



## EDITORIAL COMMENT

# Aliskiren and the dual complement inhibition concept

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## ABSTRACT

In this issue of *Clinical Kidney Journal*, Plasse *et al.* report on the use of high-dose aliskiren as an adjunct therapy in a patient treated with eculizumab for haemolytic uraemic syndrome (HUS). This follows the recent description of the complement factor 3 (C3) activating activity of the enzyme renin and the successful therapeutic use of the direct renin inhibitor aliskiren in three cases of C3 glomerulopathy/dense deposit disease. We discuss the potential clinical and pathophysiological implications of these reports on nephropathies linked to complement, from HUS to C3 glomerulopathy to immunoglobulin A nephropathy as well as the concept of dual complement inhibition for kidney disease.

**Keywords:** aliskiren, complement, dense deposit disease, haemolytic uraemic syndrome, paroxysmal nocturnal haemoglobinuria, renin

In this issue of *Clinical Kidney Journal* (CKJ), Plasse *et al.* [1] report on the use of high-dose aliskiren as an adjunct therapy in a patient treated with eculizumab for haemolytic uraemic syndrome (HUS). This follows the recent description of the complement factor 3 (C3) activating activity of the enzyme renin and the successful therapeutic use of aliskiren in three cases of dense deposit disease [2]. We discuss the potential clinical and pathophysiological implications of these reports as well as the concept of dual complement inhibition for kidney disease.

## WHAT IS ALISKIREN?

Aliskiren is a direct renin inhibitor with low bioavailability (2–3%) and long half-life (40 h) [3]. The European Medicines Agency lists the indication for the treatment of essential hypertension in adults, a recommended dose of 150 mg once daily that may be increased to 300 mg once daily and the contraindication of the combination with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) in patients with diabetes mellitus or renal impairment [4]. However, aliskiren is not widely used, given that physicians are

more familiar with other less expensive renin–angiotensin system (RAS) blockers, and aliskiren cannot be combined with other RAS blockers for common indications given the suboptimal adverse effect profile and lack of clearly demonstrated advantages of dual RAS blockade with combinations of aliskiren, ACEIs and/or ARBs over single RAS blockade [5]. In fact, the number of PubMed-listed publications on aliskiren has progressively decreased over the past 7 years (Figure 1) [6].

## WHAT IS RENIN?

Renin is an aspartyl protease secreted by the juxtaglomerular apparatus in the kidneys [7]. The main known function of renin is to cleave angiotensinogen to form angiotensin I, the angiotensin II precursor peptide (Figure 2). Renin release is increased by lower blood pressure inside the afferent arterioles, lower tubular fluid chloride content at the macula densa of the distal tubule and  $\beta$ -adrenergic receptor activity [7, 8]. In addition, angiotensin II exerts a negative feedback inhibition on renin release. In this regard, RAS blockade may result in renin release and chronic dual ARB/ACEI may cause severe juxtaglomerular

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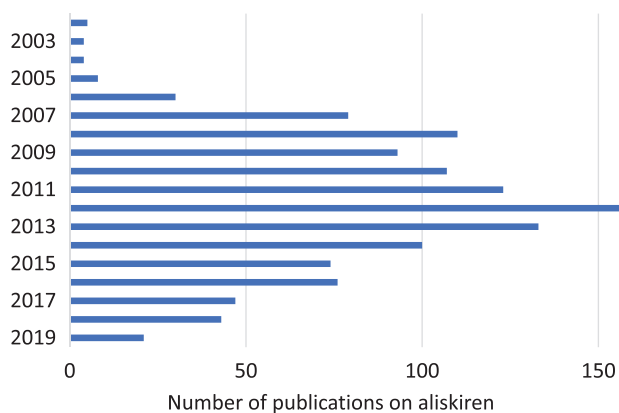


FIGURE 1: Annual number of PubMed-listed aliskiren publications as of 29 August 2019 [6].

hyperplasia characterized by increased renin staining [9]. Juxtaglomerular cells are specialized smooth muscle cells located mainly in the afferent arteriole. Under chronic renin stimulation situations, additional kidney cells may be recruited to secrete renin. In these circumstances, renin release will ultimately depend on the number of renin-secreting cells [8]. Thus the highest renin concentrations will be found in glomeruli and kidneys.

### WHAT IS THE NEW INFORMATION ON RENIN?

In 2018, Békássy *et al.* [2] found that human renin has enzymatic activity to cleave human C3 into C3a and C3b, that is, renin initiates the apical event in the alternative pathway for complement activation (Figure 2). They hypothesized that this may partly explain the sensitivity of the kidneys to complement-mediated injury. They went on to show that aliskiren use in three girls (ages 7–12 years) with dense deposit disease was associated with decreased systemic and renal complement activation (increased circulating C3 and decreased C3a and C5a levels, decreased renal C3 and C5b-9 deposition and/or decreased glomerular basement membrane thickness) and clinical stability of the kidney disease over a follow-up period of 4–7 years.

### WHAT ARE THE CLINICAL IMPLICATIONS OF THESE FINDINGS?

If confirmed, these findings may call for preferential use of aliskiren to lower blood pressure in C3 glomerulopathy. However, this is a rare disease. Thus confirmation will take time, and in the meantime it may seem reasonable to use aliskiren as a first-line therapy for these patients. Indeed, in an accompanying editorial, Nakano and Nishiyama [10] raised the issue of the safety of usual RAS blockers for C3 glomerulopathy, because they increase renin activity, and called for clinical studies comparing aliskiren versus ACEIs or ARBs for this disease. The rationale for raising questions may extend to other complement activation-related kidney diseases that represent a growing number of conditions. An example is immunoglobulin A nephropathy (IgAN) [11]. And IgAN is also an example of nephropathy for which classical RAS blockade is currently considered a key therapeutic approach [12]. At the height of interest on aliskiren in the earlier part of this decade, two clinical studies reported a

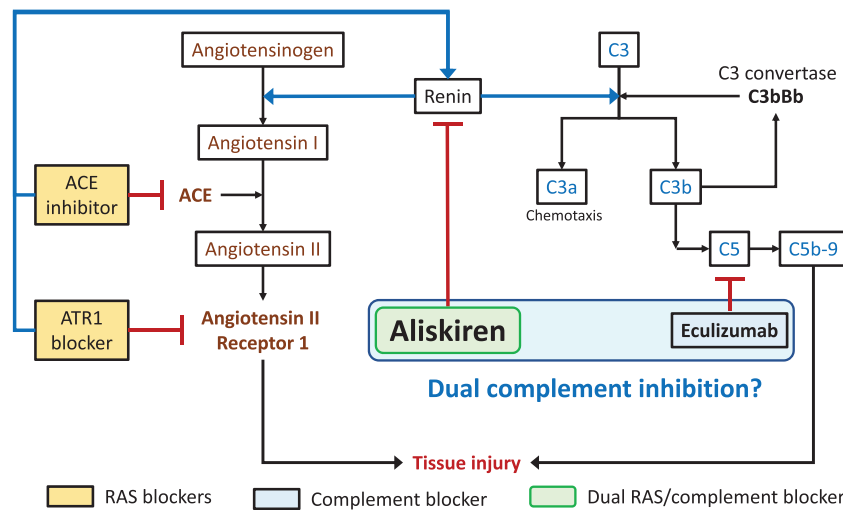
decrease in residual albuminuria by aliskiren in IgAN patients with significant residual albuminuria while on conventional RAS blockade [13, 14]. More recently, a case report described a complete proteinuria remission associated with initiation of aliskiren in an IgAN patient unresponsive to conventional RAS blockers, steroids and immunosuppressants [15]. However, in more common diseases, such as IgAN, any change of paradigm regarding routine clinical care must be preceded by clinical trials.

### HOW DOES THE NEW KNOWLEDGE FIT WITH OLDER LITERATURE DATA?

Almost 15 years ago, rats harbouring human renin and angiotensinogen genes were observed to develop hypertension and renal complement activation that preceded albuminuria [16]. Aliskiren reduced albuminuria and evidence of complement activation, which would be in line with a role for human renin in activating complement. However, an ARB also prevented complement activation and albuminuria, supporting a direct role of angiotensin II in these events. Thus, whatever the mechanism, aliskiren did not appear to offer an advantage over conventional RAS blockade and this older report would not have clearly predicted recent findings on the human renin–C3 interaction. Since recombinant murine renin did not cleave murine C3, the ARB-related potential increase in regulated murine renin expression was not expected to modulate C3 activation [2]. The lack of murine renin impact on murine C3 may have hampered research into this interaction.

### WHAT DOES THE RECENT CKJ REPORT ADD TO THE EVOLVING CONCEPTS ON RENIN AND COMPLEMENT?

Plasse *et al.* [1] report on the use of high-dose aliskiren as an adjunct therapy in a haemodialysis patient treated with eculizumab for HUS, thus potentially expanding the range of complement-related disease where aliskiren may be useful and adding key information on the impact of dose. Interpretation of results should depart from the observational and single nature of the report that does not allow us to exclude that the natural history of the disease overlapped with aliskiren use. However, the findings are intriguing, and for rare diseases, single case reports may generate hypotheses that improve disease management. Three key messages were (i) the patient remained on dialysis despite eculizumab/aliskiren and improvement in blood pressure and lab parameters, including C3 levels. Thus success was not complete. (ii) However, an increase in aliskiren dose to 600 mg/day was followed by an increase in C3 levels and improvement in other disease parameters within 1 month. Dosing considerations are discussed below. There are reports of renal function recovery when eculizumab was initiated after 4 months on dialysis and of recovery of renal function 2.0–3.5 months after initiation of eculizumab in dialysis-dependent patients with C3 glomerulopathy or HUS [17]. Thus the observed time line is a key to link the increase in aliskiren dose, 5 months after starting eculizumab, to benefit. (iii) Dialysis doctors should still be familiar with the molecular mechanisms of kidney disease, as shown by the rapid implementation of advances from recent reports to patient care.



**FIGURE 2:** Molecular pathways for RAS and alternative complement activation with sites of action of aliskiren and eculizumab. Drawn based on novel information on renin and complement interaction [2]. The dual complement inhibition concept is a hypothetical concept that requires clinical validation and is based on results published in this issue of CKJ [1]. Both ACE inhibition and angiotensin receptor blockade increase renin secretion. The C5 inhibitor eculizumab is currently used to treat complement-related kidney conditions such as atypical HUS (aHUS). Recent publications suggest that renin may also activate C3, and in observational case reports, aliskiren was associated with benefit in patients with dense deposit disease or aHUS [1, 2]. In the latter case, aliskiren was associated with benefit in association with eculizumab: the dual complement inhibition concept. ATR1, angiotensin II receptor 1.

## WHAT IS THE BIOLOGICAL PLAUSIBILITY AND DOSING IMPLICATIONS OF ALISKIREN INHIBITION OF RENIN?

In the original report, aliskiren inhibited C3 conversion *in vitro* at concentrations  $\geq 10$ – $>100$  nM depending on assay condition [2]. However, this is well above the mean and upper limit of the steady-state plasma aliskiren  $C_{max}$  in healthy volunteers or chronic kidney disease individuals on a 300-mg daily dose that may reach up to 0.001–0.002 nM, respectively, for mean and upper limit  $C_{max}$  in the presence or absence of irbesartan [18]. Based on this information, it seems unlikely that aliskiren inhibits C3 conversion *in vivo*. In this regard, the doses administered to children with dense deposit disease were not reported [2]. However, aliskiren accumulates in the kidney; in mice, the kidney:plasma ratio is 20:40 [19]. Another feature is that aliskiren has non-linear kinetics. Thus, after single-dose administration in the dose range of 75–600 mg, a 2-fold increase in dose results in a ~2.3- and 2.6-fold increase in the area under the curve and  $C_{max}$ , respectively, and at steady state the non-linearity may be more pronounced [4]. Thus the eventual local kidney concentration under steady-state high-dose conditions is unknown and a sustained dose increase to 600 mg/day, as done by Plasse *et al.* [1], may have led to substantially high local aliskiren levels.

## DOES RENIN REPRESENT A LOCAL COMPLEMENT ACTIVATION SYSTEM?

The local availability of high concentrations of renin together with local C3 production may result in a local pathway for alternative complement activation in the kidney. The local release of renin may contribute to activate locally released or circulating C3. In this regard, transplantation experiments involving  $C3^{+/+}$  and  $C3^{-/-}$  mice suggest a key role for locally synthesized C3 (mostly identified in tubular cells) for complement-mediated reperfusion damage after kidney ischaemia, whereas circulating C3 had a negligible effect [20]. In contrast, there is disagreement

on the role of local C3 on albumin overload-induced kidney injury, with the larger study suggesting it does play a role [21, 22]. Since these are murine studies and murine renin does not activate complement, they do not support a role for renin in murine complement-mediated disease, but they do raise the issue of such an interaction in humans in the context of diseases not usually associated with complement by physicians. In any case, under physiological conditions, C3 activation by renin may be controlled by negative regulators of complement activation. The interaction may eventually have pathological consequences if complement control systems are disabled. However, the experimental approach of this hypothesis is not easy and may involve genetically modified animals expressing human renin.

## DUAL COMPLEMENT INHIBITION FOR COMPLEMENT-MEDIATED KIDNEY DISEASE

The report by Plasse *et al.* [1] in this issue of CKJ may illustrate a novel concept for therapy of complement-mediated kidney disease: dual complement inhibition with eculizumab and high-dose aliskiren. For the moment, it is a sole case report and we cannot exclude that they only observed the natural history of the disease, modified by eculizumab. In any case, the close temporal relationship between the prescription of high-dose aliskiren and the improvement in analytical parameters coupled with the recent report on aliskiren inhibition of C3 processing and its use in three cases of dense deposit disease may portend a new era of dual complement inhibition for complement-related kidney disease [2] (Figure 2).

## UNANSWERED QUESTIONS

At present, recent clinical reports of an association between aliskiren use and improvement in laboratory, pathological and/or clinical parameters in patients with complement-mediated diseases raise more questions than answers. What is the relative contribution of renin and C3bBb to local kidney C3 activation? Is this different in untreated versus individuals on

conventional RAS blockade? Does conventional RAS blockade interfere with optimal outcomes in complement-related disease? Or dual conventional RAS blockade? If RAS blockade results in renin release, why is there a large body of evidence supporting RAS blockade as a key nephroprotective manoeuvre even in nephropathies that may be complement mediated? Do renin-secreting tumours develop complement activation? Do angiotensinogen and C3 compete for renin? What is the optimal complement activation inhibitor dose for aliskiren? Will aliskiren move from outdated dual RAS blockade to novel dual complement inhibition? And, above all, should aliskiren become the RAS blocker of choice for complement-mediated kidney disease while we wait for results of controlled studies? The scientific response to this last question is unclear. However, it is likely that as word spreads of recent publications, this becomes the default attitude by physicians.

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## CONFLICT OF INTEREST STATEMENT

None declared.

## REFERENCES

- Plasse RA, Nee R, Olson SW. Aliskiren as an adjunct therapy for atypical hemolytic uremic syndrome. *Clin Kidney J* 2020; 13: 39–41
- Békássy ZD, Kristoffersson AC, Rebetz J et al. Aliskiren inhibits renin-mediated complement activation. *Kidney Int* 2018; 94: 689–700
- Friedrich S, Schmieder RE. Review of direct renin inhibition by aliskiren. *J Renin Angiotensin Aldosterone Syst* 2013; 14: 193–196
- European Medicines Agency. Annex I. Summary of Product Characteristics. Rasilez. [https://www.ema.europa.eu/en/documents/product-information/rasilez-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/rasilez-epar-product-information_en.pdf) (29 August 2019, date last accessed)
- Esteras R, Perez-Gomez MV, Rodríguez-Osorio L et al. Combination use of medicines from two classes of renin-angiotensin system blocking agents: risk of hyperkalemia, hypotension, and impaired renal function. *Ther Adv Drug Saf* 2015; 6: 166–176
- <https://www.ncbi.nlm.nih.gov/pubmed/?term=aliskiren> (29 August 2019, date last accessed)
- Kurtz A. Renin release: sites, mechanisms, and control. *Annu Rev Physiol* 2011; 73: 377–399
- Gomez RA, Sequeira-Lopez M. Renin cells in homeostasis, regeneration and immune defence mechanisms. *Nat Rev Nephrol* 2018; 14: 231–245
- Fernandez-Fernandez B, Ortiz A, Gomez-Guerrero C et al. Juxtaglomerular apparatus hyperplasia under dual angiotensin blockade. A footprint of adequate RAS inhibition or a concern for renal fibrosis? *BMC Nephrol* 2012; 13: 21
- Nakano D, Nishiyama A. A novel role of renin inhibitor in the complement cascade. *Kidney Int* 2018; 94: 650–652
- Tortajada A, Gutierrez E, Pickering MC et al. The role of complement in IgA nephropathy. *Mol Immunol* 2019; 114: 123–132
- Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2012; 2: 139–274
- Szeto CC, Kwan BC, Chow KM et al. The safety and short-term efficacy of aliskiren in the treatment of immunoglobulin a nephropathy – a randomized cross-over study. *PLoS One* 2013; 8: e62736
- Tang SC, Lin M, Tam S et al. Aliskiren combined with losartan in immunoglobulin A nephropathy: an open-labeled pilot study. *Nephrol Dial Transplant* 2012; 27: 613–618
- Simeoni M, Nicotera R, Pelagi E et al. Successful use of aliskiren in a case of IgA- mesangial glomerulonephritis unresponsive to conventional therapies. *Rev Recent Clin Trials* 2019; 14: 72–76
- Shagdarsuren E, Wellner M, Braesen JH et al. Complement activation in angiotensin II-induced organ damage. *Circ Res* 2005; 97: 716–724
- Rodríguez-Osorio L, Ortiz A. Timing of eculizumab therapy for C3 glomerulonephritis. *Clin Kidney J* 2015; 8: 449–452
- Vaidyanathan S, Bigler H, Yeh C et al. Pharmacokinetics of the oral direct renin inhibitor aliskiren alone and in combination with irbesartan in renal impairment. *Clin Pharmacokinet* 2007; 46: 661–675
- Lange S, Fraune C, Alenina N et al. Aliskiren accumulation in the kidney: no major role for binding to renin or prorenin. *J Hypertens* 2013; 31: 713–719
- Farrar CA, Zhou W, Lin T et al. Local extravascular pool of C3 is a determinant of postischemic acute renal failure. *FASEB J* 2006; 20: 217–226
- Sheerin NS, Risley P, Abe K et al. Synthesis of complement protein C3 in the kidney is an important mediator of local tissue injury. *FASEB J* 2008; 22: 1065–1072
- Abbate M, Zoja C, Corna D et al. Complement-mediated dysfunction of glomerular filtration barrier accelerates progressive renal injury. *J Am Soc Nephrol* 2008; 19: 1158–1167