PRESENT STATUS OF RENIN INHIBITORS

ABSTRACT

Five decades ago, investigators identified renin inhibition as the preferred pharmacologic approach to blockade of the renin–angiotensin system. Renin is a monospecific enzyme that catalyzes the rate-limiting step in the synthesis of angiotensin II. Amplified enzymatic activity and additional physiological effects occur when renin and pro-renin bind to the (pro)renin receptor. Until recently, development of clinically effective renin inhibitors remained elusive. Molecular modeling was used to develop aliskiren, a potent, low-molecular-weight, nonpeptide, direct renin inhibitor with sufficient bioavailability to produce sustained suppression of plasma renin activity after oral administration. In patients with hypertension, aliskiren produces dose-dependent blood pressure (BP) reduction and 24-h BP control up to a dose of approximately 300 mg once daily; at these doses, aliskiren shows placebo-like tolerability. The ultimate aim of antihypertensive therapy, however, is to reduce the risk of adverse cardiovascular and renal outcomes. The effect of aliskiren on surrogate markers of organ damage and clinical outcomes is being assessed in the ongoing ASPIRE HIGHER programme, the largest clinical trials programme in the cardio-renal disease area. Results from the ALOFT, AVOID and ALLAY studies suggest that aliskiren has positive effects on markers of cardiovascular and renal damage in patients with type 2 diabetes and nephropathy, heart failure and left ventricular hypertrophy. ASPIRE HIGHER also includes four large-scale studies assessing the potential outcome benefits of aliskiren, and the results of these trials will help define the clinical utility of aliskiren in the treatment of cardiovascular and renal diseases.

INTRODUCTION

It is more than 10 years since the introduction of the angiotensin receptor blockers (ARB), and whilst the ARBs and other classes of antihypertensive agents lower BP effectively and improve clinical outcomes, rates of cardiovascular and renal morbidity and mortality remain high. Novel therapeutic approaches to the management of hypertension, and related cardiovascular and renal diseases are therefore to be welcomed.

Aliskiren is the first in a new class of direct rennin inhibitors (DRIs) and has been approved for the treatment of hypertension by the US Food and Drug Administration and European Medicines Agency at once-daily doses of 150 and 300 mg. Clinical trials in over 14,000 patients have demonstrated that aliskiren, alone or in combination with other antihypertensive therapies, provides effective BP reduction with a good safety and tolerability profile. Whether aliskiren has the ability to retard or prevent the progression of cardiovascular and renal diseases (for which hypertension is a major risk factor) is being investigated in the ongoing ASPIRE HIGHER programme, the largest clinical trials programme in the cardio-renal disease area.

THE STRUCTURE AND FUNCTION OF RENIN

Renin belongs to a family of enzymes referred to as aspartic proteases, which also includes the enzymes pepsin, cathepsin, and chymosin. Renin is a monospecific enzyme that displays remarkable specificity for its only known substrate, angiotensinogen. Renin consists of 2 homologous lobes, with the active site residing in the deep cleft located between them. The catalytic activity of the active site is due to 2 aspartic acid residues, 1 located in each lobe of the renin molecule. The reaction catalyzed by renin is the rate-limiting step in A II formation. Neither A I nor A II can be synthesized at all in the absence of renin.

In 1957, Skeggs et al. with rather remarkable foresight postulated 3 possible approaches to pharmacologic inhibition of the renin–angiotensin system (RAS):
Present Status of Renin Inhibitors

Figure 2: The Renin–Angiotensin Cascade and the 3 Available Approaches to Pharmacologic Inhibition of Production or Action of Angiotensin II.

Direct renin inhibitors (DRI), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin (AT) type I receptor blockers (ARB).

1. Inhibition of angiotensin-converting enzyme (ACE).
2. Direct interference with the action of angiotensin II (A II).
3. Inhibition of the circulating enzyme, renin.

In the intervening 50 years, ACE inhibition and angiotensin II receptor type 1 (AT1) blockade have indeed become integral components of cardiovascular pharmacotherapy (9). The recent U.S. Food and Drug Administration approval of the first direct renin inhibitor, aliskiren, thus constitutes an important milestone in the history of RAS blockade (10), making it possible for the Skeggs et al. (10) theoretically preferred approach to receive widespread clinical application and testing.

WHY DO WE NEED DRIS?

The ultimate aim of antihypertensive drug treatment is to reduce the risk of adverse cardiovascular, cerebrovascular and renal outcomes. This has been widely demonstrated for most antihypertensive drugs in large randomised controlled clinical trials, with a correlation between the magnitude of the benefit and the drug-induced BP decrease. However, despite the wide availability of a range of antihypertensive therapies, the majority of patients with high BP do not have their BP controlled to recommended target levels. Moreover, clinical trials have shown that cardio-renal morbidity and mortality remain high, especially in patients with the highest baseline risk, underlining the continuing requirement for novel therapeutic approaches.

DEVELOPMENT OF RENIN INHIBITORS

The first-generation renin inhibitors were peptide analogues of the pro-segment of renin or substrate analogues of the N-terminal amino-acid sequence of the renin substrate, angiotensinogen. Several of these peptide-like analogues were tested in animals and humans for their mechanistic and hemodynamic effects. As a group, the peptidomimetic renin inhibitors (e.g. remikiren and zankiren) showed high in vitro and in vivo potency. However, their large molecular size and lipophilicity resulted in poor intestinal absorption and considerable first-pass hepatic metabolism, significantly limiting oral bioavailability (7). In addition, all of these agents had short elimination half lives and high costs of synthesis and production. These factors precluded their successful development as antihypertensive agents (11).

Aliskiren is the first in a new class of direct rennin inhibitors (DRIs) and has been approved for the treatment of hypertension by the US Food and Drug Administration and European Medicines Agency.

ALISKIREN

The development of aliskiren represents a significant breakthrough in medicinal chemistry. Drs. Alice Huxley (for whom aliskiren is named) using retrosynthesis analysis were successful in simplifying the synthetic process and reducing the high cost of manufacture. Aliskiren is an extremely potent competitive inhibitor of renin with an IC50 (concentration inhibiting 50% of activity) of 0.6 nmol/l (9). It has high specificity for primate renin, and shows a 10,000-fold lower affinity for related aspartic peptidases. This high specificity for renin makes it unlikely to produce adverse effects through interaction with other enzymes. In comparison with earlier renin inhibitors, aliskiren has favorable physiochemical properties with high aqueous solubility and lower lipophilicity, rendering it more resistant to degradation. This leads to improved bioavailability after oral administration.

Clinical pharmacology

In healthy male subjects over a wide range of doses (40 to 1,800 mg), the plasma concentration of aliskiren peaks at 2 to 4 h after oral administration. The terminal half is 23 to 36 h, making the drug suitable for once-daily administration (10). The maximum serum concentration (Cmax) at steady state, and area under the curve all increase proportionally after doses >80 mg. Administration of aliskiren with food results in lower mean Cmax and area under the curve values than are obtained in the fasting state, although the drug was given without regard to meals in clinical trials (11). Aliskiren seems to have low potential for significant drug interactions. Co-administration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril, hydrochlorothiazide (HCTZ), or warfarin. When aliskiren was co-administered with furosemide, the area under the curve and Cmax of furosemide were reduced by about 30% and 50%, respectively.

ALISKIREN IN HYPERTENSION

Aliskiren has been extensively evaluated, as monotherapy and in combination with other agents, in clinical trials involving more than 11,000 adult patients with hypertension.

Comparison with placebo

A pooled analysis reported by Dahlöf et al. (12) included 8,481 patients who participated in double-blind trials and received treatment with aliskiren monotherapy or placebo for 8 to 12
were almost identical (13.0/9.0 mm Hg, 12.8/9.7 mm Hg, p = ns) (16). Food and Drug administration-approved dosage (aliskiren 300 mg, valsartan 320 mg); reductions in systolic BP and diastolic BP in which both drugs were forced-titrated to their maximum u.s.

In a 4-week study that included ambulatory BP monitoring, there was no statistical difference in the magnitude of BP reduction in men and women or in patients younger or older than 65 years. Comparison with other antihypertensive agents

Two trials have compared the BP-lowering effects of aliskiren with that of the ACE inhibitor ramipril. In hypertensive diabetic patients, aliskiren (300 mg) was equally effective in lowering mean sitting diastolic BP (the primary efficacy variable) compared with ramipril (10 mg) (13). A significantly greater reduction in sitting systolic BP was seen in aliskiren-treated patients. Similar results were obtained in a longer term (6 months) comparison of aliskiren and ramipril in nondiabetic hypertensive patients (14).

Multiple studies have evaluated the efficacy and safety of aliskiren in comparison with various ARBs (losartan, irbesartan, valsartan). In a 4-week study that included ambulatory BP monitoring, there was no statistical difference between the change in daytime systolic BP with 100 mg/day losartan and 300 mg aliskiren (15). Aliskiren was compared directly with valsartan as part of an 8-week study in which both drugs were forced-titrated to their maximum U.S. Food and Drug Administration-approved dosage (aliskiren 300 mg, valsartan 320 mg); reductions in systolic BP and diastolic BP were almost identical (13.0/9.0 mm Hg, 12.8/9.7 mm Hg, p = NS) (16).

Safety of aliskiren

In a pooled analysis of data including 2,316 patients who received aliskiren monotherapy, the tolerability profile of aliskiren was similar to that of placebo or ARBs at doses up to 300 mg daily (17). At the 600-mg dose, an increased incidence of diarrhea was reported.

The effects occurring after abrupt withdrawal of aliskiren have been investigated in several studies. Rebound hypertension has not been reported. On the contrary, persistence of BP-lowering effects has been consistently documented (18).

Combination therapy

Most patients with hypertension require multiple drugs, and the safety and efficacy of aliskiren has been studied in combination with thiazide diuretics, calcium channel blockers, ACE inhibitors, and ARBs. In a large factorial design study, 2776 patients with stage I and II hypertension received placebo, aliskiren (75, 150, or 300 mg), HCTZ (6.25, 12.5, or 25 mg), or various combinations of aliskiren + HCTZ over an 8-week period (19). The BP reduction with combinations of aliskiren and HCTZ seemed to be fully additive (i.e., the BP-reducing effect observed with combinations was approximately equal to the sum of BP reduction obtained with each component).

In one study, patients showing an inadequate response to amlodipine 5 mg/day were randomized to either continued therapy with amlodipine 5 mg, up-titration to amlodipine 10 mg, or the addition of aliskiren 150 mg to amlodipine 5 mg. Uptitration of amlodipine or addition of aliskiren resulted in significantly greater BP reduction than continuation of amlodipine 5 mg/day, with no difference between the low-dose combination and high-dose amlodipine. The 10-mg amlodipine dose was associated with a higher incidence of treatment-related peripheral edema (20).

The effects of dual RAS blockade with aliskiren and the ACE inhibitor ramipril were studied in 837 patients with diabetes and hypertension (17). The doses used in this study were the most commonly used dose of ramipril (10 mg), the maximum recommended dose of aliskiren (300 mg), and the combination of these doses (aliskiren/ramipril 300/10 mg). The BP was reduced by 16.6/12.8 mm Hg with combination therapy, which was statistically greater than the BP reduction seen with aliskiren (14.7/11.3 mm Hg) or ramipril (12.0/10.7 mm Hg) alone.

THE ASPIRE HIGHER CLINICAL TRIALS PROGRAMME

The place of aliskiren among the range of treatment options for hypertension, CHF and proteinuric nephropathies will ultimately be decided by its ability to prevent organ damage and reduce cardiovascular morbidity and mortality. ASPIRE HIGHER is the largest clinical trials programme in the cardio-renal disease area, involving more than 35,000 patients across 14 randomised, double-blind studies. Importantly, the ASPIRE HIGHER programme includes trials evaluating the effects of aliskiren on clinical outcomes, in addition to surrogate marker studies. Moreover, this clinical trials programme will involve a wide range of patient groups, including those with hypertension, heart failure, renal dysfunction, diabetes or previous MI, and includes some groups that have not previously been investigated in major outcome trials.
Present Status of Renin Inhibitors

Completed ASPIRE HIGHER studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Number of patients</th>
<th>Treatment arms</th>
<th>Double-blind treatment period</th>
<th>Key study objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVOID21</td>
<td>Type 2 diabetes with hypertension and proteinuria</td>
<td>599</td>
<td>Aliskiren (150–300 mg) + losartan (100 mg) and optimal antihypertensive therapy Placebo + losartan (100 mg) and optimal antihypertensive therapy</td>
<td>24 weeks</td>
<td>Primary-Change in UACR Secondary-Propotion of patients with ≥ 50% reduction in UACR Change in BP</td>
</tr>
<tr>
<td>ALOFT32</td>
<td>Stable heart failure and raised BNP levels (&gt; 100 pg/ml)</td>
<td>302</td>
<td>Aliskiren (150 mg) + standard therapy (including ACE inhibitor or ARB, and betablocker) Placebo + standard therapy</td>
<td>12 weeks</td>
<td>Primary-Safety and tolerability Secondary-Change in BNP Change in NT-proBNP Change in plasma aldosterone</td>
</tr>
<tr>
<td>ALLAY34</td>
<td>Overweight with hypertension and LV hypertrophy</td>
<td>465</td>
<td>Aliskiren (150–300 mg) Losartan (50→100 mg) Aliskiren/losartan (150–300/50→100 mg)</td>
<td>36 weeks</td>
<td>Primary-Change in LV mass index Secondary-Proportion of patients with ≥ 50% reduction in UACR Change in BP</td>
</tr>
<tr>
<td>AGELESS35</td>
<td>≥ 65 years of age, with systolic hypertension (140 to &lt; 180 mmHg)</td>
<td>912</td>
<td>Aliskiren (150–300 mg) + optional HCT and amlodipine Ramipril (5→10 mg) + optional HCT and amlodipine</td>
<td>36 weeks</td>
<td>Primary-Change in SBP at Week 12 (i.e. monotherapy phase) Secondary-Change in BP at study Endpoint, Safety and tolerability</td>
</tr>
</tbody>
</table>

Ongoing ASPIRE HIGHER studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Number of patients</th>
<th>Treatment arms</th>
<th>Double-blind treatment period</th>
<th>Key study objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALTITUDE</td>
<td>Type 2 diabetes at high risk for cardiovascular or renal events (i.e. with albuminuria and/or history of cardiovascular disease)</td>
<td>≈8,600</td>
<td>Aliskiren (150–300 mg) + conventional therapy (including ACE inhibitor or ARB) Placebo + conventional therapy</td>
<td>≈4 yearsb</td>
<td>Primary - Cardiovascular and renal morbidity and mortality Secondary-Occurrence of cardiovascular Complications,Occurrence of renal complications</td>
</tr>
<tr>
<td>AVANT-GARDE</td>
<td>Stabilised acute coronary syndrome with preserved left ventricular systolic function</td>
<td>≈1,100</td>
<td>Aliskiren (75→150→300 mg) Valsartan (80→160→320 mg)</td>
<td>8 weeks</td>
<td>Primary Change in NT-proBNP  Exploratory Rate of adverse cardiac eventse</td>
</tr>
<tr>
<td>ASPIRE</td>
<td>Post-MI associated with LV systolic dysfunction</td>
<td>≈800</td>
<td>Aliskiren (75→150→300 mg) + optimised standard therapy (including ACE inhibitor or ARB) Placebo + optimised standard therapy</td>
<td>36 weeks</td>
<td>Primary-Change in LV end-systolic volume Secondary-Effect on composite clinical endpointf</td>
</tr>
</tbody>
</table>

Arrows indicate dose titration steps.

aHCT and amlodipine added if SBP ≥ 140 mmHg.
bALTITUDE is an event-drive study and will complete when approximately 1,628 patients have reached the primary endpoint.
cDefined as cardiovascular death, resuscitated sudden death, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure, onset of end-stage renal disease, renal death or doubling of baseline serum creatinine concentration sustained for at least 1 month.
dPatients start treatment with valsartan monotherapy, followed by forced titration to maximum dose, and subsequent addition of aliskiren and dose titration.
eDefined as death, recurrent myocardial infarction or hospitalisation for chronic heart failure.
fDefined as cardiovascular death, hospitalisation for heart failure, recurrent myocardial infarction, stroke and resuscitated sudden death.

AGELESS = Aliskiren for GEriatric LowEring of SyStolic Hypertension; ALLAY = ALiskiren Left Ventricular Assessment of Hypertrophy; ALOFT = ALiskiren Observation in Heart Failure Treatment; ALTITUDE = ALiskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints; ASPIRE = Aliskiren Study in Post-MI Patients to Reduce REmodelling; AVANT-GARDE = Aliskiren and VALsartan to Reduce NT-proBNP via Renin-AnGiotensin-Aldosterone Rone System Blockade; AVOID = Aliskiren in the EValuation of PrOteinuria In Diabetes. BNP = B-type natriuretic peptide; BP = blood pressure; HCT = hydrochlorothiazide; LV = left ventricular; MI = myocardial infarction; NT-proBNP = N-terminal fragment of proBNP; SBP = systolic blood pressure; UACR = urinary albumin:creatinine ratio.

Completed short-term studies

Four of the ASPIRE HIGHER studies have already been completed (table 1). Three trials have demonstrated beneficial effects of aliskiren on established surrogate markers of cardiovascular or renal disease, while a fourth trial showed that aliskiren (150 or 300 mg) provided significantly greater BP-lowering effects

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concomitant use of three RAAS inhibitors. Interestingly, aliskiren add-on therapy with aliskiren 150 mg was not associated with patients in aLoFT also received an aldosterone antagonist, yet failure.(23) with improved cardiovascular outcomes in patients with heart and n-terminal proBNP with other RAAS inhibitors have been associated in BNP compared with placebo (figure 4b). Reductions in BNP and NT-proBNP with other RAAS inhibitors have been associated with improved cardiovascular outcomes in patients with heart failure.(24)

The ALOFT study showed that aliskiren (150 mg) was associated with improvements in key indicators of heart failure when added to standard therapy in 302 patients with stable heart failure and hypertension. Aliskiren 150 mg was well tolerated in this selected population of patients when added to standard therapy, which could include an ACE inhibitor or an ARB (but not both); there was no significant difference between aliskiren and placebo for the prespecified safety assessments of renal dysfunction, symptoms of hypotension and hyperkalaemia.(25) Moreover, a third of the patients in ALOFT also received an aldosterone antagonist, yet add-on therapy with aliskiren 150 mg was not associated with an increased risk of adverse events in these patients despite the concomitant use of three RAAS blockers. Interestingly, aliskiren produced significant improvements in B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) and urinary aldosterone, all important markers of heart failure. Indeed, aliskiren was associated with a five-fold greater decrease in BNP compared with placebo (figure 4b). Reductions in BNP and NT-proBNP with other RAAS inhibitors have been associated with improved cardiovascular outcomes in patients with heart failure.(21)

The ALLAY (ALiskiren in Left Ventricular Hypertrophy) study compared the effects on left ventricular (LV) mass (assessed by magnetic resonance imaging) of aliskiren 300 mg and losartan 100 mg, alone or in combination, over 36 weeks in 465 overweight patients with hypertension and LV hypertrophy. ALLAY showed that the combination of aliskiren and losartan provided additional numerical reductions in LV mass index compared with losartan alone (5.8 vs. 4.8 g/m2), although this difference did not achieve statistical significance.(28) Importantly, the combination of aliskiren and losartan showed a similar safety and tolerability profile to the individual monotherapies, with no significant increase in the risk of adverse events or safety issues such as hyperkalaemia.

The AGELESS (Aliskiren for GEiatric LowErSing of SyStolic Hypertension) study(29) compared the antihypertensive efficacy, and safety and tolerability of aliskiren- and ramipril-based regimens over 36 weeks of treatment in 901 elderly patients (≥65 years) with systolic hypertension (140 to 180 mmHg). At week 12 endpoint, aliskiren monotherapy (150 or 300 mg) provided significantly greater BP reductions compared with ramipril 5 or 10 mg alone. Moreover, after 36 weeks, aliskiren-based therapy (with optional sequential addition of HCT 12.5 or 25 mg and amlodipine 5 or 10 mg) lowered BP by 20.8/8.2 mmHg, more than ramipril-based therapy (18.1/7.0 mmHg; systolic BP, p = 0.0747; diastolic BP; p<0.05). Aliskiren-based therapy also demonstrated a good tolerability profile in elderly patients. The overall incidence of adverse events was similar in the aliskiren and ramipril treatment groups, but as expected, the incidence of cough was lower in patients who received aliskiren than those who received ramipril (4% vs. 13%). The effects of aliskiren-based therapy on morbidity and mortality in elderly patients will be assessed in the APOLLO (Aliskiren in Prevention Of Later Life Outcomes) trial.

Ongoing and future studies

Large-scale outcome studies are a key component of the ASPIRE HIGHER clinical trials programme. They are summarised in table 1.

Three further outcomes trials are planned. The ATMOSPHERE (Aliskiren Trial to Minimize OutcomeS in Patients with HEart FailurE) study will evaluate whether aliskiren delays time to cardiovascular death or hospitalisation for heart failure in patients with chronic heart failure, whereas the ASTRONAUT (Aliskiren Trial ON Acute Heart Failure OUTComes) study will assess the potential benefits of aliskiren therapy in reducing cardiovascular mortality and heart failure re-hospitalisation in patients stabilised after hospitalization for acute decompensated heart failure. APOLLO is a long-term trial that will assess the effectiveness of aliskiren-based therapy in the primary and secondary prevention of cardiovascular morbidity and mortality in elderly patients with additional risk factors, with or without previous cardiovascular events.

ASPIRE HIGHER also features several head-to-head BP-lowering trials that will compare aliskiren with standard-of-practice antihypertensive therapies. TARGET HIGHER will assess the antihypertensive efficacy of the combination of aliskiren and valsartan in hypertensive patients with diabetes and/or
microalbuminuria. The ACCELERATE (Aliskiren and the Calcium ChannEl BlockER Amlodipine Combination as Initial TreatmenT Strategy in Stage I and II Hypertension) study, in collaboration with the British Hypertension Society, will investigate whether BP levels with the combination of aliskiren and amlodipine remain lower over 32 weeks of treatment in patients who start these agents simultaneously compared with those who receive the drugs sequentially.[26]

CONCLUSIONS

Early clinical experience from numerous studies shows that aliskiren offers effective BP lowering with good tolerability, when administrated alone or in combination with other antihypertensive therapies. Aliskiren is also an effective and well-tolerated therapy in the elderly[23] and obese. Theoretical considerations suggest that aliskiren may also have significant potential in the management of cardiovascular risk and nephropathy, particularly in patients with diabetes and those with existing cardiovascular disease. This is further supported by the results of the first three studies of the ASPIRE HIGHER clinical trials programme, which showed positive effects of aliskiren on surrogate markers of cardiovascular and renal outcomes in patients with type 2 diabetes and nephropathy (AVOID), heart failure (ALOFT) and LV hypertrophy (ALLAY). However, outcomes data will be the ultimate yardstick by which this new class of antihypertensive agent will be judged. Such data will be generated by the ongoing and planned trials that form part of the extensive ASPIRE HIGHER programme, and will define the role of aliskiren in the management of cardiovascular and renal diseases.

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