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Aliskiren/Hydrochlorothiazide Combination

In Mild to Moderate Hypertension

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Contents

Abstract

▲ Aliskiren/hydrochlorothiazide is a single-pill combination of the first in the new class of non-peptide direct renin inhibitors (aliskiren) and a thiazide diuretic (hydrochlorothiazide [HCTZ]) that achieves blood pressure (BP) reductions greater than those seen with either component alone.

▲ In double-blind, 8-week clinical trials, aliskiren and HCTZ (as a combination of the individual components or as single-pill combinations) reduced mean sitting systolic and diastolic BP from baseline to a significantly greater extent than placebo, aliskiren monotherapy and HCTZ monotherapy. Aliskiren/HCTZ produced additional BP reductions in patients inadequately responsive to 4 weeks' prior treatment with aliskiren or HCTZ alone.

▲ Responder rates and BP control rates further demonstrated the benefits of aliskiren/HCTZ combination therapy over monotherapy with individual components in patients with mild to moderate hypertension.

▲ Aliskiren plus HCTZ appeared to be effective as long-term (up to 1 year) combination treatment in an open-label trial.

▲ In a 12-week placebo-controlled trial in obese patients with hypertension, BP reductions and responder and control rates were significantly greater with aliskiren/HCTZ than with HCTZ alone.

▲ Aliskiren/HCTZ was generally well tolerated in clinical trials, with most adverse events being mild and transient in nature.

Features and properties of aliskiren/hydrochlorothiazide (aliskiren/HCTZ; Rasilez HCT®)	
Indication	
Hypertension not adequately controlled with aliskiren or HCTZ alone; substitution treatment for hypertension adequately treated with aliskiren plus HCTZ, at the equivalent single-pill dosage	
Mechanism of action	
Direct renin inhibitor (aliskiren) plus thiazide diuretic (HCTZ)	
Dosage and administration	
Available single-pill aliskiren/HCTZ combinations (mg/mg)	150/12.5, 150/25, 300/12.5, 300/25
Route and frequency	Oral, once daily
Pharmacokinetics of aliskiren 150 and 300 mg single dose in healthy volunteers	
Mean maximum plasma concentration (C_{max})	72 and 202 ng/mL
Median time to C_{max} (t_{max})	2.5 and 3.0 h
Mean area under the plasma concentration-time curve (AUC) from 0 to 96 h	530 and 1480 ng • h/mL
Pharmacokinetics of HCTZ 12.5 and 25 mg/day in healthy volunteers	
Mean C_{max}	70 and 142 ng/mL
Mean t_{max}	1.5–4 and 2–5 h
Mean AUC from time 0 to 9 h	351 and 613 ng • h/mL
Most frequent adverse events	
Dizziness, influenza, diarrhoea, cough, vertigo, asthenia, arthralgia	

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) specifies the goal of antihypertensive therapy as the reduction of cardiovascular and renal morbidity and mortality, with systolic/diastolic blood pressure (SBP/DBP) targets of <140/90 mmHg, or <130/80 mmHg in patients with additional complications such as diabetes mellitus or renal disease.[1] A large number of patients treated for hypertension do not attain adequate blood pressure (BP) control with monotherapy, and many require two or more pharmacological agents to reach and maintain their BP goals.[1]

Aliskiren/hydrochlorothiazide (Rasilez HCT®) is a single-pill combination of the first in the new class of non-peptide direct renin inhibitors (aliskiren) and a thiazide diuretic (hydrochlorothiazide [HCTZ]), which may achieve BP reductions greater than those seen with either component alone. Aliskiren acts to neutralize the compensatory rise in plasma renin activity (PRA) induced by HCTZ.[2] The single-pill combination has been developed with the aim of improving convenience and compliance due to the single-tablet once-daily treatment regimen,[3] and also offers the flexibility of four available fixed-dose combinations.

The aliskiren/HCTZ single-pill combination is available in the US[4] and Europe[5] for the treatment of adults with essential hypertension whose BP is not adequately controlled with aliskiren or HCTZ alone, and as a substitution treatment in patients with hypertension adequately treated by the two individual drugs concomitantly at the equivalent fixed dosage.

This article focuses on the use of the aliskiren/HCTZ single-pill combination in the treatment of mild to moderate hypertension. However, while trials evaluating this specific formulation are preferentially reviewed, some larger, well designed studies in which aliskiren plus HCTZ was administered by combining the individual components are also discussed.

Medical literature on the use of aliskiren/HCTZ in patients with hypertension was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

The pharmacodynamic properties of aliskiren and HCTZ are well documented and have been previously reviewed in *Drugs*.[6-9] The individual mechanisms of action and pharmacodynamic effects of aliskiren and HCTZ are outlined in this section, with discussion of their combined pharmacodynamic effects where data are available.

Mechanism of Action

- Aliskiren demonstrates high affinity and specificity for human renin, binding to its catalytic site and thereby blocking its actions upon angiotensinogen and the subsequent conversion of angiotensinogen to angiotensin I (ultimately preventing production of the potent vasoconstrictor angiotensin II).[6] Blockade of this first step in the renin-angiotensin system cascade has the ultimate effect of reducing BP in hypertensive patients.[4]
- The thiazide diuretic HCTZ directly decreases renal tubular electrolyte reabsorption,[4] thereby reducing osmotic pressure and water reabsorption. Although BP reduction follows, volume depletion stimulates renin release from the kidney, which may limit the antihypertensive benefits of diuretic agents.[2]
- When aliskiren and HCTZ are administered in combination, aliskiren opposes the compensatory activation of the renin-angiotensin system by HCTZ and the adverse hypokalaemic effects of thiazide diuretics.[2]

Effects on the Renin-Angiotensin System

- In normotensive healthy volunteers on a sodium-regulated diet, aliskiren 40–600 mg/day dose-dependently decreased PRA (the capacity of renin to form angiotensin I), angiotensin I and angiotensin II levels, and increased plasma renin concentration (PRC).[10] In another study in mildly sodium-depleted healthy volunteers, single oral doses of aliskiren

300 mg decreased PRA and levels of angiotensin I and II for 48 hours, and reduced urinary aldosterone excretion, but increased PRC.[11]

- HCTZ 12.5 mg increased diuresis and natriuresis to a significantly greater extent than placebo in healthy volunteers; no further increases in diuresis and natriuresis were seen at higher HCTZ dosages.[12] Nevertheless, the antihypertensive efficacy of HCTZ dosages up to 50 mg/day, alone or in combination with other antihypertensives, is well established.[1,7-9]
- In a study in patients with mild to moderate hypertension, aliskiren 75, 150 and 300 mg/day decreased (the geometric) mean PRA from baseline by 54.2%, 65.1% and 57.6%, respectively.[2] Conversely, HCTZ monotherapy increased PRA from baseline by 3.5%, 44.7% and 71.9% at 6.25, 12.5 and 25 mg/day dosages, respectively. When combined, aliskiren/HCTZ reduced PRA by 46.1–63.5% compared with an increase of 0.7% with placebo.[2]
- Sustained PRA suppression was seen when aliskiren was administered alone or in combination with HCTZ for up to 1 year in patients with mild to moderate hypertension (reported as an abstract and poster).[13] PRA suppression continued during a 1-month aliskiren withdrawal period, suggesting that aliskiren may inhibit the renin system for durations beyond the plasma half-life of the drug.[13]
- Aliskiren elevated PRC from baseline in a dose-related manner in hypertensive patients, with increases of 164%, 192% and 348% at dosages of 75, 150 and 300 mg/day, respectively.[2] HCTZ 25 mg/day increased PRC by 108%, whereas lower dosages did not cause alterations in PRC that significantly differed from placebo. PRC increased with all aliskiren plus HCTZ combinations, with the magnitude of increases relating to the dosages of both aliskiren and HCTZ; the largest increase was 1211% from baseline with aliskiren plus HCTZ 300 mg/25 mg once daily.[2]
- PRA was significantly increased ($p < 0.05$ vs baseline) after 4 weeks' treatment with HCTZ 25 mg/day in obese patients with hypertension.[14] The addition of aliskiren counteracted this effect, resulting in a significant ($p < 0.05$) overall decrease in PRA compared with baseline, whereas combined treatment with irbesartan plus HCTZ or amlodipine plus HCTZ produced further significant increases in PRA.[14]

Other Effects

- There were no significant effects of aliskiren 300 or 1200 mg/day on the corrected QT interval duration in a randomized double-blind trial investigating its effects on cardiac repolarization and conduction in healthy volunteers.[15]

2. Pharmacokinetic Profile

The individual pharmacokinetic profiles of aliskiren and HCTZ have been well characterized and extensively reviewed elsewhere,[6,12,16] and are only briefly outlined here. Information regarding the pharmacokinetic profile of the aliskiren/HCTZ single-pill combination has been obtained from the European Summary of Product Characteristics[5] and US prescribing information.[4]

Aliskiren

- Aliskiren has an absolute bioavailability of 2.6%, achieving maximum plasma concentrations (C_{max}) within 1–3 hours of an oral dose.[16] Food can markedly reduce aliskiren exposure. Although this is not considered to be clinically relevant,[16] this is reflected in the dosage and administration recommendations for the aliskiren/HCTZ combination (section 5).
- Aliskiren 75–600 mg displayed dose-linear pharmacokinetics in a randomized crossover study involving 32 healthy volunteers (reported as an abstract).[17] Following a single oral 150 mg dose, the mean C_{max}, median time to C_{max} (t_{max}) and mean area under the plasma concentration-time curve (AUC) between 0 and 96 hours values were 72 ng/mL, 2.5 h and 530 ng • h/mL, with respective values of 202 ng/mL, 3.0 h and 1480 ng • h/mL for the 300 mg single oral dose.[17]
- Interindividual variability with regard to the pharmacokinetics of aliskiren is relatively high,[18] with observed variabilities of 40–70% for the AUC,

and 30–50% for C_{max} values,[16] although the clinical relevance of this variability is unclear.

- Steady state is reached after 7–8 days of once-daily administration. The drug has an apparent volume of distribution of 135 L and is moderately bound to plasma proteins (47–51%; concentration-independent between 10–500 ng/mL).[16]
- Aliskiren appears to undergo minimal metabolism, with cytochrome P450 3A4 being the major enzyme responsible for its metabolism.[17] It is not known whether the metabolites of aliskiren have any pharmacological activity.[19]
- Following a single oral dose of radiolabelled aliskiren in aqueous solution in healthy volunteers, the terminal elimination half-life for aliskiren was 44 hours.[19] The majority of radioactivity was excreted via the biliary/faecal route (total excretion 91.5% [range 85–95%] over the 168-hour collection period), and 0.6% was recovered in the urine.[19] Unchanged aliskiren accounted for ≈0.4% of the dose recovered in the urine, and 77.5% of the dose recovered in the faeces. Oxidized metabolites accounted for ≈1.4% of the excreted radioactivity.[19]
- No clinically relevant alterations in the pharmacokinetics of aliskiren are seen in the presence of renal or hepatic impairment.[16] There appears to be a low potential for clinically significant drug interactions with aliskiren owing to its minimal hepatic metabolism.[19] Numerous drug-drug interaction studies have confirmed a lack of pharmacokinetic interaction between aliskiren and other drugs likely to be coadministered, including antihypertensive therapies[16] (notably, HCTZ) [reported as an abstract].[20]

Hydrochlorothiazide (HCTZ)

- Two studies in healthy volunteers showed dose-dependent increases in mean C_{max} and AUC values for HCTZ after single oral doses between 12.5 and 100 mg.[12,21] In one of the studies, mean C_{max} values after 12.5 and 25 mg doses were 70 ng/mL after 1.5–4 hours with an AUC from 0 to 9 hours (AUC_9) of 351 ng • h/mL, and 142 ng/mL after 2–5 hours with an AUC_9 of 613 ng • h/mL.[12]
- The mean renal clearance values for the single 12.5 and 25 mg doses in healthy volunteers were 20.7 and 19.9 L/h.[12]
- HCTZ is not metabolized, but is rapidly eliminated via the kidneys; within 24 hours of oral administration, ≥61% of the HCTZ dose is eliminated unchanged with a half-life of 5.8–18.9 hours.[4]

Aliskiren/HCTZ Single-Pill Combination

- Median t_{max} values following oral administration of the aliskiren/HCTZ single-pill combination are ≤1 hour and ≤2.5 hours for the two respective components.[5] The mean AUC and C_{max} values are reduced by 60% and 82% for aliskiren (although PRA is unaffected),[22] and increased by 13% and 10% for HCTZ when single-pill aliskiren/HCTZ is administered with food[4] (see section 5).

3. Therapeutic Efficacy

The efficacy of aliskiren and HCTZ combined for the treatment of patients with mild to moderate uncomplicated hypertension has been evaluated in several well designed clinical trials. Two trials used the single-pill combination,[3,23] and three combined the individual components,[2,14,24] with aliskiren and HCTZ administered orally as single daily doses in all studies.

Trials were of 8,[2,3,23] 12[14] or ≤52[24] weeks' duration and all but one[24] were of randomized, double-blind, multicentre design. In the only long-term study (available as an abstract only),[24] patients who received open-label aliskiren 300 mg/day plus HCTZ 25 mg/day for ≥8 months in an initial phase of the study (n = 868) were permitted to enter a 4-month open-label extension phase (n = 198).[24]

Four of the trials enrolled patients with mild to moderate essential hypertension (mean sitting DBP [msDBP] between 90 and 110 mmHg),[2,3,23,24] three of which also included subgroups of patients with obesity (defined as body mass index [BMI] of ≥30 kg/m^2) [≈38–42% of patients].[2,3,23] One trial enrolled obese hypertensive patients only (baseline msDBP between 95 and 110 mmHg).[14] Where specified, the mean patient age was 52.9–55.5

years,[2,3,14,23] and patients with severe, secondary or complicated hypertension were excluded.[2,3,14,23]

In the largest of the three 8-week randomized trials,[2] 2276 patients were randomized to treatment with aliskiren alone (75, 150 or 300 mg/day; n = 183–185), HCTZ alone (6.25, 12.5 or 25 mg/day; n = 176–194), aliskiren plus HCTZ (at every possible dose combination excluding aliskiren 300 mg plus HCTZ 6.25 mg; n = 173–193) or placebo (n = 195). The other two 8-week trials evaluated the single-pill combination of aliskiren/HCTZ (300 mg/25 mg,[3,23] 150 mg/25 mg[23] and 300 mg/12.5 mg[3] once daily) in patients whose hypertension had not responded adequately to prior HCTZ 25 mg/day[23] or aliskiren 300 mg/day[3] monotherapy. In the study enrolling obese hypertensive subjects only,[14] patients unresponsive to a prior 4-week single-blind period of HCTZ treatment were randomized to receive aliskiren 150 mg/day (n = 122), irbesartan 150 mg/day (n = 119), amlodipine 5 mg/day (n = 126) or placebo (n = 122), in addition to continuing HCTZ 25 mg/day. Aliskiren, irbesartan and amlodipine dosages were doubled after 4 weeks and the combination therapies were continued for a further 8 weeks.[14]

All four of the double-blind trials specified the change from baseline in msDBP at 8 weeks as the primary endpoint.[2,3,14,23] Secondary efficacy measures included the change in mean sitting SBP (msSBP), the proportion of patients with successful response to treatment (defined as msDBP <90 mmHg and/or a ≥10 mmHg decrease from baseline) and the proportion of patients attaining BP control (defined as msDBP <90 mmHg and msSBP <140 mmHg).[2,3,14,23] The long-term study measured msDBP and msSBP at regular intervals during the trial, including the extension period.[24]

The effects of treatment on PRA and PRC were assessed in a number of trials, the results of which are discussed in section 1.

- In the largest of the 8-week trials, aliskiren, HCTZ and aliskiren plus HCTZ combined reduced msDBP (primary endpoint) from baseline to a significantly ($p < 0.0002$) greater extent than placebo in patients with mild to moderate hypertension.[2]

- The effects of aliskiren monotherapy on msDBP were dose dependent, with least squares mean (LSM) decreases from baseline of 8.7, 8.9 and 10.3 mmHg for the 75, 150 and 300 mg/day dosages, respectively.[2] Reductions in msDBP were not linearly related to HCTZ dosage, with LSM decreases from baseline at 8 weeks of 9.1, 10.1 and 9.4 mmHg at the 6.25, 12.5 and 25 mg/day dosages, respectively. Corresponding reductions in msDBP with the aliskiren plus HCTZ combination ranged from 10.4 to 14.3 across dosages (all $p \leq 0.0001$ vs placebo; $p < 0.05$ vs each component monotherapy for all combinations except aliskiren 75 mg plus HCTZ 12.5 mg and aliskiren 150 mg plus HCTZ 6.25 mg).[2]

- Similarly, aliskiren and HCTZ, as monotherapies, in combination and at the majority of dosages, decreased msSBP from baseline at 8 weeks to a significantly ($p < 0.05$) greater extent than placebo.[2] Furthermore, the aliskiren plus HCTZ combination (at all but the 75 mg/12.5 mg and 150 mg/6.25 mg once daily dosages) was significantly ($p < 0.05$) better than the component monotherapies in this regard; LSM reductions in msSBP ranged from 14.3 to 21.2 mmHg.[2]

- According to a *post hoc* analysis in a subset of patients with stage 2 hypertension (baseline msSBP ≥160 mmHg),[25] aliskiren plus HCTZ was associated with LSM reductions from baseline in msSBP of 22.2–27.2 mmHg, and in msDBP of 11.9–13.3 mmHg. Corresponding LSM reductions from baseline in msSBP/msDBP for aliskiren 150 and 300 mg/day were 15.5/8.4 mmHg and 19.4/8.4 mmHg, and for HCTZ 12.5 and 25 mg/day were 17.3/8.7 mmHg and 18.9/9.7 mmHg. In this regard, the differences between the combination and monotherapies at respective dosages were significant ($p < 0.05$) for the majority of aliskiren plus HCTZ dosages.[25]

- In the other randomized 8-week trials, single-pill aliskiren/HCTZ was an effective treatment option, producing additional reductions in msDBP (primary endpoint) and msSBP in patients with mild to moderate hypertension inadequately responsive to

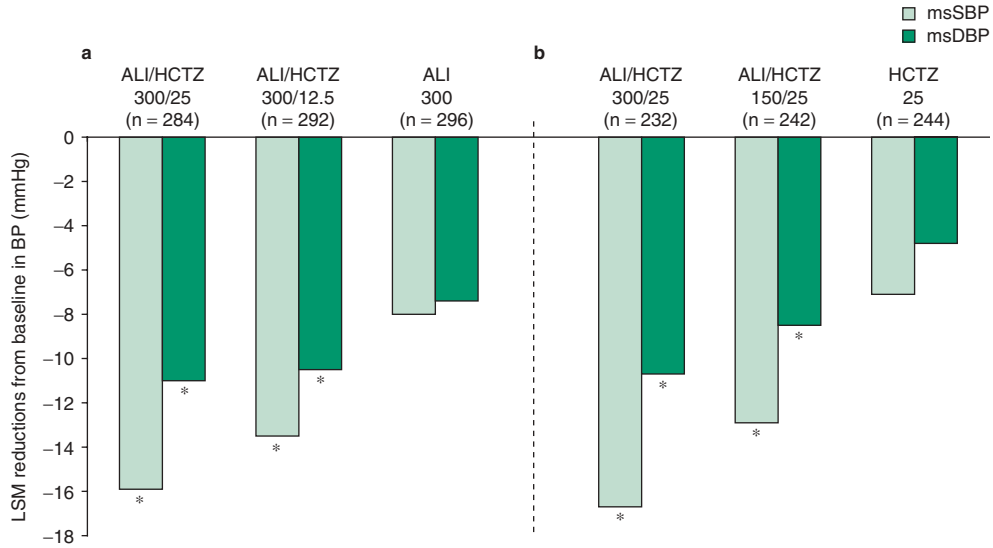

Fig. 1. Blood pressure (BP) reductions with single-pill aliskiren/hydrochlorothiazide (ALI/HCTZ) in patients with an inadequate response to monotherapy with individual components. Results of two randomized, double-blind, 8-week trials in patients whose hypertension had not responded adequately to prior (**a**) ALI 300 mg/day[3] or (**b**) HCTZ 25 mg/day[23] for 4 weeks. Patients received 8 weeks of once-daily treatment with ALI/HCTZ (300 mg/25 mg,[3,23] 300 mg/12.5 mg[3] and 150 mg/25 mg[23]) and ALI 300 mg[3] or HCTZ 25 mg.[23] Results are shown for the least-squares mean (LSM) reductions from baseline (randomization) to week 8 in mean sitting systolic and diastolic BP (msSBP and msDBP), the latter being the primary endpoint, in the intent-to-treat population. * $p < 0.001$ vs monotherapy comparator.

4 weeks' prior treatment with aliskiren[3] or HCTZ[23] alone (figure 1).

- In patients with an inadequate response to aliskiren alone, LSM decreases from baseline in msSBP/msDBP were significantly greater in those treated with the aliskiren/HCTZ single-pill combinations than with aliskiren 300 mg/day alone[3] (figure 1a). Similarly, in patients with an inadequate response to prior HCTZ monotherapy, LSM decreases from baseline in msSBP/msDBP were significantly greater in those treated with the aliskiren/HCTZ single-pill combinations than with HCTZ 25 mg/day alone[23] (figure 1b).
- Responder rates and BP control rates demonstrated the benefits of aliskiren/HCTZ combination therapy in patients with mild to moderate hypertension.[2,3,23] For example, in one trial, approximately 81% of patients treated with aliskiren 300 mg plus HCTZ 12.5 mg once daily were deemed treatment responders ($p < 0.05$ vs placebo), and BP was controlled in 37.4–59.5% of patients who received combination treatment ($p < 0.02$ vs placebo for all but the aliskiren 75 mg plus HCTZ 6.25 mg combination).[2] BP control and response rates were significantly ($p < 0.001$) higher with the aliskiren/HCTZ combinations than with the component monotherapies in the other 8-week trials.[3,23]
- Aliskiren plus HCTZ appeared to be effective as long-term combination treatment in patients with mild to moderate hypertension.[24] At the end of the initial ≥8-month open-label treatment period, msSBP/msDBP reductions in aliskiren plus HCTZ recipients (n = 868) were 12.1/18.7 mmHg (vs 13.3/17.4 mmHg in the group of patients who had responded adequately to aliskiren monotherapy). The BP reductions from baseline were maintained through the 4-month extension phase, with decreases in msSBP/msDBP at endpoint of 10.4/17.4 mmHg with aliskiren plus HCTZ combination treatment.[24]

In Obese Hypertensive Patients

In the trial in obese hypertensive patients,[14] the primary comparison was between aliskiren/HCTZ combination therapy and HCTZ monotherapy in the

intent-to-treat population. The 8-week endpoint was specified because study treatment was discontinued (for safety reasons) at, or after, this time in patients with msDBP ≥100 mmHg or msSBP ≥160 mmHg. Secondary comparisons included the changes in msDBP and msSBP from baseline at weeks 4, 8 and 12 with aliskiren plus HCTZ versus each of the three other treatments.[14]

- Aliskiren plus HCTZ reduced msDBP (primary endpoint) and msSBP to a significantly greater extent than placebo plus HCTZ in obese patients (mean BMI of 34.4 kg/m^2) with arterial hypertension (baseline msDBP 96.6–97.2 mmHg and msSBP 149.1–149.8 mmHg) previously unresponsive to HCTZ monotherapy.[14]
- At the 8-week endpoint (after 4 weeks of treatment at the highest dosages), msSBP/msDBP was decreased from baseline by 11.9/15.8 mmHg, 11.3/15.4 mmHg, 10.3/13.6 mmHg and 7.9/8.6 mmHg in aliskiren plus HCTZ, irbesartan plus HCTZ, amlodipine plus HCTZ, and placebo plus HCTZ recipients, respectively ($p < 0.0001$ for aliskiren plus HCTZ vs placebo plus HCTZ, but not significant vs irbesartan plus HCTZ or amlodipine plus HCTZ).[14]
- BP reductions achieved with aliskiren plus HCTZ at the 4- and 12-week endpoints were also significantly greater than those with placebo plus HCTZ, as were responder and control rates at the 8- and 12-week endpoints (all $p < 0.02$).[14]
- According to a *post hoc* subgroup analysis, ≈69% of aliskiren plus HCTZ recipients with grade 3 obesity (BMI ≥40 kg/m^2; $n = 54$) achieved BP control, significantly higher than rates achieved with HCTZ monotherapy (≈17%; $p < 0.01$) or amlodipine plus HCTZ (≈44%; $p < 0.05$) in this notably hard-to-treat patient group.[26] There was no significant difference between aliskiren plus HCTZ and irbesartan plus HCTZ in this regard.

4. Tolerability

- Aliskiren/HCTZ, as a single-pill combination or as concurrently administered individual components, was generally well tolerated in the trials reviewed in section 3. Adverse events were mild and transient in nature, with the most commonly reported events including nasopharyngitis,[2,3,14,23,24] headache,[2,3,14,23,24] bronchitis,[24] dizziness,[14,23] back pain,[23] vertigo[23] and hypercholesterolaemia.[3]
- Adverse events reported in placebo-controlled trials evaluating the tolerability of the single-pill combination, occurring in ≥1% of patients and with a higher incidence in aliskiren/HCTZ recipients than placebo recipients are presented in figure 2.[4]
- Rates of hypokalaemia (defined as serum potassium levels <3.5 mmol/L) were numerically lower with aliskiren/HCTZ than with HCTZ alone,[2,23] and with aliskiren/HCTZ 300 mg/12.5 mg once daily than with the 300 mg/25 mg once-daily dosage,[3] in trials in patients with mild to moderate hypertension. In obese hypertensive patients, hypokalaemia occurred in 4.9% of aliskiren plus HCTZ combination recipients versus 2.5%, 10.3% and 4.1% of patients treated with irbesartan plus HCTZ, amlodipine plus HCTZ or HCTZ alone, respectively.[14]
- Angioedema has been rarely reported with aliskiren use in controlled clinical trials at rates

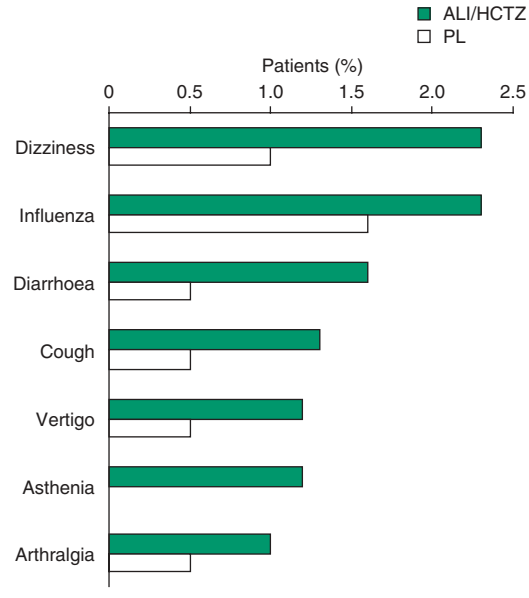

Fig. 2. Tolerability of the aliskiren/HCTZ (ALI/HCTZ) single-pill combination in patients with hypertension. Adverse events reported in ≥1% of patients and with an incidence greater in ALI/HCTZ recipients than placebo (PL) recipients in trials of ≤1 year in duration.[4]

not dissimilar to those seen with placebo or HCTZ, and in postmarketing experience (frequency unknown)[5] [section 5].

5. Dosage and Administration

For the second-line treatment of patients with hypertension, the recommended dosages of aliskiren/HCTZ (in order of increasing mean effect) are 150 mg/12.5 mg, 150 mg/25 mg, 300 mg/12.5 mg and 300 mg/25 mg, which should be administered orally once daily in a routine pattern with regard to meals.[5] Titration of the aliskiren/HCTZ dosage should occur after a 2- to 4-week period in the event BP remains uncontrolled. Aliskiren/HCTZ is not indicated as an initial therapy for hypertension.

The use of aliskiren/HCTZ should be avoided during pregnancy.[4,5] As with other aliskiren-containing medicines, the use of aliskiren/HCTZ is contraindicated in patients who have previously experienced angioedema with this treatment.[5,27] Local prescribing information should be consulted for details of contraindications, warnings and precautions, and use in special populations.

6. Aliskiren/HCTZ: Current Status in Mild to Moderate Hypertension

The single-pill aliskiren/HCTZ combination is available in the US and Europe for the second-line treatment of hypertension in patients whose BP is not adequately controlled with either drug alone, or as a substitution treatment (at the equivalent fixed-dosage) in patients with hypertension adequately treated by the two individual drugs concomitantly. Aliskiren/HCTZ combination therapy was effective and generally well tolerated in clinical trials evaluating its antihypertensive effects in adults with mild to moderate uncomplicated hypertension, and in patients with obesity plus hypertension.

The aliskiren/HCTZ single-pill combination offers the convenience of a single-tablet treatment regimen, which may improve treatment compliance and subsequent BP control. Further long-term trials evaluating the efficacy and tolerability of the combination would be of interest to ascertain the ultimate effects of treatment on the cardiovascular, cerebral and renal complications of hypertension.

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