The independent review of medical treatment

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High blood pressure is a major risk factor for cardiovascular disease worldwide.1 Drug treatments include those that target the renin-angiotensin system, a key hormone cascade in the regulation of blood pressure. One of these is ▼ aliskiren (Rasilez – Novartis), which belongs to a new class of drugs, direct renin inhibitors.2 Here we assess its place in managing adults with hypertension.

The renin-angiotensin system
Renin released from the kidney cleaves circulating angiotensinogen to generate the inactive pro-hormone angiotensin I.3 This, in turn, is converted by angiotensin converting enzyme (ACE) to the active hormone angiotensin II.4 Angiotensin II acts at multiple sites including vascular smooth muscle, where it causes vasoconstriction, and the adrenal glands, where it stimulates the release of aldosterone. Aldosterone promotes renal sodium reabsorption and volume expansion.5 Blockade of the renin-angiotensin system with either an ACE inhibitor or an angiotensin-II receptor antagonist reduces blood pressure, helping to prevent the complications of hypertension including major cardiovascular events.6

What is aliskiren?
Aliskiren (pronounced a-lis-ki-ren) is a direct inhibitor of renin and so prevents the conversion of angiotensinogen to angiotensin I.2 It is licensed for the treatment of adults with essential hypertension at a dose of 150–300mg daily either as monotherapy or in combination with other antihypertensive drugs.2 After oral administration, the plasma concentration of aliskiren peaks within 1–3 hours. Meals high in fat can reduce absorption.2 Steady-state plasma concentrations of aliskiren are reached within 5–7 days. The drug is excreted in faeces largely unchanged.2

Mild-moderate hypertension
Nine published double-blind randomised controlled trials that recruited patients with mild to moderate hypertension (sitting diastolic blood pressure [DBP] of 90–110mmHg) have compared aliskiren alone with either placebo or other antihypertensive monotherapy.5-10 Also, combinations of aliskiren plus another drug have been compared with placebo,4-8 with the other drug alone6-9,12-14-16 or with other drug combinations.6,15,17 In most studies, the primary outcome measure was the fall in mean sitting DBP, and none assessed the effect of aliskiren on cardiovascular outcomes. All of the studies discussed below lasted 8 weeks unless otherwise stated.5-17

Aliskiren alone vs. placebo
In six studies, involving a total of 7,475 patients, aliskiren (75mg, 150mg, 300mg or 600mg daily) reduced DBP by 1.7–7.6mmHg more than placebo,5-10 systolic blood pressure (SBP) by 1.9–12.0mmHg more than placebo.

Aliskiren alone vs. other antihypertensives
Hydrochlorothiazide
In a study involving 2,776 patients in total, falls in DBP appeared similar in groups on daily aliskiren 75mg, 150mg or 300mg, or hydrochlorothiazide 6.25mg, 12.5mg or 25mg (8.7–10.3mmHg with aliskiren vs. 9.1–10.1mmHg with hydrochlorothiazide; SBP: 9.4–15.7mmHg vs. 11.0–14.3mmHg, no p value stated).8

ACE inhibitors
Two published studies have compared aliskiren with ACE inhibitors.15,12 In the first, 355 patients aged at least 65 years with a mean sitting SBP of 145–180mmHg and mean 24-hour ambulatory SBP of 135mmHg or above were randomised to aliskiren 75mg, 150mg or 300mg daily, or lisinopril 10mg daily.11 The fall in mean ambulatory SBP (the primary outcome measure) did not differ significantly between three of the groups (aliskiren 75mg: 8.4mmHg; 300mg: 8.7mmHg; lisinopril 10mg: 10.2mmHg) but the aliskiren 150mg dose was less effective than lisinopril 10mg (7.1mmHg, p<0.01). The fall in ambulatory DBP was smaller with aliskiren (75mg: 4.5mmHg; 150mg: 3.6mmHg; 300mg: 3.9mmHg, all p<0.05 vs. lisinopril 10mg: 6.3mmHg).
In the second trial (which tested for non-inferiority of aliskiren*), 837 patients with type 1 or type 2 diabetes mellitus received daily aliskiren 150mg or ramipril 5mg for 4 weeks, then double these doses for 4 more weeks. For the change in blood pressure, the difference between the two drugs was smaller than the pre-specified non-inferiority margins of 2mmHg for DBP (aliskiren reduced DBP by 11.3mmHg and ramipril by 10.7mmHg) and of 4mmHg for SBP (aliskiren reduced SBP by 14.7mmHg and ramipril by 12.0mmHg).

Angiotensin-II receptor antagonists

In three studies, involving a total of 3,572 patients, similar falls in DBP occurred with daily aliskiren 150mg (9.0–10.3mmHg), irbesartan 150mg or valsartan 80–160mg (8.9–11.0mmHg).5–7 The falls in SBP with aliskiren (11.4–13.0mmHg) were also similar to those with the angiotensin-II receptor antagonists (11.2–15.5mmHg).

In a 4-week trial involving a total of 226 patients with a daytime ambulatory SBP of 140mmHg or above, aliskiren 150mg daily reduced this pressure (the primary outcome measure) by 8.0mmHg and aliskiren 300mg daily by 11.0mmHg, falls similar to that with losartan 100mg daily (10.9mmHg).13 Sitting DBP fell by 2.2mmHg with aliskiren 150mg, 5.7mmHg with 300mg and 5.5mmHg with losartan 100mg (no p value stated).

Aliskiren combinations versus placebo

In three trials involving a total of 5,696 patients, aliskiren plus either valsartan or hydrochlorothiazide reduced DBP by 3.3–8.1mmHg, and SBP by 4.5–13.7mmHg, more than placebo.6–8

Aliskiren combinations versus monotherapy

With ACE inhibitors

In a trial testing for non-inferiority of aliskiren, 837 patients with type 1 or type 2 diabetes received daily aliskiren 150mg, ramipril 5mg or both for 4 weeks, then double these doses for 4 more weeks.12 The fall in DBP with aliskiren plus ramipril was greater than with ramipril alone (12.8mmHg vs. 10.7mmHg, p=0.004) or aliskiren alone (11.3mmHg, p=0.043). The fall in SBP with the combination was greater than with ramipril alone (16.6mmHg vs. 12.0mmHg, p<0.0001) but not aliskiren alone (14.7mmHg, p=0.088).

With angiotensin-II receptor antagonists

In a trial involving 1,797 patients in total, daily aliskiren 150mg plus valsartan 160mg for 4 weeks, then double these doses for 4 more weeks, reduced DBP more than valsartan alone (12.2mmHg vs. 9.7mmHg, p<0.0001) or aliskiren alone (9.0mmHg, p<0.0001).7 The combination of aliskiren and valsartan also reduced SBP more than valsartan alone (17.2mmHg vs. 12.8mmHg, p<0.0001) or aliskiren alone (13.0mmHg, p<0.0001).

In another trial, involving 1,123 patients in total, which was primarily a comparison of aliskiren with placebo, other groups received daily aliskiren 75mg, 150mg or 300mg plus valsartan 80mg, 160mg or 320mg, respectively, or valsartan alone.6 The combinations reduced DBP by 11.8–12.9mmHg, falls similar to those with valsartan alone (10.5–11.3mmHg) or aliskiren alone (10.3–12.3mmHg). The combinations reduced SBP by 14.5–18.0mmHg; valsartan alone reduced SBP by 11.2–16.5mmHg and aliskiren alone by 12.1–15.0mmHg (no p value stated).

In a third trial, 599 patients with hypertension and type 2 diabetes with nephropathy received losartan 100mg daily plus additional antihypertensive therapy aimed at achieving a blood pressure below 130/80mmHg, and were then randomised to additional aliskiren 150mg daily for 3 months then 300mg for 3 months, or to placebo for 6 months.14 Around 63% received three or more other antihypertensives. The percentage reduction in early-morning urinary albumin-to-creatinine ratio from baseline (the primary outcome measure) was 20% with aliskiren compared to no reduction with placebo (95% CI 9% to 30%, p<0.001). The mean difference in blood pressure between the groups was only 2mmHg systolic and 1mmHg diastolic in favour of the aliskiren group; after adjustment for the change from baseline in SBP, the reduction in urinary albumin-to-creatinine ratio with aliskiren compared with placebo was 18% (95% CI 7% to 28%, p=0.002).

The authors concluded that the aliskiren combination appeared to have a renoprotective effect independent of its blood-pressure lowering. However, they also indicated that studies lasting over 2 years were needed to see whether the beneficial effect on the kidney was sustained, and that changes in antihypertensive drugs after randomisation might have confounded the study results.

With amlodipine

In a 6-week trial, 545 patients with a mean sitting DBP of 90–109mmHg despite amlodipine 5mg daily received daily aliskiren 150mg plus amlodipine 5mg, amlodipine 10mg alone, or amlodipine 5mg alone.8 The combination reduced blood pressure more than amlodipine 5mg alone (DBP: 8.5mmHg vs. 4.8mmHg, p<0.0001; SBP: 11.0mmHg vs. 5.0mmHg, p<0.0001) and similarly to amlodipine 10mg (DBP: 8.0mmHg; SBP: 9.6mmHg; neither significantly different from combination therapy).

With hydrochlorothiazide

In a study involving 2,776 patients in total, daily aliskiren 150mg plus hydrochlorothiazide 6.25mg, 12.5mg or 25mg, or aliskiren 300mg plus hydrochlorothiazide 12.5mg or 25mg reduced mean sitting DBP by 10.4–14.3mmHg; all combinations except the lowest-dose combination were more effective than either monotherapy (by 1.8–4.9mmHg).8 Similarly, combinations reduced SBP by 15.3–21.2mmHg; and all combinations except the lowest-dose combination were more effective than either monotherapy (by 3.7–7.3mmHg).

In another trial, involving a total of 489 patients with a body mass index (BMI) of 30kg/m2 or above, who had not responded to 4 weeks of treatment with hydrochlorothiazide 25mg daily, one group received daily aliskiren 150mg for 4 weeks and then 300mg for 8 weeks, and another group received placebo, both in addition to the

*For an explanation of non-inferiority trials, see DTB 2008; 46: 55–6.
hydrochlorothiazide 25mg daily. The aliskiren combination reduced DBP at 8 weeks (the primary outcome measure) by more than hydrochlorothiazide 25mg plus placebo (DBP: 11.9mmHg vs. 7.9mmHg, p<0.0001; SBP: 15.8mmHg vs. 8.6mmHg, p<0.0001).

Aliskiren vs. other combinations

In a trial involving 1,123 patients in total, daily aliskiren 75mg, 150mg or 300mg plus valsartan 80mg, 160mg or 320mg, respectively, reduced DBP by 11.8–12.9mmHg compared to 13.5mmHg with daily valsartan 160mg plus hydrochlorothiazide 12.5mg (no p value stated). Similarly, SBP fell by 14.5–18.0mmHg with the aliskiren combinations, compared to 18.9mmHg with the hydrochlorothiazide combination (no p value stated).

In another trial, involving a total of 489 patients with a BMI of 30kg/m² or above not responding to hydrochlorothiazide 25mg daily, participants were randomised to additional treatment for 4 weeks with daily aliskiren 150mg, irbesartan 150mg, or amlodipine 5mg, then for 8 weeks with double the dose of aliskiren, irbesartan or amlodipine, respectively. The aliskiren combination reduced DBP at 8 weeks (the primary outcome measure) by 11.9mmHg, which was similar to the reduction with the irbesartan combination (11.3mmHg) and the amlodipine combination (10.3mmHg). Similarly, the SBP reductions were not significantly different (aliskiren 15.8mmHg; irbesartan 15.4mmHg; amlodipine 13.6mmHg).

In a third trial, 842 patients were randomised to daily aliskiren 150mg or ramipril 5mg with an optional increase to 300mg or 10mg, respectively, at 6 weeks. After another 6 weeks, hydrochlorothiazide 12.5mg daily could be added if necessary (added in 46.1% of patients on aliskiren vs. 49.5% on ramipril, not significantly different). After another 6 weeks, hydrochlorothiazide could be increased to 25mg (this occurred in 22.0% of patients on aliskiren vs. 31.3% on ramipril, p=0.0024). At 26 weeks, reductions from baseline were greater with aliskiren for DBP (13.2mmHg vs. 12.0mmHg with ramipril, p=0.025) and SBP (17.9mmHg vs. 15.2mmHg, p=0.0036).

Severe hypertension

In a randomised controlled trial, 183 patients with severe hypertension (mean sitting DBP 105–120mmHg) received daily aliskiren 150mg or lisinopril 20mg (titrated to 300mg or 40mg, respectively), plus hydrochlorothiazide 25mg if required (added in 53.6% of patients on aliskiren vs. 44.8% on lisinopril). The two groups had similar falls in DBP (18.5mmHg with aliskiren vs. 20.1mmHg with lisinopril) and in SBP (20.0mmHg vs. 22.3mmHg).

Summary of efficacy data

The published trials on the use of aliskiren were mainly short and focused on blood-pressure lowering in patients with mild to moderate hypertension. Therefore, the drug’s effects on mortality, cardiovascular morbidity and target organ damage are unknown. The studies indicate that aliskiren’s effect on blood pressure is similar to that of the other antihypertensive drugs used as monotherapy and that there was little benefit in increasing the dose beyond 300mg. There was also little added benefit on DBP in adding aliskiren to ACE inhibitors (a reduction of 2.1mmHg) or to angiotensin-II receptor antagonists (a reduction of 1.1–2.5mmHg). Aliskiren combinations were similar in effectiveness to other drug combinations (difference in DBP 0.6–1.6mmHg).

Unwanted effects

In trials, unwanted effects with aliskiren were generally mild and transient; the most common adverse drug reaction (occurring in 1–10% of patients) was diarrhoea. Less common unwanted effects included rash (0.1–1% of patients), and angioedema has occurred rarely. Increases in serum potassium concentration were minor and infrequent in patients with essential hypertension treated with aliskiren alone (0.9% vs. 0.6% with placebo). However, in one study, where aliskiren was used with an ACE inhibitor in patients with diabetes, increases in serum potassium concentration were more frequent (5.5%).

In trials involving patients with mild to moderate hypertension, rates of withdrawal due to unwanted effects were similar when patients on aliskiren were compared with those on placebo, hydrochlorothiazide, ACE inhibitors or angiotensin-II receptor antagonists. In a trial involving patients with severe hypertension on daily aliskiren 150–300mg or lisinopril 20–40mg (plus hydrochlorothiazide if required), similar proportions in each group reported an unwanted effect (aliskiren 32.8% vs. lisinopril 29.3%), or discontinued treatment due to an adverse event (3.2% vs. 3.4%). The most frequent unwanted effects in both groups were headache, nasopharyngitis and dizziness.

Contraindications and precautions

The summary of product characteristics (SPC) for aliskiren states that other drugs acting on the renin-angiotensin system have been associated with serious fetal malformations and neonatal death, so aliskiren should not be used in women who are, or planning to become, pregnant; also, it is not recommended in women who are breast-feeding. The drug is not recommended for children and adolescents below 18 years old due to a lack of data.

Before starting aliskiren, volume- and salt-depletion (e.g. in patients receiving high doses of diuretics) should be corrected to prevent symptomatic hypotension. The SPC recommends that aliskiren should be used “with caution” in patients with heart failure (due to limited data), and that “caution should be exercised” in patients with hypertension and severe renal impairment (due to the lack of safety information). No data are available on the use of aliskiren in patients with unilateral or bilateral renal artery stenosis or stenosis in a solitary kidney. Patients receiving other medicines that inhibit the renin-angiotensin system (e.g. ACE inhibitors), and those with reduced kidney function or diabetes, are at increased risk of hyperkalaemia during aliskiren therapy. As with other drugs acting on this system, routine monitoring of electrolytes and renal function data.
is indicated in patients on aliskiren with diabetes, kidney disease or heart failure.2 Therapy should be stopped in the event of severe and persistent diarrhoea.2

Cost

The annual cost to the NHS of daily aliskiren 150mg is £258, and 300mg, £310. This is more expensive than most other antihypertensives, many of which are available as generics. For example, atenolol 50mg daily for 1 year costs around £4; bendroflumethiazide 2.5mg, £5; losinopril 10mg, £10; amlopidine 5mg, £17 and 10mg, £16; and irbesartan 150mg, £164 and 300mg, £220.

[R=randomised controlled trial; M=meta-analysis]

2. Rasilez tablets 150 mg and 300 mg. Summary of product characteristics, EU Novartis Europharm Limited, August 2007.

Retapamulin for impetigo and other infections

Retapamulin (Altargo – GlaxoSmithKline), a new antibacterial, has been licensed in the European Union as a short-term treatment for impetigo and infected small lacerations, abrasions or sutured wounds in people aged 9 months or above.2 Advertisements claim that the product “treats localised impetigo in just 5 days”3; by comparison, the British National Formulary (BNF) advises a 7-day course of fusidic acid.4 Here we consider the place of retapamulin in impetigo and its other licensed indications.

About impetigo

Impetigo is a superficial, contagious, bacterial skin infection that mainly affects children and is common in primary care. It has two clinical forms: crusted impetigo (in which small blisters, most often on the face, break down rapidly to form a yellowish-brown crust); and the less common bullous impetigo (where large, fluid-filled blisters burst, leaving raw areas on the skin).1 Infection is usually caused by *Staphylococcus aureus*, although other bacteria may be present.1 In a study of 40 children with crusted impetigo, *S. aureus* with another organism, usually group-A beta-haemolytic streptococci, was found in 40% of specimens, *S. aureus* alone in 33%, and group-A haemolytic streptococci alone in 8%.5

Previously, we have recommended that for localised crusted impetigo, topical fusidic acid for 7 days is the first-line drug treatment, with oral antibacterial therapy reserved for more extensive disease.1 We also recognised that resistance to fusidic acid in the community is known to be increasing.1 The prevalence of meticillin-resistant *S. aureus* (MRSA) causing impetigo in the UK is unknown, but thought to be low.1 Both the BNF and Health Protection Agency advise that topical mupirocin should be used for impetigo only when MRSA is the cause.4