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ADIS DRUG EVALUATION

Irbesartan/Amlodipine: A Review of its Use in Adult Patients with Essential Hypertension Not Adequately Controlled with Monotherapy

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Abstract Combination therapy is often required in patients with hypertension, and fixed-dose single-pill combinations have been shown to provide an easier regimen for patients, improving adherence. Irbesartan/amlodipine (Aprovasc®) is an angiotensin-receptor blocker/calcium-channel blocker fixed-dose single-pill combination, whose constituent drugs exert additive effects when coadministered. In two randomized, open-label, multicentre, phase III trials, fixed-dose combination therapy with irbesartan/amlodipine was more effective than continuation of irbesartan or amlodipine monotherapy in patients with hypertension not adequately controlled with initial irbesartan or amlodipine monotherapy; there was a significantly greater decrease from baseline in mean seated home systolic blood pressure (primary endpoint) with the fixed-dose combination. The fixed-dose combination was also associated with a greater decrease in mean seated home diastolic blood pressure and mean seated office systolic and diastolic blood pressure than monotherapy. The fixed-dose combination of irbesartan/amlodipine was well tolerated in these patients; most treatment-emergent adverse events were of mild or moderate severity. The most frequent adverse event was peripheral oedema, generally associated with amlodipine treatment.

Irbesartan/amlodipine in essential arterial hypertension inadequately controlled with irbesartan or amlodipine monotherapy: a summary

Fixed-dose, single-pill combination therapy that is administered once daily

Acts via the combined effects of irbesartan (an angiotensin II receptor antagonist) and amlodipine (a dihydropyridine calcium channel antagonist)

More effective than either constituent drug alone in decreasing systolic and diastolic blood pressure in patients with inadequately controlled hypertension

Well tolerated, with a tolerability profile consistent with those of the individual drugs. The most frequent adverse event was peripheral oedema, which is generally associated with amlodipine treatment

Use is contraindicated in patients with cardiogenic shock, clinically significant aortic stenosis and unstable angina

1 Introduction

Hypertension is a widely recognised major cause of common serious diseases [1]. Approximately half of all coronary disease and approximately two thirds of all strokes can be attributed to blood pressure (BP) that is not at an optimal level, thus accounting for ≈7 million deaths worldwide each year [1].

When classified as an average BP measurement of >140 mmHg systolic or >90 mmHg diastolic (or use of hypertensive medication), hypertension occurs in approximately 26 % of adults worldwide, equating to almost 1 billion people (estimated number in 2000) [2]. This is expected to increase to 1.56 billion people (29 %) by 2025 [2].

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The goal of antihypertensive therapy is to remove the increased risk of morbidity and mortality associated with elevated BP, while avoiding tolerability issues and without adversely affecting quality of life [3].

The cause of BP elevation is usually multifactorial, so the chances of normalizing pressure by targeting a single pressor mechanism are very low; moreover, compensatory responses often occur via the other mechanisms, decreasing the response to the drug [3]. As a result, combination therapy using drugs with different mechanisms of action is often required to achieve adequate BP control [3].

Recommended combinations include angiotensin-converting enzyme (ACE) inhibitor/diuretic, angiotensin-receptor blocker (ARB)/diuretic, ACE inhibitor/calcium channel blocker (CCB) and ARB/CCB [3]. Treatment adherence may be an issue with drug combinations if the drugs are administered separately; thus, single-pill combinations have been developed, providing an easier regimen for patients and improving adherence to treatment [3–5], potentially also decreasing cost of healthcare [5].

Irbesartan/amlodipine (Aprovasc®) is an ARB/CCB single-pill, fixed-dose combination administered once daily for the treatment of hypertension. This article reviews the available pharmacologic properties of irbesartan/amlodipine and its clinical efficacy and tolerability for the treatment of adult patients with essential arterial hypertension inadequately controlled with amlodipine or irbesartan monotherapy.

Data sources: Medical literature (including published and unpublished data) on irbesartan/amlodipine in patients with hypertension was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 22 February 2013], bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search terms: irbesartan/amlodipine, hypertension

Study selection: Studies in patients with hypertension who received irbesartan/amlodipine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Keywords: Irbesartan/amlodipine, hypertension, pharmacokinetics, pharmacodynamics, therapeutic use, tolerability

2 Pharmacodynamic Properties

The pharmacodynamic properties of irbesartan [6–9] and amlodipine [10, 11] are well documented. This section briefly discusses their pharmacodynamic effects. The antihypertensive effects of combination therapy with irbesartan/amlodipine are discussed in Section 4 [12, 13].

Irbesartan is a specific angiotensin II receptor (AT_1 subtype) antagonist and amlodipine is a dihydropyridine calcium antagonist [14]. They both decrease BP via the reduction of peripheral resistance; however, the mechanisms of action of the two drugs are complementary, and, when administered together, the effect on BP is additive [14].

In phase III trials in patients with hypertension uncontrolled by either irbesartan [13] or amlodipine [12] monotherapy (see Sect. 4 for treatment details), 10 weeks' treatment with irbesartan/amlodipine fixed-dose combination appeared to result in similar laboratory parameter outcomes to those observed with irbesartan [13] or amlodipine [12] monotherapy. In I-ADD, potassium levels increased by 143 and 157 mmol/L in irbesartan/amlodipine and irbesartan monotherapy recipients, respectively; sodium levels increased by 141 and 154 mmol/L and creatinine levels increased by 144 and 155 μmol/L [13]. In I-COMBINE, corresponding increases in these parameters with irbesartan/amlodipine and amlodipine monotherapy recipients were 130 and 128 mmol/L (potassium), 130 and 126 mmol/L (sodium), and 132 and 128 μmol/L (creatinine), respectively [12].

In a study comparing the effects of irbesartan 150 mg plus amlodipine 5 mg with those of irbesartan 150 mg or amlodipine 5 mg monotherapy in healthy adult volunteers, the combined treatment was found to be more effective than either monotherapy with regard to inhibition of oxidative stress; oxidative stress plays a major role in cardiovascular disease development [15].

Irbesartan induces the activity of peroxisome proliferator-activated receptor-gamma (PPARγ; a regulator of glucose and lipid metabolism), promoting PPARγ-dependent differentiation of 3T3-L1 adipocytes in vitro [16]. Irbesartan 10 μmol/L and telmisartan 10 μmol/L were associated with a 3.3- and 3.1-fold increase versus vehicle in expression of the adipogenic marker gene adipose protein 2 (aP2) in these cells (both $p < 0.01$). Losartan was only associated with an increase in aP2 expression at the highest concentration (100 μmol/L; 3.6-fold increase; $p < 0.01$), and eprosartan had no significant effects [16]. The half maximal effective concentrations (EC_{50}) for induction of aP2 were 3.5 μmol/L for irbesartan and 0.13 μmol/L for telmisartan. Similar results were observed with regard to PPARγ transcriptional activity, which was increased 3.4- and 2.6-fold with irbesartan 10 μmol/L and telmisartan

10 μmol/L, respectively (both $p < 0.05$ versus vehicle), and 2.2-fold with losartan 100 μmol/L only ($p < 0.05$); eprosartan again had no significant effect [16]. PPARγ activation by irbesartan and telmisartan was independent of AT_1 activity [16].

Irbesartan exhibits renoprotective effects [9]. In patients with hypertension, irbesartan tended to decrease renal blood flow and renal vascular resistance, without affecting glomerular filtration rate, and it had no effect on serum uric acid levels in patients with hypertension and hyperuricaemia [9]. In hypertensive patients with type 2 diabetes and microalbuminuria, irbesartan was associated with a delayed progression to overt nephropathy, and in hypertensive patients with type 2 diabetes and nephropathy, irbesartan slowed the progression of renal damage; these effects were partly independent of the decrease in BP associated with irbesartan treatment [9]. Moreover, irbesartan is associated with improved glycaemic control (in patients with hypertension and type 2 diabetes) and improved insulin sensitivity (in patients with hypertension, obesity and insulin resistance) [9]. In general, irbesartan is associated with no change in cholesterol or triglyceride levels [9].

Amlodipine is associated with increased renal blood flow and glomerular filtration rate and lowered renal vascular resistance in hypertensive patients [11]. Reduced urinary microalbumin excretion has been observed in some patients. No clinically significant changes in plasma renin activity, aldosterone and catecholamine levels, urine volume and urinary excretion have been observed with amlodipine use [11]. Furthermore, no adverse effects on insulin sensitivity, circulating insulin or glucose levels have been observed [11].

Non-steroidal anti-inflammatory drugs (NSAIDs) may attenuate the antihypertensive action of angiotensin II receptor antagonists, such as irbesartan [14]. The coadministration of amlodipine with sildenafil results in both agents independently exerting its own effect on blood pressure [14].

Drugs that affect the renin-angiotensin system (which includes irbesartan) have been observed to have a lesser effect on blood pressure in Black patients [17].

3 Pharmacokinetic Properties

This section provides an overview of the pharmacokinetics of irbesartan and amlodipine as individual agents (previously reviewed in detail [6–11]), as well as the pharmacokinetics of the drugs in combination (summarised in Table 1).

3.1 Irbesartan

Irbesartan is rapidly and completely absorbed following oral administration; maximum plasma concentrations (C_{max}) are reached after 1.5–2 hours (see Table 1) [18–20]. The absolute bioavailability of oral irbesartan is 60–80 % [21] and it is not affected by food [22]. Steady-state irbesartan concentrations in plasma are reached within 3 days of initiation of once daily dosing, and no clinically relevant accumulation was observed in plasma with repeated daily doses [23].

The volume of distribution (V_d) of irbesartan is 53–93 L/kg [21]. The drug is 96 % bound to plasma proteins, but has no significant binding to blood cells [14].

Metabolism of irbesartan occurs via glucuronide conjugation and oxidation, and its main circulating metabolite is irbesartan glucuronide (≈7 % of the plasma radioactivity) [24]. Unchanged drug represents the majority of an oral or intravenous dose (76–88 % of a radiolabelled dose) in plasma [24]. Oxidation mainly occurs via cytochrome P450 (CYP)2C9 [14]. Irbesartan neither induces nor inhibits CYP3A4, and it has a negligible effect on the metabolism of irbesartan [14].

Excretion of irbesartan and its metabolites occurs via the biliary and renal routes [14]. Approximately 20 % of a radiolabelled dose is recovered in urine; the rest is recovered in faeces [21, 24].

Table 1 Mean pharmacokinetic parameters of irbesartan/amlodipine when administered as an irbesartan/amlodipine fixed-dose combined tablet, at three of the approved dosages in three randomized, crossover, open-label, single-dose studies in healthy volunteers

Irbesartan/amlodipine dosage	Pharmacokinetic values for	t_{max} (h)	C_{max} (ng/mL)	AUC_∞ (h • ng/mL)	$t_{½}$ (h)
150/10 mg/day [18]	Irbesartan	1.5	2,310	11,925.56	15.45
	Amlodipine	5.0	7.33	320.14	47.03
300/5 mg/day [20]	Irbesartan	2.0	3,100	21,911.02	10.64
	Amlodipine	5.0	3.52	163.84	50.03
300/10 mg/day [19]	Irbesartan	1.5	3,000	20,956.46	12.41
	Amlodipine	5.0	7.91	384.82	49.53

AUC_∞ area under the plasma concentration-time curve, C_{max} maximum plasma concentration, $t_{½}$ elimination half-life, t_{max} time to maximum plasma concentration

Intravenously administered irbesartan has a total body clearance of ≈157 mL/min, of which 3.0 mL/min is eliminated via the kidneys [21]. The terminal elimination half-life (terminal $t_{½}$) is 10.64–15.45 hours (see Table 1) [18–20].

No clinically significant differences in irbesartan pharmacokinetics were observed between men and women, elderly and young, or black and white patients with hypertension [25]. Moreover, hepatic and renal impairment had no effect on irbesartan pharmacokinetic parameters [25]. Irbesartan is not removed by haemodialysis [25].

3.2 Amlodipine

Amlodipine is also well absorbed following oral administration of therapeutic doses; C_{max} is reached 5 hours after administration (see Table 1) [18–20]. It has an estimated absolute bioavailability of 64–90 %, and absorption is not affected by food [14]. The V_d for amlodipine is ≈21 L/kg, and, according to in vitro studies, ≈97.5 % of circulating amlodipine is plasma protein-associated [14].

Metabolism of amlodipine occurs in the liver, forming inactive metabolites [14]. A total of 10 % of the dose is excreted in urine as unchanged drug and 60 % as metabolites [14]. Amlodipine $t_{½}$ in plasma is ≈47–50 hours (see Table 1) [18–20].

Amlodipine elimination is decreased in elderly patients, leading to increased AUC and $t_{½}$ [26]; however, dosage adjustments are not required (see Sect. 6).

As it is a calcium antagonist, amlodipine $t_{½}$ is prolonged in patients with impaired liver function; irbesartan/amlodipine should be administered with caution in these patients (see Sect. 6) [14]. The pharmacokinetic parameters of amlodipine in patients with hypertension on haemodialysis did not differ from historical data in healthy volunteers, indicating no need for dosage adjustment in patients undergoing haemodialysis [27].

3.3 Irbesartan/Amlodipine

The pharmacokinetics of both irbesartan and amlodipine appear to be linear over the therapeutic range (150 or 300 mg/day and 5 or 10 mg/day respectively) [14]. The bioavailabilities of both drugs are not influenced by concurrent administration of the two drugs, either as a fixed-dose combined tablet or free-dose combination; there are no pharmacokinetic interactions between the two drugs [14].

Table 1 shows the pharmacokinetic parameters of irbesartan and amlodipine when administered as an irbesartan/amlodipine fixed-dose combined tablet, at three of the approved dosages [18–20]. No pharmacokinetic data are available for the irbesartan/amlodipine 150/5 mg/day dosage.

All three irbesartan/amlodipine fixed-dose combinations investigated (150/10, 300/5 and 300/10 mg/day) were bioequivalent to the corresponding free-dose combinations in three randomized, crossover, open-label, single-dose studies in healthy volunteers [18–20]. The 90 % CI for relative treatment difference for both C_{max} and AUC_{∞} were within the bioequivalence range of 0.80–1.25 for all dosages [18–20]. Moreover, t_{max} and $t_{½}$ did not significantly differ between the fixed-dose and free dose combinations for all dosages [18–20]. The relative bioavailability of irbesartan was 95 % and for amlodipine was 98 %, when administered together, and the elimination of both drugs was unaltered when they were concomitantly administered [14].

3.4 Drug Interactions

No drug interaction studies have been carried out with irbesartan/amlodipine fixed-dose combination and other drugs [14].

While irbesartan is mainly metabolized by CYP2C9, no significant interactions were observed when irbesartan was coadministered with warfarin, which is also metabolized by CYP2C9 [28]. There are no clinically significant drug-drug pharmacokinetic interactions when irbesartan is coadministered with other commonly used cardiovascular drugs, including nifedipine, hydrochlorothiazide, simvastatin and digoxin [14].

As irbesartan affects the renin-angiotensin system, its coadministration with potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium may lead to an increase in serum potassium, based on experience with other drugs that affect the renin-angiotensin system [14].

Amlodipine has been coadministered safely with thiazide diuretics, beta blockers, alpha blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual glycerol trinitrate, non-steroid anti-inflammatory drugs, antibiotics and oral hypoglycaemic agents, and has no effect on the protein binding of digoxin, warfarin, phenytoin or indomethacin, according to in vitro studies [14].

There are no clinically significant drug-drug pharmacokinetic interactions when irbesartan is coadministered with cimetidine [14], grapefruit juice [29, 30] aluminium/magnesium [14], atorvastatin [14], digoxin [31] or cyclosporine [14]. The coadministration of diltiazem with amlodipine in elderly hypertensive patients was associated with a significant ($p < 0.01$) increase in amlodipine C_{max} and AUC from time zero to 48 hours [32]. When amlodipine was coadministered with simvastatin in patients with hypertension and hypercholesterolemia, simvastatin C_{max} and AUC were both significantly increased [33].

4 Therapeutic Efficacy

The efficacy of irbesartan/amlodipine fixed-dose combination treatment for hypertension not adequately controlled with monotherapy with either drug has been investigated in two randomized, open-label (blinded endpoint), multicentre, phase III trials [12, 13], one (I-ADD) [13] comparing the fixed-dose combination with irbesartan monotherapy (following irbesartan treatment) and the other (I-COMBINE) [12] with amlodipine monotherapy (following amlodipine treatment).

Key patient characteristics and baseline demographic data for I-ADD and I-COMBINE are presented in Table 2 [12, 13]. Baseline demographic data did not generally differ between treatment groups [12, 13].

Following ≥4 weeks' oral irbesartan 150 mg/day [13] or oral amlodipine 5 mg/day [12] monotherapy, patients who met initial inclusion criteria received a further 7–10 days' monotherapy, taking one tablet once daily in the morning (lead-in period). At the end of this period, if patients met randomization criteria (see Table 2), they were randomized to receive the fixed-dose combination therapy (irbesartan/amlodipine 150/5 mg/day [12, 13]) or continued monotherapy (irbesartan 150 mg/day [13] or amlodipine 5 mg/day [12]) for 5 weeks. Following this lower-dosage period, the dosage of drugs was increased in both the fixed-combination therapy (to irbesartan/amlodipine 300/5 mg/day [13] or 150/10 mg/day [12]) and the monotherapy (to irbesartan 300 mg/day [13] or amlodipine 10 mg/day [12]) groups for a further 5 weeks' treatment (higher-dosage period). No investigational product was taken on the morning of the last day of each treatment period [12, 13].

The primary endpoint was the change from baseline in mean home seated systolic BP (SBP) at week 10 [13] or week 5 [12] (in the modified intent-to-treat population), based on measurements made by the patient for the last 6 days of each period, using a maximum of 24 measurements and a minimum of 12 correct measurements. Home measurements were taken twice in the morning and twice in the evening on measurement days, after a 5-minute rest in the seated position [12, 13]. Three office BP measurements were taken in the morning of each visit (beginning and end of each period), after a 5-min seated rest [12, 13].

While patients were not blinded to treatment, BP measurements were evaluated independently during data management [12, 13].

Fixed-dose combination therapy with irbesartan/amlodipine 150–300/5–10 mg/day was more effective than continuation of irbesartan 150–300 mg/day [13] or amlodipine 5–10 mg/day [12] monotherapy in patients with hypertension not adequately controlled with initial irbesartan or

Table 2 Key patient characteristics of two randomized, open-label (blinded endpoint), multicentre, phase III trials

	I-ADD [13]	I-COMBINE [12]
Inclusion criteria	Aged ≥18 years, established essential hypertension, treatment with amlodipine 5 mg/d [12] or irbesartan 150 mg/d [13] for ≥4 weeks, mean office SBP ≥145 mmHg after 4 weeks of monotherapy	
Key exclusion criteria	Mean office SBP ≥180 mmHg and/or mean DBP ≥110 mmHg at beginning of lead-in treatment; known or suspected causes of secondary hypertension, bilateral artery stenosis, renal artery stenosis in a solitary kidney, renal transplant, or only one functioning kidney; known type 1 diabetes mellitus, severe hepatic cytolysis, or severe renal failure	
Randomization criteria	Mean SBP ≥135 mmHg at end of lead-in treatment; good compliance with home BP measurement protocol (≥12 correct measurements over the last 6 d of the first period of measurements); estimated glomerular filtration rate ≥30 mL/min	
Randomized population (n)	325	290
mITT population (n)	320	287
Per protocol population (n)	275	262
Safety population (n)	325	288
Key patient characteristics at baseline		
Mean age (y)	57	57
BMI ≥30 kg/m^2 (%)	42	42
Dyslipidaemia (%)	20	31
Current smoking (%)	8	16
Type 2 diabetes mellitus (%)	20	15
Any cardiovascular history (%)	6	7
Mean home SBP (mmHg)	151.5	148.8
Mean home DBP (mmHg)	86.3	85.0

BMI body-mass index, *BP* blood pressure, *DBP* diastolic blood pressure, *mITT* modified intent-to-treat, *SBP* systolic blood pressure

amlodipine monotherapy (see Table 3) [12, 13]. After 5 weeks, the change from baseline in mean seated SBP at home (primary endpoint in one study [12]) was significantly ($p < 0.001$) greater among recipients of irbesartan/amlodipine 150/5 mg/day than among recipients of monotherapy with irbesartan 150 mg/day [13] or amlodipine 5 mg/day [12]. After 10 weeks, the change from baseline in mean seated SBP at home (primary endpoint in the other study [13]) was also significantly ($p < 0.001$) greater among recipients of irbesartan/amlodipine 300/5 [13] or 150/10 [12] mg/day than among recipients of monotherapy with irbesartan 300 mg/day [13] or amlodipine 10 mg/day [12].

Irbesartan/amlodipine fixed-dose combination therapy was also associated with a significantly ($p < 0.001$) greater mean change from baseline in seated diastolic BP (DBP) at home than irbesartan or amlodipine monotherapy in these patients at 5 and 10 weeks (see Table 3) [12, 13].

Moreover, the proportions of patients achieving a home seated SBP <135 mmHg or a controlled home seated BP (<135/85 mmHg) were significantly ($p < 0.01$) greater in recipients of fixed-dose combination therapy than monotherapy with either drug, at 5 and 10 weeks (see Table 3) [12, 13].

Similarly, the decreases from baseline in mean seated SBP and DBP taken at the office, and the proportions of patients achieving an office seated SBP <140 mmHg or a controlled office seated BP (<140/90 mmHg), were significantly ($p < 0.01$) greater in recipients of fixed-dose combination therapy than monotherapy with either drug at 5 and 10 weeks (see Table 4) [12, 13].

Overall, compliance did not significantly differ between treatment groups [12, 13]. At 5 and 10 weeks, respectively, compliance was 100.7 % and 102.2 % in fixed-dose combination therapy recipients versus 99.6 % and 100.5 % in irbesartan monotherapy recipients in I-ADD [13]; corresponding compliance in I-COMBINE was 101.1 % and 102.8 % in fixed-dose combination therapy recipients versus 99.6 % and 99.8 % in amlodipine monotherapy recipients [12]. The proportions of patients with good compliance (defined as a compliance of 80–100 % [13] or 80–120 % [12]) at 5 and 10 weeks were 97.4 % and 96.6 % of fixed-dose combination therapy recipients versus 98.8 % and 96.9 % of irbesartan monotherapy recipients in I-ADD [13]; corresponding proportions in I-COMBINE were 96.6 % and 89.0 % of fixed-dose combination therapy recipients versus 97.9 % and 98.5 % of amlodipine monotherapy recipients [12].

5 Tolerability

Fixed-dose combination therapy with irbesartan/amlodipine 150–300/5–10 mg/day was well tolerated in patients with hypertension not adequately controlled with initial amlodipine or irbesartan monotherapy [12, 13]. Drug-related treatment-emergent adverse events occurred in <15 % of patients during any treatment period, and at a generally similar incidence to that observed in patients receiving monotherapy with either irbesartan 150–300 mg/day [13] or amlodipine 5–10 mg/day [12] (see Table 5). According to the Mexican prescribing information, the most frequent treatment-emergent adverse events possibly related to treatment with the irbesartan/amlodipine fixed-dose combination that were reported in clinical trials included peripheral oedema, vertigo, dizziness, upper

Table 3 Efficacy of oral irbesartan/amlodipine in patients with hypertension uncontrolled with oral irbesartan [13] or amlodipine [12] monotherapy. Home seated blood pressure results at weeks 5 and 10 from randomized, open-label (blinded endpoint), multicentre, phase III trials. Data were taken from the modified intent-to-treat population

Study (Study name)	Treatment[a]	No. of pts	Mean change from BL in SBP (mmHg)		Mean change from BL in DBP (mmHg)		SBP <135 mmHg (% pts)		BP <135/85 mmHg (% pts)	
			At 5 weeks	At 10 weeks	At 5 weeks	At 10 weeks	At 5 weeks	At 10 weeks	At 5 weeks	At 10 weeks
Bobrie et al. [13]	IRB/AML	155	−15.4**	−18.7**[b]	−14.7**	−8.6**	46.1**	58.9**	41.6**	54.1**
(I-ADD)	IRB	165	−5.6	−9.9[b]	−5.1	−3.9	26.2	37.7	22.0	31.8
Bobrie et al. [12]	IRB/AML	144	−12.4** [b]	−18.1**	−10.8**	−9.4**	54.6**	69.7*	44.7**	67.4**
(I-COMBINE)	AML	143	−6.3[b]	−13.5	−3.3	−6.2	25.9	51.9	21.6	44.3

AML amlodipine, *BL* baseline, *BP* blood pressure, *DBP* diastolic blood pressure, *IRB* irbesartan, *pts* patients, *SBP* systolic blood pressure

* $p < 0.01$, ** $p < 0.001$ vs. monotherapy

[a] Following 7-10 days of monotherapy with irbesartan 150 mg/day [13] or amlodipine 5 mg/day [12], pts received 10 weeks' treatment with a fixed-dose combination (irbesartan/amlodipine 150/5 mg/day for 5 weeks followed by irbesartan/amlodipine 300/5 [13] or 150/10 mg/day [12] for 5 weeks) or monotherapy (irbesartan 150 mg/day [13] or amlodipine 5 mg/day [12] for 5 weeks followed by irbesartan 300 mg/day [13] or amlodipine 10 mg/day [12] for 5 weeks)

[b] Primary endpoint

Table 4 Efficacy of oral irbesartan/amlodipine in patients with hypertension uncontrolled with oral irbesartan [13] or amlodipine [12] monotherapy. Office seated blood pressure results at weeks 5 and 10 from randomized, open-label (blinded endpoint), multicentre, phase III trials. Data were taken from the modified intent-to-treat population

Study (Study name)	Treatment[a]	No. of pts	Mean change from BL in SBP (mmHg)		Mean change from BL in DBP (mmHg)		SBP < 140 mmHg (% pts)		BP < 140/90 mmHg (% pts)	
			At 5 weeks	At 10 weeks	At 5 weeks	At 10 weeks	At 5 weeks	At 10 weeks	At 5 weeks	At 10 weeks
Bobrie et al. [13]	IRB/AML	155	−14.7**	−17.9**	−7.3**	−7.7**	55.2**	61.7**	50.6**	59.7**
(I-ADD)	IRB	165	−5.1	−8.4	−2.4	−3.5	29.1	41.1	26.1	39.3
Bobrie et al. [12]	IRB/AML	144	−10.8**	−18.4**	−3.8*	−8.7**	52.1**	74.1**	49.3**	72.6**
(I-COMBINE)	AML	143	−3.3	−12.4	−1.2	−5.6	28.7	55.1	25.9	52.9

AML amlodipine, *BL* baseline, *BP* blood pressure, *DBP* diastolic blood pressure, *IRB* irbesartan, *pts* patients, *SBP* systolic blood pressure

* $p < 0.01$, ** $p < 0.001$ vs. monotherapy

[a] Following 7–10 days of monotherapy with irbesartan 150 mg/day [13] or amlodipine 5 mg/day [12], pts received 10 weeks' treatment with a fixed-dose combination (irbesartan/amlodipine 150/5 mg/day for 5 weeks followed by irbesartan/amlodipine 300/5 [13] or 150/10 mg/day [12] for 5 weeks) or monotherapy (irbesartan 150 mg/day [13] or amlodipine 5 mg/day [12] for 5 weeks followed by irbesartan 300 mg/day [13] or amlodipine 10 mg/day [12] for 5 weeks)

gastrointestinal pain, nausea, tongue disorder, glossodynia, cough, dermatitis by contact, hot flushes, somnolence, orthostatic hypotension, gingival tumefaction and proteinuria [14]. These adverse events were similar to those observed with monotherapy with either drug [14]. The most frequently reported adverse event was peripheral oedema, which was in general associated with amlodipine treatment [14].

In the two phase III trials I-ADD and I-COMBINE, most treatment-emergent adverse events were of mild or moderate severity, and no deaths were reported in either trial [12, 13]. Only one serious adverse event was deemed to be drug-related in either trial (hyperkalaemia in a patient receiving the fixed-dose combination treatment in I-COMBINE [12]) (see Table 5) [12, 13].

Proportions of patients discontinuing treatment as a result of adverse events were also low in both studies, and similar between treatment groups (see Table 5) [12, 13]. The most common treatment-related adverse events leading to treatment discontinuation were peripheral oedema and oedema in recipients of the fixed-dose combination therapy in the lower-dosage period in I-ADD (three events in three patients) [13]. In I-COMBINE, the most frequent treatment-emergent adverse event that led to treatment discontinuation was peripheral oedema in recipients of amlodipine monotherapy (three events) [12].

The Mexican prescribing information [14] carries warnings and precautions regarding hypotension (irbesartan has been rarely associated with hypotension in hypertensive patients with no other concomitant illness), potential foetal/neonatal morbidity and mortality in pregnant women (injuries and foetal death can be caused by exposure to ACE inhibitors during the second and third quarters of pregnancy), patients with heart failure (amlodipine has been associated with increased reports of pulmonary oedema in patients with heart failure, but no

Table 5 Tolerability of oral irbesartan/amlodipine in patients with hypertension uncontrolled with oral irbesartan [13] or amlodipine [12] monotherapy. Results are presented as during the lower-dosage period/during the higher-dosage period

Study (Study name)	Treatment[a]	No. of pts	≥1 drug-related TEAE (% pts)	≥1 serious drug-related TEAE (% pts)	Treatment discontinuation caused by TEAEs (% pts)
Bobrie et al. [13]	IRB/AML	156/152	6/5	0/0	2/0
(I-ADD)	IRB	169/166	1/1	0/0	0/1
Bobrie et al. [12]	IRB/AML	145/139	4/11	0/1	1/1
(I-COMBINE)	AML	143/141	5/11	0/0	2/1

AML amlodipine, *IRB* irbesartan, *pts* patients, *TEAE* treatment-emergent adverse event

[a] Following 7-10 days of monotherapy with irbesartan 150 mg/day [13] or amlodipine 5 mg/day [12], pts received 10 weeks' treatment with a fixed-dose combination (irbesartan/amlodipine 150/5 mg/day for 5 weeks followed by irbesartan/amlodipine 300/5 [13] or 150/10 mg/day [12] for 5 weeks) or monotherapy (irbesartan 150 mg/day [13] or amlodipine 5 mg/day [12] for 5 weeks followed by irbesartan 300 mg/day [13] or amlodipine 10 mg/day [12] for 5 weeks)

significant worsening of heart failure), and liver impaired patients (amlodipine half-life is prolonged in patients with impaired liver function, as it is a calcium antagonist). Refer to the prescribing information for treatment recommendations in these cases. Moreover, as irbesartan is an angiotensin II receptor antagonist, there is a possibility of oliguria and/or progressive elevation of nitrogen-containing compounds (and potential for acute kidney failure and death) in patients whose kidney function depends on the activity of the renin-angiotensin-aldosterone system, such as hypertensive patients with renal artery stenosis or severe congestive heart failure); these effects have been observed with other drugs affecting this system [14].

While doses of irbesartan up to 900 mg/day were not associated with additional toxicity, amlodipine overdosage may result in excessive peripheral vasodilation and potential reflex tachycardia [14].

Amlodipine is not associated with any adverse metabolic effects or changes in plasma lipids, and the use of amlodipine is suitable in patients with asthma, diabetes and gout [14].

In the elderly, volume-depleted patients, or those with impaired kidney function, coadministration of angiotensin II receptor antagonists, such as irbesartan, with NSAIDs (e.g. selective cyclooxygenase-2 [COX-2] inhibitors) may result in impaired kidney function, including potential kidney failure; these effects are generally reversible [14].

Orthostatic effects with irbesartan are rare; however, orthostatic events can be expected in patients with sodium depletion and/or volume depletion, as seen with ACE inhibitors [14]. Acute hypotension is generally avoided with amlodipine, as a result of its slow onset of action [14].

6 Dosage and Administration

Oral irbesartan/amlodipine fixed-dose combination treatment is indicated in Mexico in adult patients with essential arterial hypertension not adequately controlled with irbesartan or amlodipine monotherapy [14]. It can also be administered as continuation of treatment in patients receiving irbesartan and amlodipine as separate tablets.

Irbesartan/amlodipine is administered as one tablet once daily, with or without food, at a dosage of 150/5, 150/10, 300/5 or 300/10 mg/day [14]. The maximum recommended dosage is 300/10 mg/day. The administered dosage should be individualized and adjusted based on the antihypertensive response required, as well as the treatment response observed with monotherapy.

Irbesartan/amlodipine should be administered with caution in patients with impaired liver function, as it contains amlodipine (amlodipine $t_{½}$ is prolonged in these patients; see Sect. 3.2) [14]. No dosage adjustment is necessary in patients with impaired kidney function or the elderly. Irbesartan/amlodipine safety and efficacy have not been established in paediatric patients.

Irbesartan/amlodipine administration is contraindicated in patients with cardiogenic shock, clinically significant aortic stenosis and unstable angina [14].

Local prescribing information should be consulted for further, detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

7 Current Status of Irbesartan/Amlodipine in Essential Hypertension Not Adequately Controlled with Monotherapy

US guidelines for the treatment of hypertension in general recommend first-line treatment of patients with stage 1 hypertension (BP of 140–159/90–99 mmHg) with thiazide diuretics for most patients, although ACE inhibitors, ARBs, beta-blockers, CCBs or a combination of these drugs may also be considered; stage 2 hypertension (BP of ≥160/≥100 mmHg) should be treated with two-drug combinations (usually a thiazide-type diuretic plus either an ACE inhibitor, an ARB, a beta-blocker or a CCB) [34]. European guidelines recommend initial treatment with one (or more) of five major classes of antihypertensive drugs: thiazide diuretics, CCBs, ACE inhibitors, ARBs and beta-blockers, with specific recommendations depending on organ damage, clinical events, or comorbid conditions [35]. Other potential treatments include alpha-blockers and direct vasodilators [34].

Combination therapy may be of use for both tolerability and efficacy reasons. Tolerability may be improved as a result of lower dosages being required or even direct action by the concomitant drug [3]. For example, a pooled analysis found that renin-angiotensin system blocker/CCB combination therapy was associated with a significantly lower incidence of peripheral oedema, a common adverse event associated with CCBs, than CCB monotherapy [36]. Efficacy, in general already greater than monotherapy at the same dosage, may also be greater with combination therapy than with higher doses of monotherapy; in a subgroup analysis in Japanese patients with hypertension and chronic kidney disease, ARB plus CCB combination therapy was more effective than high-dose ARB monotherapy in the prevention of cardiovascular events, likely due to better BP control [37].

Interestingly, while US guidelines recommend the use of thiazide diuretics as one of the drugs in combination therapy, data from the ACCOMPLISH trial suggest that this may not be necessary; in high-risk patients with hypertension, combination therapy with benazepril plus amlodipine was more effective than combination therapy with benazepril plus hydrochlorothiazide [38].

Irbesartan/amlodipine is marketed in Mexico [14] and registered in Japan (at a lower dose of irbesartan) [39] for the treatment of adult patients with essential arterial hypertension not adequately controlled with irbesartan or amlodipine monotherapy. Oral irbesartan/amlodipine is also approved for the treatment of hypertension in Chile, Colombia, Ecuador, Guatemala, and Honduras.

In phase III trials, oral irbesartan/amlodipine was effective and well tolerated in patients with hypertension not adequately controlled with initial amlodipine or irbesartan monotherapy; it was more effective than monotherapy with either drug, and the tolerability profile was generally similar to that observed with monotherapy.

However, placement of irbesartan/amlodipine in the management of essential hypertension is not yet possible, due to a current lack of direct head-to-head trials comparing it to other antihypertensive treatments, in particular other fixed-dose, single-pill combination therapies. Moreover, further investigation into other endpoints, for example decreased morbidity, would be of interest. Long-term data would also be beneficial.

A further phase III, 16-week trial has recently been completed (although no data are yet available), investigating four different dosages of irbesartan/amlodipine (150/5, 150/10, 300/5 and 300/10 mg/day) in adult patients with established essential hypertension that is uncontrolled by irbesartan 150 mg/day or amlodipine 5 mg/day monotherapy [40].

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