

FOCUS ON ALDOSTERONE

Selective aldosterone synthase inhibitors: just-in-time delivery for Aldosterone and Aldosteronism's 70th birthdays



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In 1953/4, the Taits in London discovered aldosterone, and Conn the first aldosterone-producing adenoma. He predicted that Primary Aldosteronism (PA), in which one or both adrenals have gone into automode, would be the commonest secondary cause of Hypertension. Estimates from prospective study of newly diagnosed Hypertension are, indeed, 5-13% of all patients.^{1,2} But, outside such studies, fewer than 1% of PA patients are diagnosed (e.g. only 79/107,407 patients with Hypertension in UK Biobank). This is a Public Health catastrophe since major cardiovascular morbidity/mortality is twice as high in PA as in Essential Hypertension of similar severity, and potentially reversible.^{3,4} Even this statistic underplays the true risk, as PA patients are much more likely to develop treatment-resistant hypertension. PA patients are readily suspected, having a suppressed plasma renin despite treatment with an ARB or ACEi.⁵ PA under-diagnosis might largely disappear if renin were routinely measured when hypertension is uncontrolled on these drugs. A clarion call!

Since the British Hypertension Society's PATHWAY-2 study of 2015, it has been clear that targeting the mineralocorticoid axis, with spironolactone or amiloride, trumps conventional antihypertensive drugs in achieving BP control in resistant hypertension.^{5,6} But adverse effects, particularly hyperkalaemia, have limited their use and dosage. There are two approaches to protecting target tissue from an undesirable hormone or mediator.

One is to block its receptor, or downstream pathway, and the other is to inhibit its synthesis. This is known to Hypertension doctors from the choice between ARBs and ACE inhibitors. For efficacy there is little to choose between these classes, but ARBs avoid the risks of dry cough or angioneurotic oedema. Similarly, aldosterone synthase inhibitors (ASI) have long been a tempting alternative to mineralocorticoid receptor blockade, in the hope of better tolerability and, consequently, effectiveness. This hope has two origins. First is the highly restricted expression of the enzyme, in just a few adrenocortical cells, limiting likelihood of off-target adverse effects. Second is the empirical observation, in human and mouse genetic knockouts, that only loss of both copies of the enzyme gene ("CYP11B2") has a phenotype, largely restricted to infancy; whereas the homozygous knockout of the receptor is lethal.⁷

So why has the ASI class taken so long to deliver? In most domestic species, aldosterone and cortisol are made by the same enzyme. In rodents and primates, the CYP11B1 gene, encoding cortisol synthesis, is duplicated as CYP11B2, encoding aldosterone synthase, and the two enzymes share 93% identity. This has had two consequences. The first was unawareness of molecular events driving the frequency of PA, especially the dramatic disappearance of aldosterone synthase from most of adult human adrenal. This disappearance likely results from excessive salt consumption,

rendering aldosterone largely redundant, but was only appreciated when Dr Celso Gomez Sanchez developed and shared specific monoclonal antisera to aldosterone synthase.⁸ PA, I believe, is a maladaptive response to salt excess, consequent on the involution of aldosterone-producing cells when no longer required.^{9,10} Only mutation-driven constitutive aldosterone production can save the cells, resulting in physiological clusters responsive to stress hormone or cation fluxes, and in pathological aldosterone-producing adenomas. Darwin in action.

The second consequence of the 93% identity has been the difficulty of inhibiting aldosterone without compromising cortisol synthesis. This is illustrated by LCI699, a Novartis ASI whose development was stopped at phase 2, when ACTH stimulated cortisol levels were reduced. The drug was repurposed, and is now marketed as Osilodrostat for treatment of Cushing's. But the drought has now ended, and – like we say about London buses – you wait ages for one, then three come along at once. Leading the pack is baxdrostat, a Roche development with 100:1 selectivity for aldosterone vs cortisol inhibition.¹¹ After Roche paused its cardiometabolic programme in 2014, the drug sat on the shelf until licensed in 2018 to a single-drug US start-up, Cincor. The lack of cortisol inhibition was confirmed in a multiple ascending dose study, and baxdrostat entered a Phase 2 trial of 248 patients with resistant hypertension.¹² Although the lower US vs Europe threshold for diagnosing resistant hypertension resulted in a 10 mmHg lower entry systolic BP than to PATHWAY-2, the primary outcome of placebo-corrected fall on baxdrostat 2 mg was 11.0 mmHg, similar to that on spironolactone 50 mg in PATHWAY-2.¹³ There were also dose-related falls, approaching 70%, in plasma and urine aldosterone. The results, presented at AHA and published in NEJM, made Cincor hot property, and shortly afterwards AZ placed a \$1.3B bet on the potential value of ASI.

Lorundrostat, similarly, started in Big Pharma – Mitsubishi – before moving to a US start-up, Mineralys. Its phase 2 trial was presented at ACC, but full results are not yet published. In a pre-specified sub-group of resistant hypertension, 30 patients with BMI >30, had a placebo-corrected fall in SBP of 16.7 mmHg.

Dexdrofadostat (FAD286) is the dextro-isomer of an old drug, fadrozole, whose laevo-isomer inhibits cortisol and oestrogen synthesis. FAD286 long precedes the previous two drugs, and suppressed aldosterone but not cortisol in hypertensive rats (SHR). However, it was not patented and therefore not developed clinically. The breakthrough came with a patented method, by Damian Pharmaceuticals, of separating the isomers with high purity. Its selectivity in SHRs has now been reproduced in volunteers¹⁴ and PA, in which substantial falls in BP and aldosterone were reported in Munich and Kyoto (PIPA7 and ISH-2022).

Hopefully, a judicious blend of academic and commercial competition and collaboration augur long-awaited new treatments for both PA and resistant hypertension – and realisation that patients with the former greatly outnumber the latter. Advent of highly efficacious, well-tolerated once-daily drugs – if confirmed in phase 3 – will also challenge the surgical removal of a whole adrenal gland in order to suppress aldosterone production. With prospective trial evidence that only 30% of adrenalectomies completely cure Hypertension, in a largely identifiable subset of PA patients, the race is on to find less invasive treatments.¹⁵ In my lifetime, coincidentally co-terminous with that of aldosterone, treatment for another small benign lesion, peptic ulcer (PU), has morphed from removal of an organ to a course of omeprazole. If ASIs prove the omeprazole of PA, they will be not just class-of-'23, but class-of-their-own.

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