Aldosterone synthase inhibition in humans

Michel Azizi1,2,3, Laurence Amar1,2,3 and Joël Menard1,2,3

1Faculté de Médecine, The Université Paris Descartes, Paris F-75006, France, 2Assistance Publique des Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris F-75015, France and 3INSERM, CIC 9201, Paris F-75015, France

Correspondence and offprint requests to: Michel Azizi; E-mail: michel.azizi@egp.aphp.fr

Abstract

Aldosterone synthase (CYP11B2) inhibition has emerged as a new option for the treatment of hypertension, heart failure and renal disorders, in addition to mineralocorticoid receptor (MR) blockade. The aim is to decrease aldosterone concentrations in both plasma and tissues, thereby decreasing MR-dependent and MR-independent effects in the cardiac, vascular and renal target organs. LC1699 was the first orally active aldosterone-synthase inhibitor to be developed for human use. Its structure is similar to that of FAD286, the dextroenantiomer of the inhibitor to be developed for human use. Its structure is

doi: 10.1093/ndt/gfs388
Advance Access publication 8 October 2012

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Received for publication: 29.2.2012; Accepted in revised form: 20.5.2012

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cannot replace the MR blockade in patients with hypertension, other cardiovascular or renal disorders. The development of second-generation aldosterone synthase inhibitors with a higher selectivity index for CYP11B2 than LCI699 should make it possible to test this approach at much higher doses in these patients, after the necessary toxicology and Phase I studies.

**Keywords:** aldosterone; enzyme; human; hypertension; inhibitors

### Introduction

The description by J.W. Conn in 1955 of the tumoural form of primary aldosteronism (PA) [1] and the potential extension of this syndrome to a large proportion of hypertensive patients with low levels of plasma renin activity [2] has stimulated active research into the role of the primary mineralocorticoid hormone, aldosterone, in humans, in the homeostasis of sodium and potassium, metabolism and blood pressure (BP) control [3]. However, the biological effects of aldosterone on the renal excretion of sodium and potassium and BP regulation [1, 4-6] extend far beyond extracellular volume regulation and potassium homeostasis. Independent of its renal epithelial effects [7, 8], aldosterone, together with high-sodium intake, stimulates inflammatory reactions, cellular hypertrophy, matrix formation and apoptosis in the vessels, heart and kidneys [3, 7, 8]. It is also directly involved in target organ damage in various cardiovascular and renal diseases [3, 9]. Finally, a series of observations over the last 10 years have confirmed that a relative aldosterone excess is frequently observed in patients with hypertension [10–12], particularly those with resistant hypertension and evidence of intravascular volume expansion [13, 14], and in overweight normotensive subjects [15]. High aldosterone concentrations have also been associated with insulin resistance [16]. Besides aldosterone receptor blockers, a new option to block the biological effects of aldosterone has recently emerged by the use of orally active aldosterone synthase inhibitors. This review will focus on hormonal and haemodynamic effects of the lead compound of this new class of drugs.

### Aldosterone and aldosterone synthase

Aldosterone has both genomic and non-genomic renal and extrarenal effects [8, 17]. The genomic effects are mediated via activation of the mineralocorticoid receptor (MR), whereas the non-genomic effects are controlled by both the MR and other receptors and do not require signalling through the classic pathways of gene activation, transcription and protein synthesis [8, 17]. The magnitude of these two types of effect depends on the circulating concentrations of aldosterone produced by the glomerulosa cells of the outer zone of the adrenal cortex and, possibly, the local production of aldosterone by other organs which also express aldosterone synthase [3, 18]. The relative contributions of the genomic and non-genomic effects of aldosterone to the pathogenesis of the enhanced risk of cardiovascular and chronic kidney disease, target organ damage, metabolic syndrome and resistant hypertension remain unclear [7, 19, 20].

The capacity of adrenal glomerulosa cells to produce aldosterone is controlled largely by the regulated transcription of CYP11B2, the gene encoding aldosterone synthase. This enzyme is a member of the cytochrome P450 family that catalyses a rate-limiting step of aldosterone synthesis other than cholesterol transport to mitochondria [18]. Aldosterone synthase, which is located in the inner mitochondrial membrane, catalyses the final three steps in aldosterone synthesis: 11-β-hydroxylation of 11-deoxycorticosterone (DOC) to corticosterone (B), followed by 18-hydroxylation of B and 18-oxidation of 18OH-B [3, 18, 21] (Figure 1). New 19- and 18-hydroxylated minor products following the conversion of DOC by recombinant human aldosterone synthase expressed in *Escherichia coli* have also been identified *in vitro* [21]. The effects of aldosterone synthase are mediated by an NADPH-linked redox adrenodoxin/adrenodoxin reductase system [22]. The expression of aldosterone synthase seems to be restricted to the zona glomerulosa of the adrenal cortex and its presence and functionality in other organs remain a matter of debate [3, 23]. The acute and chronic regulation of aldosterone synthesis is mediated principally by angiotensin II, potassium and adrenocorticotropic hormone (ACTH) [3, 24].

The synthesis of aldosterone is closely linked to that of cortisol, which occurs in the zona fasciculata of the adrenal cortex. Indeed, the final step in cortisol synthesis is the 11-β-hydroxylation of 11-deoxycortisol (S) to cortisol by 11-β-hydroxylase, the product of the CYP11B1 gene [3, 25] (Figure 1). The CYP11B2 and CYP11B1 genes are located 40 kb apart, on chromosome 8q22. The sequences of the coding regions of these genes are 95% identical and the encoded proteins are 93% identical [3, 25]. However, CYP11B2 expression is confined to the zona glomerulosa, whereas CYP11B1 is expressed in the zona fasciculata and zona reticularis. This difference in expression pattern in the adrenal cortex is accounted for by major differences between the regulatory regions of the two genes. The S′ promoter region of CYP11B2 is regulated by angiotensin II and potassium, whereas the promoter region of CYP11B1 includes elements that respond to ACTH. The similarity of these genes has complicated the search for highly selective CYP11B2 inhibitors (see below).

### Rationale for the development of aldosterone synthase inhibitors

Blockade of the biological effects of aldosterone has mostly been achieved with the two MR antagonists currently on the market, spironolactone and eplerenone [26, 27]. Low doses of these two drugs (25–50 mg o.d.), in addition to conventional treatment with renin–angiotensin system (RAS) blockers and β-blockers, have been shown to decrease cardiovascular mortality and morbidity effectively in patients with Class II–IV chronic congestive
heart failure or with left ventricular dysfunction after myocardial infarction [28–30]. International guidelines now recommend the use of these drugs for the treatment of these patients [31]. Small studies have shown that MR blockade in addition to angiotensin I-converting enzyme (ACE) inhibition decreases proteinuria in patients with Type 2 diabetes [32–34]. However, large clinical trials are required to demonstrate both the safety and the nephroprotective effects of such an approach in the long term [35]. Both the currently available MR antagonists are also used, at higher doses, for the treatment of hypertension [27], particularly for forms of hypertension in which aldosterone is thought to play a major role, such as PA [36, 37], low-renin hypertension [38], resistant hypertension [39–41], metabolic syndrome [20] and complicated hypertension with left ventricular hypertrophy [42]. However, several factors may limit the use of MR antagonists. First, spironolactone has a poor tolerance profile because of its lack of selectivity for the MR [26]. Indeed, it also binds the progesterone and androgen receptors, thereby triggering progestogenic and antiandrogenic effects [26]. Its long-term use is therefore associated with a dose-related incidence of gynaecomastia in males, sexual dysfunction and menstrual irregularities [43], which may occur at any time during the course of treatment and may be reversed by stopping treatment. These adverse effects are not observed with eplerenone administered at the marketed doses (50–100 mg) [26]. However, eplerenone is less potent than spironolactone on a milligram per milligram basis, in patients with essential hypertension [44] or PA [37]. Secondly, both these drugs induce a counter-regulatory increase in plasma renin and aldosterone concentrations [37, 45], potentially limiting the efficacy of the MR blockade and enhancing the MR-independent effects of aldosterone.

**Figure 1.** Adrenal steroid biosynthesis. 3β-HSD, 3β-hydroxysteroid dehydrogenase.

**Aldosterone synthase inhibition**

Aldosterone synthase inhibition has thus emerged as a new option for treatment, in addition to MR blockade. The aim is to decrease hormone concentrations in both the plasma and tissues, thereby reducing MR-dependent and MR-independent effects in the cardiac, vascular and renal target organs.

Initial attempts to inhibit aldosterone synthesis involved the use of various non-selective inhibitors of steroidogenesis, such as aminoglutethimide (P450 side chain cleavage enzyme inhibitor) [46], metyrapone (11β-hydroxylase inhibitor) [36, 46] or trilostane (3β-hydroxysteroid dehydrogenase inhibitor) [36, 46] to treat small series of hypertensive patients with or without PA [36]. The inhibition, by these drugs, of early steps of steroidogenesis involved in both the glucocorticoid and mineralocorticoid axes was a major safety problem and these inhibitors generally did not control BP effectively in the long term.

The consequences of a targeted pharmacological approach to the specific inhibition of aldosterone synthesis have only recently been investigated in humans (see below) [47–49], following the discovery that fadrozole, a non-steroidal aromatase inhibitor effective for advanced breast cancer treatment when administered in the 1–2 mg dose range, inhibited 11β-hydroxylase and corticosterone methyloxidase Type II enzymes both *in vitro* [50] and in humans, when administered at higher doses [51, 52]. Trunet *et al.* [52] showed that the administration of fadrozole at doses >4 mg/day for 2 weeks in healthy male subjects blocked the aldosterone response to acute ACTH injection without impairing the glucocorticoid response.
In vitro and preclinical studies

Fadrozole is a racemic mixture of two enantiomers, with the dextroenantiomer, FAD 286A being much more selective for aldosterone synthase than for aromatase in rat adrenal cells. This enantiomer was thus a key candidate molecule for the selective inhibition of aldosterone synthase [53]. Fadrozole and its dextroenantiomer FAD286A have been characterized in vitro in cell systems and in vivo in various rat and dog models. In vitro, FAD286A inhibits human recombinant CYP11B2 with an IC50 of 1.6 nM but also CYP11B1, with an IC50 of 9.9, giving a selectivity ratio of only ≥6 [54]. FAD286 dose-dependently inhibits angiotensin II-stimulated aldosterone production in NCI-H295R human adrenocortical carcinoma cells [55]. The proof-of-concept studies in animal models showed that FAD286A dose-dependently decreases plasma and urine aldosterone concentrations and increases plasma renin activity in spontaneously hypertensive rats on a low-sodium/high-potassium diet. It also neutralizes furosemide-induced hypokalaemia and decreases plasma aldosterone concentration in spontaneously hypertensive rats [45]. In combination with spironolactone, it induces severe dehydration and hyperkalaemia, demonstrating the important role of residual aldosterone concentrations in counteracting the effects of the MR blockade [45]. FAD286A administration also prevents target organ damage in animal models. Indeed, it was found to prevent death, and to decrease cardiac hypertrophy and albuminuria in rats double-transgenic for human renin and angiotensinogen, albeit to a lesser extent than with an angiotensin II receptor blocker (ARB), because FAD286A only slightly decreased BP whereas the ARB normalized BP [55]. In a rat model of chronic heart failure, FAD286A improved left ventricular haemodynamics, remodelling and function, to a similar extent to spironolactone [56]. Finally, it prevented albuminuria and azotaemia and decreased left ventricular hypertrophy and fibrosis in uninephrectomized rats treated with angiotensin II and a high-salt diet, to a similar extent to spironolactone [57].

Following these preclinical studies, LC1699 was subsequently synthesized, based on the chemical structure of FAD286A, as the first orally active aldosterone synthase inhibitor for human use.

Phase I studies with LC1699

LC1699 displays linear and supraproportional pharmacokinetics following the administration of a single oral dose (3–200 mg) to healthy subjects in fasting conditions [47]. It is rapidly absorbed (Tmax ~1 h), has a plasma half-life of ~4 h and does not accumulate following the administration of multiple doses up to 3 mg [47]. During the multiple oral dose Phase I study, LC1699 was shown to be a potent inhibitor of human aldosterone synthase: it decreased plasma and urine aldosterone concentrations in a dose-dependent manner, by up to 70 or 80%, in healthy male subjects on a low-sodium diet [47]. Due to its short plasma half-life, the LC1699-induced decreases in plasma aldosterone concentrations do not last for 24 h [47]. The repeated administration of LC1699, at doses of 0.5–3 mg q.d., caused dose-dependent counter-regulatory increases in plasma renin activity, reflecting a negative sodium balance [47]. The effect of 0.5 mg LC1699 q.d. on plasma renin activity was similar to that of 100 mg eplerenone q.d., suggesting that the blockade of the aldosterone pathway was of similar strength [47]. LC1699 did not lower basal plasma cortisol concentrations at doses of 0.5–3 mg. At the 0.5 mg q.d. dose, LC1699 selectively inhibited aldosterone synthesis without inhibiting cortisol synthesis, even after ACTH stimulation. Aldosterone synthase selectivity was lost at doses ≥1 mg q.d. and LC1699 blocked the cortisol response to ACTH at doses ≥3 mg [47]. LC1699 was generally well tolerated at all doses investigated. LC1699 at a dose of 3 mg was associated with signs of mild hypoadrenalism (postural tachycardia and weight loss in 3 of 12 participants and mild hyponatraemia in 4 of 12 participants).

Phase II studies in patients with hypertension

Primary aldosteronism

The availability of LC1699 made it possible to test this approach, for the first time, in hypertensive patients. We first investigated the haemodynamic and hormonal effects and the tolerability and safety of 4 weeks of aldosterone synthase inhibition with LC1699 in patients with PA [48]. We selected this clinical condition for a proof-of-concept study because it provided a unique opportunity to investigate the effects of this drug in a situation in which aldosterone production in the adrenal glands (i) is increased by the up-regulation of CYP11B2, particularly in tumoural forms of PA [18, 58], and (ii) is considered to be, at least partly, responsible for an increase in BP associated with increased exchangeable sodium, plasma volume and total body water, reduced exchangeable potassium and renin suppression [6]. The main objective of this single-centre, single-blind, placebo-controlled, sequential, forced-titration study was to determine whether the administration of LC1699 (0.5 mg b.i.d. for 2 weeks, force-titrated to 1 mg b.i.d. for 2 weeks) could lower BP and correct hypokalaemia in 14 patients with PA, by decreasing aldosterone production [48]. The secondary objectives were to investigate the pharmacodynamic effects of LC1699 on plasma and urine hormone and electrolyte concentrations, to assess its safety and tolerability. Doses of 0.5 and 1 mg were selected from the Phase I studies and the b.i.d. dosing scheme was selected, based on the 4-h half-life of LC1699 and the high aldosterone concentrations expected in patients with PA. Patients were studied while on a low-sodium (±50–100 mmol/day), high-potassium (±70–100 mmol/day) isocaloric diet. They were maintained on anti-hypertensive treatment that did not interfere with the RAS throughout the study, for safety reasons.

In patients with PA characterized by severe hypertension and hypokalaemia, LC1699 induced a dose-dependent and reversible decrease in plasma and urinary
aldosterone concentration of ~70–80%, associated with a massive accumulation of the aldosterone precursor DOC in the plasma (≥700%) [48], thus confirming the inhibition of the product of the CYP11B2 gene [3, 21]. Moreover, the acute stimulation of aldosterone secretion by ACTH injection was fully blunted after 4 weeks of LCI699 administration, but this effect was fully reversible 1 week after treatment withdrawal. The inhibitory effects of LCI699 on aldosterone secretion were maintained throughout the study, with no escape phenomena observed, despite the endogenous counter-regulatory stimulation of aldosterone production by the zona glomerulosa cells due to the increase in plasma potassium and renin concentrations [3, 46] and, to a lesser extent, the increase in ACTH concentration [3, 46] (see below). No rebound effect was observed after treatment withdrawal.

The inhibition of aldosterone synthase by LCI699 (0.5 mg b.i.d.) was associated with a rapid correction of hypokalaemia, within 1 week of treatment initiation [48]. In contrast to the rapid and marked effect on potassium balance, the BP-lowering effects of LCI699 were modest [4–5 mmHg decrease in 24 h ambulatory and home systolic (SBP)] and the increase in plasma renin concentration, an indirect index of sodium depletion, was slow and mild (<40%) [48]. The inhibition of aldosterone synthase by 70–80% for 4 weeks was, therefore, sufficient to normalize potassium balance but did not fully correct the positive sodium balance in patients with PA. We were unable to rule out the possibility that higher LCI699 doses would have had larger effects on sodium balance, but LCI699 was prescribed at the maximum tolerable dose and the use of larger doses of LCI699 would certainly impair glucocorticoid synthesis and trigger the ACTH-dependent accumulation of DOC to an even greater extent (see below). An analysis of the effects of aldosterone synthase inhibition provides further insight into the effects of aldosterone on potassium and sodium balance. Aldosterone simultaneously performs two different tasks—potassium elimination and sodium conservation—and there may be a balance between these tasks in the distal convoluted tubule and the later segments of the nephron. The effect on potassium retention may be more rapidly sensitive to the acute suppression of aldosterone effects, and effects on sodium elimination may require more intense and prolonged inhibition than can be achieved through the administration of LCI699 at a dose of 0.5–1 mg b.i.d. for 4 weeks. Alternatively, there may be an accumulation of various precursors with mineralocorticoid activity [46]. Indeed, all the available experimental and clinical data suggest that compensatory mechanisms are probably triggered when aldosterone synthesis is decreased, impaired or abolished, particularly as concerns the accumulation in the adrenal glands of steroid precursors with mineralocorticoid activity, such as DOC [46]. Complete studies of all the precursors of aldosterone, cortisol and androgens synthesized from cholesterol in the adrenal glands are required, in both animals and humans, for a full characterization of the effects of LCI699 and other aldosterone synthase inhibitors.

We also confirmed that the twice daily administration of 0.5–1 mg LCI699 was associated with biological signs of partial inhibition of the glucocorticoid axis. Morning basal plasma cortisol concentration remained unchanged, but we observed a dose-dependent increase in both plasma ACTH and 11 deoxycortisol concentrations, consistent with an inhibition of the product of the CYP11B1 gene. Moreover, all 14 patients had a fully blunted cortisol response to ACTH injection after 4 weeks of LCI699 treatment. As there is no physiological negative feedback loop between the pituitary gland and aldosterone secretion, the increase in plasma ACTH concentration with LCI699 reflected solely an interruption of the cortisol negative feedback loop in the hypothalamic–pituitary axis [46]. However, these effects on the glucocorticoid axis were fully reversible and the hypothalamic–pituitary adrenal axis returned to normal 1 week after LCI699 withdrawal. These results demonstrate the incomplete selectivity of LCI699 for aldosterone synthase in vivo, consistent with the in vitro data.

The mild reversible impairment of cortisol synthesis during the 4 weeks of LCI699 administration was both clinically and biologically well tolerated in these 14 highly selected and closely monitored patients with high aldosterone levels. None of the patients developed signs of hypoaldosteronism or hypocortisolism. However, it is difficult to speculate on the consequences of the lack of selectivity of LCI699 for CYP11B1 and the blunted cortisol response to ACTH. The long-term effects of inhibition of the adrenal response, particularly in acute stressful situations, are unknown [46]. Furthermore, a permanent slight increase in plasma ACTH concentration may affect adrenal steroid synthesis and induce trophic changes in the long term [46].

**Essential hypertension**

The efficacy of LCI699 for lowering BP was investigated in an 8-week double-blind, randomized, placebo-controlled, parallel group, Phase II study in 524 patients with Stage 1–2 essential hypertension comparing LCI699 (0.25 mg q.d., 0.5 mg q.d., 1.0 mg q.d., and 0.5 mg b.i.d.) with eplerenone (50 mg b.i.d.) [49]. All doses of LCI699 significantly decreased 24-h ambulatory BP and office SBP, but only the 1.0 mg q.d. dose and 50 mg eplerenone b.i.d. significantly decreased office diastolic BP (DBP) [49]. The antihypertensive efficacy of 1 mg LCI699 q.d. was similar to that of eplerenone [changes in seated office DBP at week 8: −7.1 versus −7.9 mmHg, respectively]. Eplerenone at a dose of 50 mg b.i.d. and LCI699 at a dose of 0.5 mg b.i.d resulted in significantly higher levels of plasma renin activity than were observed with placebo, whereas no such increase was observed with 1 mg LCI699 q.d. [49]. The changes in mean office and ambulatory SBP/DBP values obtained with 0.5 mg LCI699 b.i.d. were smaller than those achieved with 1.0 mg LCI699 q.d., although only b.i.d. administration decreased plasma aldosterone concentration significantly from baseline values [49]. A blunted cortisol response to ACTH was observed in 20% of the patients, but none developed clinical and/or biological signs of hypocortisolism. Finally, the clinical and biological safety and tolerability of LCI699 were similar to those of placebo and eplerenone [49].
small number of patients with transient hyperkalaemia were observed in the groups, given higher doses of LCI699 or eplerenone and the incidence of hyperkalaemia was similar in these groups.

**Conclusion**

The availability of the first orally active aldosterone synthase inhibitor, LCI699, has made it possible to assess the feasibility and haemodynamic, biological and safety consequences of this new approach to aldosterone pathway blockade in hypertensive patients, as well as its limitations (Table 1). However, as the effects of LCI699 on the glucocorticoid axis limit the use of higher doses because of the loss of selectivity for CYP11B2, this aldosterone synthase inhibitor cannot replace the MR blockade in patients with hypertension or other cardiovascular or renal disorders. Nevertheless, its characteristics open up new possibilities for treating patients with glucocorticoid excess, such as Cushing’s disease, through the use of higher doses of LCI699. The development of second-generation aldosterone synthase inhibitors with a higher selectivity index for CYP11B2 than LCI699 [59] should make it possible to test this approach at much higher doses, after the necessary toxicology and Phase I studies have been carried out. Indeed, in contrast to what has been reported for MR antagonists, the exposure of organs sensitive to aldosterone, such as the heart, blood vessels and kidneys, in the presence of high dietary sodium intake [3, 7, 8] is decreased by treatment with an aldosterone synthase inhibitor. This decrease, if achieved with no change in basal cortisol concentration, may, together with BP and electrolyte effects, contribute to neutralization of the harmful long-term genomic and non-genomic effects of aldosterone on these organs.

However, the use of aldosterone synthase as a treatment target, even with very selective and potent inhibitors, may be called into question, for the following reasons (Table 1). First, the magnitude of aldosterone synthase inhibition required to neutralize aldosterone in a biologically meaningful way remains unclear. Total inhibition might result in hypoaldosteronism, the risks of which are well known. Secondly, any accumulation of DOC during aldosterone synthase inhibition, even in the absence of an increase in ACTH levels, may lead to this precursor acting as a substitute for aldosterone on the MR. Thirdly, the ‘unprotected’ cardiac MR receptors may remain active locally, becoming occupied with cortisol rather than aldosterone. Fourthly, second-generation aldosterone synthase inhibitors will also have to compete with new potent dihydro-aldosterone synthase inhibitors. Fifthly, aldosterone synthase inhibition entails a risk of adverse events similar to that for MR blockade, including electrolyte disorders, hypotension, renal insufficiency and severe hypoaldosteronism, as a function of residual aldosterone production, baseline renal function, dehydration, general anaesthesia, co-morbidities (diabetes mellitus) and the additional prescription of other drugs (e.g. COX inhibitors, RAS blockers, heparin, MR blockers).

**Table 1.** Potential benefits and risks of aldosterone synthase inhibition

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
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<tbody>
<tr>
<td>- Negative Na⁺ balance, associated with a positive K⁺ balance (to be compared with the MR blockade)</td>
<td>1-Shared risks with MR blockade</td>
</tr>
<tr>
<td>- Neutralization of aldosterone proinflammatory and profibrotic effects in target organs in presence of high salt</td>
<td>- Hyperkalemia</td>
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<tr>
<td>- Reduction of target organ exposure to circulating and local aldosterone</td>
<td>- Hypotension</td>
</tr>
<tr>
<td>- Inhibition of cardiac and vascular aldosterone synthesis</td>
<td>- Renal insufficiency</td>
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<tr>
<td>- Neutralization of non genomic effects of aldosterone</td>
<td>These risks will depend on</td>
</tr>
<tr>
<td>- Absence of the aldosterone counter regulatory rise</td>
<td>• residual aldosterone production</td>
</tr>
<tr>
<td>- Beneficial metabolic effect on adipocyte functions and glycosecretion</td>
<td>• initial renal function</td>
</tr>
<tr>
<td></td>
<td>• Clinical circumstances: dehydration, general anesthesia, co-morbidities (diabetes mellitus … )</td>
</tr>
<tr>
<td></td>
<td>• Co-prescription (COX inhibitors, RAS blockers, heparin … )</td>
</tr>
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</table>

2-Specific risks due to CYP11B2 inhibition by any aldosterone synthase inhibitor

- Accumulation of DOC may lead to this precursor acting as a substitute for aldosterone on the MR
- The “unprotected” cardiac MR receptors may remain active locally, becoming occupied with cortisol rather than aldosterone.
- Severe hypoaldosteronism when combined with MR antagonists

3-Specific risks due to CYP11B1 inhibition with the aldosterone synthase inhibitor, LCI699 (lack of selectivity for CYP11B2)

- The long-term effects of inhibition of the glucocorticoid response in acute stressful situations are unknown
- A permanent slight increase in plasma ACTH concentration may affect adrenal steroid synthesis and induce trophic changes in the long term
However, as in many fields of endocrinology, the systematic investigation of receptor blockade, of inhibition of hormone synthesis and of combinations of these two approaches with different doses is required to determine the dual role of aldosterone in the regulation of potassium and sodium metabolism and BP on the one hand, and in cellular effects in conjunction with angiotensin II and sodium in the vessels, heart and kidneys, on the other.

Acknowledgements. We thank Alex Edelman and Associates for editorial assistance.

Conflict of interest statement. M.A. has acted as a consultant for and has received research funding and honoraria from Novartis, Sanofi-Aventis, Actelion, Servier, Medtronic, Cordis and Vessix Vascular. J.M. has acted as a consultant for and has received research funding and honoraria from Actelion, Servier, Medtronic, Cordis and Vessix Vascular. M.A. has acted as a consultant for and has received research funding and honoraria from Novartis, Sanofi and Actelion.

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Aldosterone synthase inhibition


Received for publication: 9.6.2012; Accepted in revised form: 18.7.2012