Direct renin inhibition in chronic kidney disease

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For approximately 6 years, the only commercially available direct renin inhibitor, aliskiren, which inhibits the renin-angiotensin-aldosterone system at the initial rate limiting step, has been marketed for the treatment of hypertension. Concurrently, much attention has been given to the possibility that renin inhibition could hold potential for improved treatment in patients with chronic kidney disease, with diabetic nephropathy as an obvious group of patients to investigate, as the activity of the renin-angiotensin-aldosterone system is enhanced in these patients and as there is an unmet need for improved treatment and prognosis in these patients. Several short term studies have been performed in diabetic nephropathy, showing a consistent effect on the surrogate endpoint lowering of albuminuria, both as monotherapy and in combination with other blockers of the renin-angiotensin-aldosterone system. In addition, combination treatment also seemed safe and effective in patients with impaired kidney function. These initial findings formed the basis for the design of a large morbidity and mortality trial investigating aliskiren as add-on to standard treatment. The study has just concluded, but was terminated early as a beneficial effect was unlikely and there was an increased frequency of side effects. Also in non-diabetic kidney disease a few intervention studies have been carried out, but there is no ongoing hard outcome study. In this review we provide the current evidence for renin inhibition in chronic kidney disease by reporting the studies published so far as well as a perspective on the future possibilities.

Introduction

During the last four decades the renin-angiotensin-aldosterone system (RAAS) has gained increasing importance in the understanding of the pathophysiology behind hypertension, heart failure and nephropathy. Renin and prorenin seem to play a special role in this pathophysiology, as demonstrated in many different settings. Luetscher *et al.* [1] made the seminal observation in 1985 that elevated levels of prorenin are associated with diabetic microangiopathy, thereby illustrating a possible point of intervention. Alderman *et al.* [2] described an epidemiological association between levels of plasma renin activity (PRA) and increased risk of cardiovascular disease in the general population, further attracting interest to the actions of renin. Recently, a *post hoc* analysis of levels of PRA in the HOPE study [3] demonstrated that high levels of PRA are an independent predictor of major vascular events and mortality in patients with high risk of cardiovascular disease.

The prognosis for diabetic patients in terms of development of end stage renal disease (ESRD) or death has improved markedly over the last two decades, mainly due to antihypertensive treatment and RAAS blockade [4–10] as is evident from renal registries from several countries [11–13]. There is, however, still a large unmet need to develop strategies for further prevention and treatment of diabetic nephropathy and the associated cardiovascular disease (CVD), and diabetic nephropathy remains the leading cause of ESRD in the developed world [14]. The same is the case for non-diabetic chronic kidney disease (CKD) as evident from a large recent metanalysis, indicating that CKD is just as important as diabetes and hypertension as a risk of mortality and progression to ESRD [15].

Renin inhibition is not a new concept in medicine. Renin was described in 1898 by Tigerstedt *et al.* [16] and it has been mentioned as an area of interest and potential benefit throughout the 20th century. Inhibiting the RAAS at the first and rate-limiting step seemed rational, but clinical development of renin inhibitors was difficult due to poor

bioavailability and high costs, so for a long time only angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blockade (ARB) therapy and aldosterone antagonism were clinically relevant modes of RAAS blockade.

Animal studies

When aliskiren was developed as the first orally available direct renin inhibitor, much interest was directed towards the potential for this new treatment. As reviewed by Feldman [17], both *in vitro* and *in vivo* studies pointed to specific renoprotective effects of aliskiren. In a transgenic mRen-2 rat model with streptozotocin-induced diabetes aliskiren ($10 \text{ mg kg}^{-1} \text{ day}^{-1}$) and perindopril ($0.2 \text{ mg kg}^{-1} \text{ day}^{-1}$) were compared [18]. Similar effects on albuminuria and glomerulosclerosis were observed, but aliskiren treated rats had lower levels of tubulo-interstitial fibrosis. In a non-hypertensive mouse model of progressive renal fibrosis, Gross *et al.* [19] showed that aliskiren treatment, initiated at a late stage of the disease, had beneficial effects on albuminuria and markers of renal fibrosis and significantly prolonged life span (18%) until occurrence of renal failure. Another interesting finding in db/db mice investigated by Dong *et al.* [20] displayed pleotropic effects of adding aliskiren to valsartan treatment. Albuminuria was attenuated, glomerular mesangial matrix expansion was reduced, and the authors stated that aliskiren enhanced the beneficial effects of valsartan treatment on glomerular expression of TGF- β collagen type IV and nephrin. In addition, one study has demonstrated that aliskiren partitions to the rat kidney, with a prolonged effect on plasma and renal tissue angiotensin II concentrations 12 days after cessation of treatment [21]. Altogether, there are many intriguing findings from animal models showing promise for clinical use of renin inhibition in humans with CKD.

Preclinical and physiological studies

From studies in primates it is clear that renal blood flow is increased during direct renin inhibition, seemingly to a higher extent than ACEI or ARB therapy, and without changes in glomerular filtration rate (GFR) suggesting more effective intrarenal blockade of the RAAS [22]. Subsequent human studies have confirmed these findings, first in healthy subjects on a low sodium diet, showing an approximately 40–50% higher increase in renal plasma flow during direct renin inhibition compared with what was seen with ACEIs and ARBs [23]. Another study found a somewhat more modest 14% increase in renal plasma flow in 10 subjects with uncomplicated type 1 diabetes on a high sodium diet [24]. Interestingly, GFR was increased in this population following direct renin inhibition.

Studies in renal dysfunction were also carried out during the development programme. Aliskiren was found to be safe in patients with impaired renal function (17

patients with creatinine clearance 50–80, 30–49 and $<30 \text{ ml min}^{-1}$, respectively) and there was no sign of altered accumulation of aliskiren [25]. Hence, it was concluded that dose reduction is not necessary in patients with impaired renal function [26].

In Japanese patients with mild to moderate hypertension and serum creatinine >1.3 and $<3.0 \text{ mg } 100 \text{ ml}^{-1}$ in males or >1.2 and $<3.0 \text{ mg } 100 \text{ ml}^{-1}$ in females, Ito *et al.* [27] demonstrated with a sequential dose titration approach in 8 weeks of study, that aliskiren 300 mg once daily was safe and effective.

Renin inhibition in diabetic nephropathy

The potential of renin inhibition as monotherapy has mainly been investigated in hypertension [28]. In a study in patients with type 2 diabetes we studied the time course of the antihypertensive and antiproteinuric effect of renin inhibition with aliskiren in a 3 month open study [29] with 15 patients with urinary albumin : creatinine ratio (UACR) $>30 \text{ mg g}^{-1}$. After a 4 week washout, patients received aliskiren 300 mg once daily for 28 days along with a stable dose of furosemide, followed by a 4 week withdrawal period. Early morning urine samples were collected every day during treatment and withdrawal. Twenty-four hour blood pressure was measured at baseline, after 3, 7, 14 and 28 days of treatment and 3, 7, 14 and 28 days after withdrawal. UACR was significantly reduced after 2–4 days of treatment by 17% with further reduction to 44% after 28 days. Systolic blood pressure was lowered by 6 mmHg after 7 days with no further reduction after 28 days. Blood pressure returned towards baseline 3 days after withdrawal, whereas UACR was still significantly reduced compared with baseline 12 days after withdrawal, indicating an antiproteinuric effect of aliskiren independent of blood pressure (BP) lowering.

The recommended antihypertensive dose for aliskiren treatment is 300 mg once daily. Higher doses do not increase antihypertensive efficacy, but instead increase gastrointestinal side effects [30]. The optimal BP lowering dose is not necessarily the optimal antiproteinuric dose. Several studies have shown that there can be differences between maximal antihypertensive dose and doses that can reduce albuminuria the most [31, 32]. We compared the effect of placebo and increasing doses of aliskiren on urinary albumin excretion rate (UAER) in a double-blind crossover trial [33]. Twenty-six patients with type 2 diabetes, hypertension and albuminuria were randomized to 2 months of treatment with placebo, aliskiren 150 mg, 300 mg or 600 mg once daily, in random order. Aliskiren 150, 300 and 600 mg daily reduced UAER significantly by 36%, 48% and 52%, respectively, compared with placebo. The UAER reduction during the 600 mg dose was not significantly different from the 300 mg dose.

Combination of renin inhibition and angiotensin II receptor blockade in diabetic nephropathy

Studies combining aliskiren with other RAAS blocking agents, such as valsartan [34] or ramipril [35] came first in hypertension. An obvious next step was to investigate renin inhibition in combination with RAAS blockade in patients with type 2 diabetes and albuminuria. The AVOID study [36] was the first large trial to investigate this by adding aliskiren or placebo to standard treatment consisting of the recommended renoprotective dose of losartan (100 mg once daily) and optimal antihypertensive treatment in 599 patients with type 2 diabetes and nephropathy. After a 12–14 week run-in period, patients were randomized to add placebo or aliskiren 150 mg daily. After 12 weeks aliskiren was force titrated to 300 mg once daily. The primary endpoint was reduction in UACR in early morning spot urine samples collected on 3 consecutive days. The change in UACR at the end of the study was an 18% reduction in the aliskiren treated group, while the placebo treated patients experienced a 2% increase in UACR despite being treated according to best practice and despite only a small reduction in blood pressure (2/1 mm Hg) at the end of the study.

Comparison of adverse events revealed no differences between the treatment groups (aliskiren 66.8% and placebo 67.1%), nor in rates of serious adverse events (9.0% and 9.4%, respectively). Special attention was directed towards the patients developing hyperkalaemia, and it turned out that 14 patients (4.7%) in the aliskiren group had at least one serum potassium measurement above 6.0 mmol l⁻¹ and five patients (1.7%) in the placebo group. Of the 14 aliskiren treated patients mentioned, nine had baseline serum potassium concentrations above the exclusion criteria of 5.1 mmol l⁻¹ and should never have been randomized to treatment. Four of these patients were subsequently excluded from the study. The beneficial results on albuminuria of this study, supported the design of the hard endpoint trial ALTITUDE [37].

In a *post hoc* analysis of the AVOID study [38] we assessed the efficacy and safety according to baseline estimated GFR (CKD stage 1–3). The antiproteinuric effects of aliskiren were consistent across CKD stages (19%, 22% and 18% reduction). In the CKD stage 3 group, baseline serum creatinine concentrations were equal but renal dysfunction, prespecified as a post-randomization serum creatinine elevation >176.8 µmol l⁻¹ (2.0 mg dl⁻¹) occurred more frequently in the placebo group (29.2% vs. 13.6%). Serum potassium elevations > 5.5 mmol l⁻¹ (based on a single measurement) were more frequent with aliskiren (22.5% vs. 13.6%) in stage 3 CKD. Adverse event rates were similar between treatments, irrespective of CKD stage.

This analysis indicates that aliskiren can be safely administered in CKD stage 1–3, but calls for caution and due monitoring of serum potassium in patients with CKD

stage 3. However, it seems to indicate a positive effect on progression on renal disease as there were reductions in albuminuria and fewer aliskiren treated patients experienced renal dysfunction as compared with placebo.

In another *post hoc* analysis of the AVOID study [39] we assessed the influence of baseline BP. The antiproteinuric effects of aliskiren were consistent across subgroups of baseline BP: Group A (prespecified target), <130/80 mmHg (*n* = 159), Group B, <140/90 mmHg but ≥130/80 mmHg (*n* = 189) and Group C (insufficient BP control), ≥140/90 mmHg (*n* = 251) (19–22% UACR reduction with aliskiren vs. placebo). In patients with insufficient BP control at baseline (≥140/90 mmHg), the decline in eGFR was significantly less with aliskiren than with placebo.

The fact that an antiproteinuric effect was seen when aliskiren was added in patients with BP levels considered to meet guidelines is important. In a clinical situation, many health care providers may dose and treat their patients according to BP level and not albuminuria level. These results indicate that further reduction in albuminuria is feasible with the addition of aliskiren, even if target BP has been reached. Special focus has to be directed towards hypotension however.

In a multicentre trial such as the AVOID study, many academic compromises have to be taken for the sake of feasibility. To achieve more detailed data, we performed a single centre double-blind, randomized, crossover trial [40] to investigate whether the antiproteinuric effect of aliskiren was comparable with irbesartan, and the effect of the combination of the two. After a 1 month washout period 26 patients with type 2 diabetes, hypertension and albuminuria (>100 mg day⁻¹) were randomized to four 2 month treatment periods in random order with placebo, aliskiren 300 mg once daily, irbesartan 300 mg once daily or the combination using identical doses. When irbesartan 300 mg once daily and aliskiren 300 mg once daily were combined during 8 weeks of treatment UAER was reduced 71% compared with placebo, and the combination lowered albuminuria 31% more as compared with irbesartan alone.

To investigate the impact of treatment on GFR all patients had ⁵¹Cr-EDTA GFR measured at the end of each treatment period. From a placebo mean GFR level of 89 ml min⁻¹ 1.73 m⁻² aliskiren treatment reduced GFR by 4.6 ml min⁻¹ 1.73 m⁻², irbesartan by 8.0 ml min⁻¹ 1.73 m⁻² and the combination by 11.7 ml min⁻¹ 1.73 m⁻². The changes in directly measured GFR were interesting, as they indicated haemodynamic changes after initiation of RAAS blockade, as usually seen, but here with signs of added potential during combination blockade.

Non-diabetic CKD

The non-diabetic CKD studies using aliskiren are fewer and shorter, certainly reflecting the weaker commercial

potential in this heterogeneous population. Nevertheless, a number of interesting studies have been performed, with promising results. It is however unlikely that large outcome studies will be performed in this area, at least for the time being. In an open-label study in 25 patients with IgA nephropathy [41], combination treatment with aliskiren (titrated to 300 mg once daily) and losartan (100 mg once daily) for 12 months reduced albuminuria by 26%. There were also significant reductions in serum interleukin-6 and TGF- β levels, compared with baseline.

Recently, Lizakowski *et al.* [42] published findings from a double masked, randomized, 12 week crossover study comparing the effects of aliskiren (300 mg once daily) and perindopril (10 mg once daily) on levels of TGF- β and pro-collagen III N-terminal propeptide (PIIINP) in 16 patients with non-diabetic kidney disease. Both aliskiren and perindopril treatment led to similar reductions in urinary levels of TGF- β , whereas PIIINP was unaffected. In addition, albuminuria was decreased during both active treatments compared with placebo [43].

In a study of 36 patients with non-diabetic stage I or II CKD, Nakamura *et al.* [44] found that combination treatment with aliskiren 300 mg once daily and olmesartan 40 mg once daily, reduced urinary levels of proteinuria as well as L-fatty acid binding protein (L-FABP), a marker of tubular injury, indicating that renin inhibition also may affect tubular injury, in part by reducing proteinuria.

Triple blockade

There are a few small reports of triple RAAS blockade in patients with CKD, aiming to reduce residual albuminuria. In a retrospective analysis of 15 patients with biopsy-proven primary membranous nephropathy with proteinuria of 1–3 g day⁻¹ (mean 2.4 g day⁻¹) [45], aliskiren (titrated to 300 mg once daily) was given in addition to dual RAAS blockade with an ACEI and an ARB. In eight of the 15 patients, proteinuria decreased to <500 mg day⁻¹ during the following 3 months.

De Nicola *et al.* [46] reported additional lowering of proteinuria in 45 patients with CKD stage 1–4 proteinuria with protein excretion > 0.5 g 24 h⁻¹, and ACEI/ARB combination therapy unchanged in the previous 3 months. Proteinuria was reduced by 22% after 6 months, and persisted after 12 months, with no major adverse events, including incidents of hyperkalaemia.

Renin inhibition in haemodialysis

In 30 diabetic/non-diabetic patients receiving haemodialysis, aliskiren as monotherapy or in combination with other RAAS blocking compounds, Morishita *et al.* [47] demonstrated a beneficial and BP-independent impact

on cardiovascular biomarkers (hs-CRP, BNP and d-ROM) during 8 weeks of treatment. One event of hypotension led to discontinuation of the drug in one patient, but other adverse events were scarce. In a long term follow-up of the study population (21 of the 30 patients originally included in the study), blood pressure decreased from 175/80 mmHg at baseline to 156/76 mmHg at month 20 [48].

Future perspectives

The concept of renin inhibition has stirred widespread interest among clinicians worldwide, much so because it holds promising effects and intervenes at the rate-limiting step in this cascade. Renin inhibitors have had several challenges such as low bioavailability and high development costs, which delayed their introduction into clinical care. Following the established evidence of ACEI and ARBs, and the much more favourable pricing of these compounds after going off patent, aliskiren has not gained widespread use and major clinical importance. Besides becoming a second/third/fourth choice in the treatment of hypertension, no other indication has been firmly established or approved, although studies in heart failure also have showed beneficial outcome in relation to the surrogate end point plasma BNP. With regards to diabetes and nephropathy, there was great anticipation of the recent results of the ALTITUDE trial [49], investigating the potential beneficial effects of adding aliskiren to established standard treatment. The study randomized 8561 high-risk patients with type 2 diabetes and evaluated hard cardiorenal endpoints. In December 2011 the study was stopped prematurely on the advice of the data safety monitoring board. Interim analysis showed an increase in adverse event rates in the aliskiren treated group and at the same time there was no sign of a beneficial effect on the primary composite cardio-renal endpoint. The final analysis of the study was recently published [50] and with the full analysis of data it is now evident that the primary endpoint occurred in 18.3% assigned to aliskiren as compared with 17.1% assigned to placebo, a non-significant difference. All secondary endpoint comparisons were also non-significant, including the occurrence of stroke, an endpoint that favoured placebo in the interim analysis that halted the study. The proportion of patients with hyperkalaemia (serum potassium concentration, ≥ 6 mmol l⁻¹) was significantly higher in the aliskiren group than in the placebo group (11.2% vs. 7.2%), as was the proportion with reported hypotension (12.1% vs. 8.3%) ($P < 0.001$ for both comparisons).

What is clear from results of the ALTITUDE study is that dual RAAS inhibition with aliskiren added to ACEI or ARB therapy, will not be a recommended future therapy in diabetic nephropathy.

Conclusion

The concept of direct renin inhibition in patients with CKD is interesting and holds potential for improved patient care and prognosis. Promising results with lowering of the surrogate endpoints blood pressure and albuminuria have been demonstrated across several subpopulations with a low level of side effects and few cautions needed. It must be emphasized however, that due to the unexpected findings in the ALTITUDE trial the use of renin inhibition in addition to RAAS blockade is considered contraindicated in high-risk type 2 diabetic patients with CKD. Whether better understanding of the trial results will clarify if there is a role for this combination is not known presently. Hard endpoint studies in non-diabetic kidney disease or in subgroups of patients with diabetic nephropathy will be essential in order for renin inhibitors to win a spot in routine clinical care, alongside and in combination with the well proven and long standing ACEI and ARBs. In many countries the pricing of renin inhibitors may also be an issue.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work. F.P. reports having received research grant and lecture fees from Novartis and owns stock in Novo Nordisk. P.R. reports having received lecture fees from Novartis and Boehringer Ingelheim, and a research grant from Novartis, has served as a consultant for Merck, and has equity interest in Novo Nordisk. H-H.P. reports having served as a consultant for Novartis, Merck, Pfizer and Sanofi-Aventis, having equity interest in Merck and Novo Nordisk and having received lecture fees from Novartis, Merck, Pfizer and Sanofi-Aventis. H-H.P. has received grant support from Novartis, AstraZeneca and Sanofi-Aventis. All authors approved the final version of the paper.

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