than in the main study. Reduction in urinary albumin creatinine ratio (UACR) over the 24-week study period in this subset of patients was 22% and 9% for aliskiren and placebo groups, respectively (NS). Compared to placebo, adding aliskiren 300 mg reduced urinary aldosterone levels by 20% after 24 weeks of treatment ($p = 0.017$) (Figure 1). PRA was reduced 93% from baseline to week 24 by aliskiren ($p < 0.001$). Aliskiren treatment increased PRC by 328% from baseline, while placebo group PRC was reduced by 17% (between-treatment $p < 0.001$) (Table 2). Mean systolic BP was reduced by 0.5 mmHg in the aliskiren group, and increased by 1.9 mmHg in the placebo group ($p = 0.33$). Mean diastolic BP was reduced by 3.1 mmHg in the aliskiren group and increased by 0.4 mmHg in the placebo group ($p = 0.013$).

Table 2. Results in urinary aldosterone, PRA and PRC according to treatment group

	Aliskiren			Placebo			
	Baseline	Week 24	Change (95% CI)	Baseline	Week 24	Change (95% CI)	*p*-value
Urinary aldosterone, nmol/day	15.8	12.0	–24% (–35, –11)	18.6	17.9	–4% (–22, +18)	0.017
PRA, ng/mL/h	2.2	0.2	–90% (–93, –87)	3.2	2.6	–19% (–36, +3)	<0.001
PRC, ng/L	26.9	88.1	+328% (+267, +404)	37.3	31.0	–17% (–31, –0)	<0.001

PRA: plasma renin activity, PRC: plasma renin concentration.

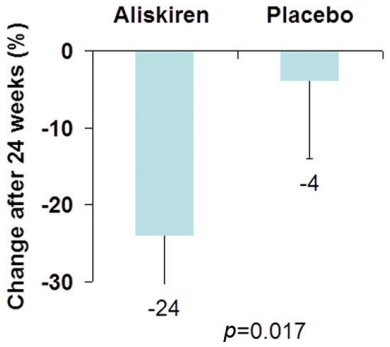

Figure 1. Geometric mean change (%) from baseline to week 24 in urinary aldosterone levels according to treatment group (between-treatment comparison p=0.017).

The proportion of patients with a reduction from baseline in urinary aldosterone (no signs of aldosterone breakthrough) was numerically higher in the aliskiren group relative to the placebo group (65% in the aliskiren group compared to 54% in the placebo group although this was not statistically significant, $p = 0.199$). There was no difference between the two groups in side effect frequency.

Discussion

Renin inhibition added to recommended renoprotective treatment including losartan 100 mg once daily reduced urinary aldosterone levels by 24% during 24 weeks of treatment. This extends findings from a smaller study that found a nonsignificant 23% difference between plasma aldosterone levels in patients treated with irbesartan combined with aliskiren as compared to irbesartan monotherapy.[9]

We found a higher proportion of patients with a reduction in urinary aldosterone levels in the aliskiren group as compared to placebo. The proportion of patients with an increase in urinary aldosterone levels (aldosterone breakthrough) was 46% in the placebo group and 35% in the aliskiren group. Schjoedt et al.[10] have reported dual RAAS blockade leading to a decrease in plasma aldosterone in 36 of 51 (70%) patients with type 1 diabetes and diabetic nephropathy.

In this subpopulation of the AVOID study the changes in albuminuria were different from the main study, suggesting less power and limiting the conclusions to be made.

The changes in PRA and PRC correspond to previous studies.[9,11] It is, however, unknown if the low activity of the renin enzyme is responsible for the reduction in urinary aldosterone.

Aldosterone is known to have numerous deleterious effects on the kidney.[12] Renin inhibition added to RAAS blockade is currently being investigated in the ALTITUDE study[13] and this will provide further data on this important issue.

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Conflict of interest

Dr Persson reports having received lecture fees from Novartis and having equity interest in NovoNordisk. Dr Rossing reports having received lecture fees from Novartis and Boehringer Ingelheim; a research grant from Novartis; having served as a consultant for Merck; and having equity interest in NovoNordisk. Dr E Lewis reports having received grant support from Keryx Biopharmaceuticals. Dr JB Lewis reports having served as a consultant for Merck and Novartis and having received grant support from Keryx Biopharmaceuticals and the National Institute of Health. Dr Hollenberg reports having received grant support from Novartis and Merck. Dr Parving reports having served as a consultant for Novartis, Merck, Pfizer and Sanofi-Aventis; having equity interest in Merck and NovoNordisk; having received lecture fees from Novartis, Merck, Pfizer and Sanofi-Aventis; and having received grant support from Novartis, AstraZeneca and Sanofi-Aventis.

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