Aldosterone synthase inhibitors

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Inhibition of aldosterone synthesis is hypothesized to be of benefit to patients with cardiovascular disease

**Background**

- Aldosterone has been implicated in the pathogenesis of hypertension, heart failure and renal disease.
- Patients with an aldosterone excess are more susceptible to premature vascular disease, cardiac fibrosis and vessel wall inflammation.
- Aldosterone escape is evident in ACE inhibitor and ARB treatment.
- Aldosterone blockade has been shown to reduce cardiorenal target organ damages and major adverse cardiovascular events in targeted CHF populations.

**Hypothesis**

- Preventing the generation of aldosterone, via inhibition of aldosterone synthase (AS), will lower BP and reduce the risk of target organ damage/CV events in patients with cardiovascular and renal diseases.
Is there a better way to block the RAAS?

DRI, direct renin inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; 
K⁺ potassium ion; ACE, angiotensin converting enzyme; ACTH, adrenocorticotropic hormone (corticotropin); BK, bradykinin; 
AT₁R, angiotensin II type 1 receptor; MR, mineralcorticoid receptor.
Why not MRAs?

Theoretical limitations of MRAs

• Non-specific – sexual side effects e.g. menstrual irregularities, gynaecomastia

• Increase in aldosterone, angiotensin II, angiotensin I and renin during MRA blockade

• Aldosterone non-genomic effects many not be mediated by mineralocorticoid receptors
Theoretical advantages

**MR Antagonists**
- Blocks all ligands for MR receptor
- No potential effect on cortisol
- Prevents even a little aldosterone having adverse effect

**AS Inhibitors**
- Blocks steroid production?
- Less hyperkalemia?
- Better BP control
- No effect on other receptors
- Less toxicity?
Aldosterone synthesis

1. Cholesterol is converted to pregnenolone by the enzyme CYP11A.
2. Pregnenolone is then converted to progesterone by the enzyme 3β-HSD.
3. Progesterone is converted to 11-deoxy-corticosterone by the enzyme CYP21.
4. 11-Deoxy-corticosterone is converted to corticosterone by the enzyme CYP11B2.
5. Corticosterone is converted to aldosterone by the enzyme CYP11B2.
6. 17-OH-pregnenolone is converted to 17-OH-progesterone by the enzyme CYP17.
7. 17-OH-progesterone is converted to 11-deoxycortisol by the enzyme CYP21.
8. 11-Deoxycortisol is converted to cortisol by the enzyme CYP11B1.
9. DHEA is converted to androstenedione by the enzyme 3β-HSD.
10. Androstenedione is converted to testosterone by the enzyme 17β-HSD3.
Goals compared with aldosterone receptor antagonists

- Similar or greater clinical efficacy.
- Similar or greater tolerability.
Hypertension

Effects of a Novel Aldosterone Synthase Inhibitor for Treatment of Primary Hypertension
Results of a Randomized, Double-Blind, Placebo- and Active-Controlled Phase 2 Trial

David A. Calhoun, MD; William B. White, MD; Henry Krum, MB, PhD; Weinong Guo, MD, PhD; Georgina Bermann, PhD; Angelo Trapani, PhD; Martin P. Lefkowitz, MD; Joël Ménard, MD

LCI 699 in primary hypertension: Study design

[Diagram showing study design with different treatment periods and dosages, including LCI699 0.25 mg qd, LCI699 0.5 mg qd, LCI699 1.0 mg qd, LCI699 0.5 mg bid, Eplerenone 50 mg bid, and Placebo.]
LCI 699 in primary hypertension

- Double-blind, placebo-controlled
- 525 patients
- LCI 699 0.25 mg qd (n=92), 0.5 mg qd (n=88), 1.0 mg qd (n=86) and 0.5 mg bid (n=97); eplerenone 50 mg bid (n=84); placebo (n=77)
- 8 weeks treatment
- Clinic and 24-hour ambulatory BP
- Basal and ACTH stimulated cortisol secretion

Circulation 2011; 124: 1945-55
Change in clinic SBP

Time (weeks)

\( \Delta MSSBP \) (mmHg)

-18

-16

-14

-12

-10

-8

-6

-4

-2

0

0

1

2

4

8

Placebo

LCI699 0.25 qd

LCI699 0.5 qd

LCI699 1.0 qd

LCI699 0.5 bid

Eplerenone 50 bid
Ambulatory monitoring: SBP

- Placebo: 1.1
- LCI699 0.25qd: -7.2 (p < 0.0001*)
- LCI699 0.5qd: -4.9 (p = 0.0006*)
- LCI699 1.0qd: -7.7 (p < 0.0001*)
- LCI699 0.5bid: -6.2 (p < 0.0001*)
- Eplerenone 50bid: -10.5 (p < 0.0001*)

* vs placebo
ACTH stimulated cortisol at week 8

Aldosterone and cortisol bio-synthetic pathway

1. Cholesterol
   - Side chain cleavage enzyme (CYP11A)

2. Pregnenolone
   - 17α-Hydroxylase (CYP17)
   - 3β-Hydroxysteroid dehydrogenase (3β-HSD)

3. Progesterone
   - 21-Hydroxylase (CYP21)

4. 11-Deoxycorticosterone
   - 11β-Hydroxylase (CYP11B2)

5. Corticosterone
   - 18-Hydroxylase (CYP11B2)

6. 18-OH-corticosterone
   - 18-Oxidase (CYP11B2)

7. Aldosterone
8. 11-Deoxycortisol
   - 11β-Hydroxylase (CYP11B1)

9. Cortisol

>93% identity in nucleotide/aa sequence

B2:B1 Selectivity ≈ 3-fold

LCI699A
Other potential limitations of aldosterone-synthase inhibition

• How much inhibition is needed?
  • The magnitude of the aldosterone-synthase inhibition necessary to neutralize aldosterone in a biologically significant way is still unknown

• Can the system escape?
  • The accumulation of desoxycorticosterone during aldosterone-synthase inhibition may act as a substitute for aldosterone.

• Can we leave MR not blocked?
  • Cardiac MR receptors may stay active locally and be occupied by cortisol instead of aldosterone.
Aldosterone synthase inhibitors versus non-steroidal MRAs?
Potential advantage of non-steroidal MRAs

- More selective for the mineralocorticoid receptor
- Greater affinity for the mineralocorticoid receptor
- Differential tissue activity: cardiac > renal; reduce risk of hyperkalaemia
- Some have residual L-type calcium channel blocking activity
Non-steroidal MRAs: more selective for cardiac/vascular than renal tissue?
**In vitro** potency and selectivity of spironolactone, eplerenone and BAY 94-8862

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<th>Spironolactone</th>
<th>Eplerenone</th>
<th>BAY 94-8862</th>
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<tr>
<td>Mineralocorticoid receptor $IC_{50}$ (nM)</td>
<td>24.2</td>
<td>990</td>
<td>17.8</td>
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<td>Glucocorticoid receptor $IC_{50}$ (nM)</td>
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<td>Androgen receptor $IC_{50}$ (nM)</td>
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<td>Progesterone receptor $IC_{50}/EC_{50}$ (nM)</td>
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<td>Oestrogen receptor $\alpha$ $IC_{50}$ (nM)</td>
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<td>Oestrogen receptor $\beta$ $IC_{50}$ (nM)</td>
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Rationale and design of ARTS: a randomized, double-blind study of BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease

Bertram Pitt¹*, Gerasimos Filippatos², Mihai Gheorghiade³, Lars Kober⁴, Henry Krum⁵, Piotr Ponikowski⁶, Christina Nowack⁷, Peter Kolkhof⁸, So-Young Kim⁹, and Faiez Zannad¹⁰

- Patients with HF-REF and mild/moderate CKD (Part A/B)
- 4 weeks treatment; 15/60 patients per group
- Placebo vs. spironolactone vs. BAY 94-8862 (3/4 doses/regimens)
Summary and conclusions

- Experimentally, aldosterone excess has many detrimental effects in the CV system and kidney.
- The benefits of MRAs post-MI and in CHF support the use of anti-aldosterone therapy.
- The role for ASIs is uncertain – perhaps in Cushing’s syndrome?
- The theoretical advantages of non-steroidal MRAs are more attractive.