Paper

Comparison of Monotherapy with Irbesartan 150 mg or Amlodipine 5 mg for Treatment of Mild-to-Moderate Hypertension

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Abstract

Objective. The primary objective of this study was to compare the antihypertensive efficacy of the angiotensin II receptor blocker irbesartan 150 mg and the calcium channel blocker amlodipine 5 mg in the treatment of patients with seated diastolic blood pressure (DBP) 95–110 mmHg.

Design. Multicentre, randomised, double-blind, comparative pilot study.

Methods. Subjects were 18–65 years of age, with DBP 95–110 mmHg, and of non-African American origin. Following a three-week, single-blind, placebo lead-in period, 181 subjects were randomised in a 1:1 ratio to receive once-daily irbesartan 150 mg (n=89) or amlodipine 5 mg (n=92) for four weeks. Trough (24±3 hours post-dosing) BP measurements were obtained at baseline and at Weeks 2 and 4 under standardised, controlled conditions. Response was defined as DBP <90 mmHg or a reduction from baseline of ≥10 mmHg.

Results. After four weeks of treatment, the mean (±SE) decrease from baseline in DBP was 9.4±0.6 mmHg in the irbesartan group *vs.* 9.6±0.6 mmHg in the amlodipine group (p=0.806). The mean decrease from baseline in seated systolic BP was 12.2±1.0 mmHg in the irbesartan group *vs.* 12.0±1.0 mmHg in the amlodipine group (p=0.885). Overall, 62% of subjects in the irbesartan group and 63% in the amlodipine group had a response (p=0.609), and 54% and 56% of patients (p=0.596), respectively, had their DBP normalised (<90 mmHg). Adverse events were reported by 21.3% of patients receiving irbesartan and 20.7% receiving amlodipine.

Conclusions. Irbesartan 150 mg demonstrated comparable efficacy to amlodipine 5 mg, thereby confirming its value as an antihypertensive treatment option in non-African American patients with DBP 95–110 mmHg.

Introduction

Numerous drugs are available for the management of hypertension, representing several distinct drug classes and employing diverse mechanisms of action. Because of the array of therapeutic choices, matching antihypertensive therapy to individual patients often presents a clinical challenge. The choice of agent is based on patient-related factors as well as drug mechanisms. These factors include the stage of hypertension, the presence of comorbid conditions, and the identification of risk factors for renal disease, cardiovascular disease, or diabetes mellitus. In addition, aspects of the treatment regimen that may affect patient adherence need to be considered such as side effects, out-of-pocket costs, and convenience.[1]

Calcium channel blockers (CCBs) are an important class of antihypertensive agents. As a class, they are well tolerated and are associated with few side effects.[1] Amlodipine, a dihydropyridine CCB, is currently the most frequently prescribed branded cardiovascular agent worldwide and is commonly considered the 'gold standard' antihypertensive treatment option in terms of efficacy, particularly in lowering systolic blood pressure (SBP).[2] Once-daily amlodipine is generally well tolerated, providing statistically significant reductions in BP over 24 hours.[3] The usual initial oral dosage is 5 mg once daily.[4]

Targeting the renin-angiotensin-aldosterone system (RAAS) is also an important strategy for lowering BP.[5] Currently, there are three classes of drugs that inhibit the RAAS: angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), and selective aldosterone receptor blockers. ACE-Is reduce the formation of angiotensin (Ang II), whereas ARBs act by specific blockade of the angiotensin II receptor subtype 1 (AT_1). Selective aldosterone blockers act at another step of the RAAS, by blocking the actions of aldosterone.

Several ARBs are available for the management of hypertension, either as monotherapy or in combination with other agents. As a class, the ARBs have demonstrated efficacy, safety, and placebo-like tolerability in recommended dosing regimes.[6-10] The fact that their side effect profile is remarkably benign[6,9,10] gives them an advantage over ACE-Is, which are commonly associated with a dry cough and the more uncommon risk of angioedema.[8,11,12]

Irbesartan is an effective, long-acting ARB that provides highly selective, insurmountable blockade of AT_1-receptors and is approved for the treatment of patients with hypertension and for the treatment of diabetic nephropathy in patients with Type 2 diabetes mellitus and hypertension.[13] Clinical trials have shown that irbesartan, at doses of 75 mg, 150 mg and 300 mg, provides significant dose-related reductions in BP with once-daily administration in patients with stage 1 hypertension and the lower limits of stage 2 hypertension, and has placebo-like tolerability.[7,14,15]

Despite the proven efficacy of irbesartan and other ARBs, there remains a misconception among some clinicians that these compounds have reduced BP-lowering efficacy compared with other well-established antihypertensive medications, such as amlodipine. This trial aimed to confirm the comparable efficacy of irbesartan and amlodipine.

Methods

Study Population

The study enrolled men and women, 18–65 years of age, of non-African American origin with seated DBP 95–110 mmHg. Subjects were recruited from 20 sites in the United States, including private medical offices, clinical settings and clinical research centres. All women of childbearing potential were required to have a negative pregnancy test (minimum sensitivity 25 IU/L of beta-human chorionic gonadotropin within 72 hours prior to the start of the study medication) and to be using an approved method of contraception.

Subjects were excluded from the study if they had a history of any of the following: cardiovascular conditions (angina pectoris, myocardial infarction, coronary revascularisation within 12 months, heart failure, obstructive valvular heart disease, hypertrophic cardiomyopathy, transient ischaemic attack/cerebrovascular accident, or cardiac arrhythmias), renal conditions (renovascular occlusive disease or renal allograft), clinically important hepatic, metabolic, neurological, pulmonary, or haematological disorders, known hypersensitivity to any component of the study treatments, or severe psychiatric disorder. African Americans were excluded from the study based on clinical evidence suggesting that this subpopulation does not respond as well to beta-blocker, ACE-I or ARB monotherapy in comparison with CCB monotherapy.[16-19]

Study Design

This was a multicentre, randomised, double-blind, parallel-group study. After an appropriate tapering of previous antihypertensive therapy according to manufacturer recommendations, subjects entered a three-week, single-blind, placebo lead-in period. Subjects who met eligibility criteria and had a mean DBP 95–110 mmHg were randomised in a 1:1 ratio at baseline (end of the placebo treatment period) to receive double-blind treatment with irbesartan 150 mg or amlodipine 5 mg once daily for four weeks. The randomisation schedule linking the randomisation number with treatment was computer-generated by the biostatistics department of Bristol-Myers Squibb (Princeton, NJ). Trough BP measurements (taken at 24±3 hours after dosing) were obtained under standardised, controlled conditions four times during the placebo lead-in period and after two and four weeks of active treatment.

The study was performed in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki International Conference on Harmonization, and requirements of the United States Food and Drug Administration. Investigators were required to obtain written informed consent from all subjects prior to participation.

Observation Methods

Efficacy

A complete medical examination was performed at the screening visit and after four weeks of active treatment. Blood pressure and heart rate were measured during scheduled office visits at screening, at four visits during the placebo lead-in period, and on days 1, 14 and 28 of the four-week active treatment period. All measurements were obtained using a calibrated mercury sphygmomanometer under controlled conditions using the same (dominant) arm and cuff size at each visit. Mean seated BP was determined at each visit from three separate measurements obtained at least 1 minute apart after a 10-minute period of rest in the seated position. If any of the three readings was not within 8 mmHg of the other two, an additional two BP readings were obtained for the calculation. Study staff were specifically trained to perform standardised BP and heart rate measurements to minimise variability due to measurement technique. Clinic visits were scheduled between 6 am and 10 am, and subjects were instructed to postpone taking their study drug until after their BP had been measured. Subjects were also required to abstain from drinking alcoholic or caffeinated beverages for at least six hours before, and from smoking for three hours before BP measurements were obtained.

Safety

Safety and tolerability were evaluated at each clinic visit by assessing adverse events (defined as a new or worsening illness, sign, symptom, or clinically significant laboratory test abnormality during the course of treatment, whether attributable to study drug or not), routine laboratory parameters, and electrocardiograms. Fasting laboratory values (haematology, serum chemistry, blood urea nitrogen, and alanine aminotransferase) were obtained at baseline and at Week 4.

Outcome Measures

The primary efficacy measure was the change from baseline in mean trough seated DBP after four weeks of active treatment. Secondary outcome measures included the change from baseline in mean trough seated SBP at Week 4, therapeutic response at Week 4 based on the proportion of subjects with normalised seated DBP (DBP <90 mmHg), and the proportion of responders (subjects with normalised seated DBP or who experienced a ≥10 mmHg reduction from baseline in DBP).

Analytical Methods

Sample Size

A sample size of 70 evaluable subjects per treatment group was required to provide a precision of ±2.5 mmHg for estimating the difference between groups with 95% confidence, assuming a standard deviation of 7.5 mmHg, for the change from baseline in mean trough seated DBP. To allow for attrition of approximately 10%, a minimum of 156 subjects were required for randomisation.

Data Sets

Safety analyses were performed on the data from all randomised subjects who received at least one dose of study medication; efficacy analyses were performed on all evaluable subjects with valid data. Data for all efficacy analyses were summarised for the baseline, Week 2, Week 4 and endpoint evaluations. An endpoint was defined as the last measurement obtained during the double-blind treatment period. Randomised subjects with protocol violations were excluded from all efficacy analyses. The exception was subjects whose only protocol violation was missing a visit for BP or heart rate measurement (scheduled visit ±3 days), and for which all other valid measurements were included.

Statistical Analyses

Statistical analyses were performed on the data from Weeks 2 and 4 and from endpoint, to assess the change from baseline in trough DBP and SBP and to assess therapeutic response. Summaries of the mean change from baseline to Week 4 in DBP were calculated for specific subgroups defined by age (<50 years or ≥50 years), gender, and baseline DBP (<100 mmHg or ≥100 mmHg). Data were summarised by treatment group for the proportion of subjects with normalised BP and the proportion of responders at Weeks 2 and 4. Treatments were compared using Cochran-Mantel-Haenszel tests, stratified by site. Data from two study sites, each having fewer than two subjects per treatment group for BP values at Week 4, were combined for analysis.

Analysis of covariance (ANCOVA) was used to compare the treatment groups with regard to changes from baseline in trough DBP and SBP at Week 2, Week 4, and at endpoint. The ANCOVA model included terms for treatment and treatment site as main effects and for baseline value as a covariate. Comparisons of the mean changes from baseline for the two groups were based on the difference between the adjusted mean changes and the associated 95% confidence intervals (CIs).

Safety Evaluations

Data from all randomised subjects who received at least one dose of study medication were included in the safety analysis.

Results

Patients

A total of 238 subjects were enrolled in the study, 181 subjects were randomised (irbesartan n=89; amlodipine n=92) and 176 subjects (irbesartan n=86; amlodipine n=90) completed the four-week, double-blind study period. Five subjects left the study prematurely (3/89 [3%] subjects in the irbesartan group and 2/92 [2%] subjects in the amlodipine group). Data sets were analysed for all randomised subjects (n=181) and for subjects with valid data (n=178). The results of both data sets were similar.

The summaries of demographic characteristics for all randomised subjects demonstrated no apparent differences between the two groups at baseline (Table 1). The majority of subjects were men (63%), Caucasian (87%), and the mean age was 51 years. At baseline, mean (±SD) seated DBP was 99.7±3.6 mmHg and mean seated SBP was 150.1±12.6 mmHg.

Reduction in Blood Pressure at Trough

The primary efficacy measure of adjusted change from baseline in mean (±SE) trough DBP at Week 4 was -9.4±0.6 mmHg in the irbesartan group and -9.6±0.6 mmHg in the amlodipine group (Table 2). The difference in reduction in mean DBP between the two treatment groups was 0.2 mmHg (95% CI: -1.5, 1.9; p=0.806). Final mean (±SD) trough DBP was 90.1±6.9 mmHg in the irbesartan group and 89.9±6.6 mmHg in the amlodipine group.

The adjusted change from baseline in mean (±SE) trough SBP at Week 4 was -12.2±1.0 mmHg in the irbesartan group and -12.0±1.0 mmHg in the amlodipine group (Table 2). The difference in reduction in mean SBP between the two groups was 0.2 mmHg (95% CI: -3.0, 2.6; p=0.885) (Table 2). Mean (±SD) trough SBP at treatment end was 138.7±13.1 mmHg in the irbesartan group and 137.5±12.7 mmHg in the amlodipine group. There were no differences in mean heart rate between the two groups at Week 4 (71.0 beats/minute in the irbesartan group *vs.* 72.4 beats/minute in the amlodipine group).

After two weeks of treatment, mean (±SD) trough DBP was 90.4±6.5 mmHg in the irbesartan group and 91.3±5.9 mmHg in the amlodipine group. The adjusted change from baseline in mean (±SE) trough DBP at Week 2 was -9.1±0.6 mmHg in the irbesartan group and -8.4±0.6 mmHg in the

Table 1
Demographic and baseline characteristics of all randomised subjects.

Characteristic	Irbesartan 150 mg (n=89)	Amlodipine 5 mg (n=92)	Total (n=181)
Age, years			
Mean±SD	50.9±8.6	51.0±9.0	51.0±8. 8
Range	29–65	32–65	29–65
<50, n (%)	38 (42.7)	35 (38.0)	73 (40.3)
Gender, n (%)			
Men	52 (58.4)	62 (67.4)	114 (63.0)
Race, n (%)			
Caucasian	77 (86.5)	80 (87.0)	157 (86.7)
Asian	2 (2.2)	2 (2.2)	4 (2.2)
Other	10 (11.2)	10 (10.9)	20 (11.0)
Body mass index, kg/m²			
Mean±SD	30.5±5.0	30.5±7.1	30.5±6.2
Range	21.4–46.9	20.9–69.8	20.9–69.8
Seated DBP, mmHg			
Mean±SD	99.7±3.5	99.8±3.7	99.7±3.6
Range	95–111	95–110	95–111
<100 mmHg-mild n (%)	52 (58.4)	60 (65.2)	112 (61.9)
≥100 mmHg-moderate n (%)	37 (41.6)	32 (34.8)	69 (38.1)
Seated SBP, mmHg			
Mean±SD	150.7±12.4	149.6±12.8	150.1±12.6
Range	119–183	121–185	119.0–185

SD = standard deviation; DBP = seated diastolic blood pressure; SBP = seated systolic blood pressure

Table 2
Results of efficacy analyses at Week 4.

	Irbesartan 150 mg (n=86)	Amlodipine 5 mg (n=90)	
Trough DBP, mmHg			
Baseline, mean±SD	99.7±3.5	99.8±3.7	
Week 4, mean±SD	90.1±6.9	89.9±6.6	
Adjusted change from baseline at Week 4, mean±SE	-9.4±0.6	-9.6±0.6	
Difference (95% CI)[1]			0.2 (–1.5, 1.9)
Trough SBP, mmHg			
Baseline, mean±SD	150.7±12.4	149.6±12.8	
Week 4, mean±SD	138.7±13.1	137.5±12.7	
Adjusted change from baseline at Week 4, mean±SE	-12.2±1.0	-12.0±1.0	
Difference (95% CI)[1]			0.2 (–3.0, 2.6)
Therapeutic response[2]			
Proportion with normalised DBP, n (%)	46 (53.5)	50 (55.6)	
Proportion of responders, n (%)	53 (61.6)	57 (63.3)	

[1]Difference = (adjusted mean change from baseline for irbesartan) – (adjusted mean change from baseline for amlodipine)

[2]Therapeutic response was defined as follows: normalised = trough DBP <90 mmHg; responders = normalised DBP or DBP decreased by ≥10 mmHg from baseline value

CI = confidence interval; SD = standard deviation; SE = standard error; DBP = seated diastolic blood pressure; SBP = seated systolic blood pressure

amlodipine group. The difference in reduction in mean DBP between the two treatment groups at Week 2 was 0.7 mmHg (p=0.402). Mean (±SD) trough SBP at Week 2 was 139.3±13.3 mmHg in the irbesartan group *vs.* 139.9±13.5 mmHg in the amlodipine group; the adjusted change from baseline in mean (±SE) SBP was -11.5±1.0 mmHg in the irbesartan group and -9.7±1.0 mmHg in the amlodipine group. The difference in reduction in mean SBP between the two treatment groups at Week 2 was 1.7 mmHg in favour of irbesartan (95% CI: -4.5, 1.0; p=0.217).

Subgroup Analyses

The treatment effect on the change from baseline in trough DBP at Week 4 in patient subgroups, as defined by age, gender, and baseline DBP, is shown in Table 3. The mean changes from baseline in DBP were of a similar magnitude in each treatment group for patients <50 years of age versus ≥50 years, for men and women, and for patients with baseline DBP <100 mmHg versus ≥100 mmHg.

Therapeutic Response

At Week 4, the percentage of subjects with normalised seated DBP (DBP <90 mmHg) was 54% in the irbesartan group and 56% in the amlodipine group (p=0.596) (Table 2). The proportion of responders (subjects with normalised DBP or who experienced a ≥10 mmHg reduction from baseline in DBP) was 62% in the irbesartan group versus 63% in the amlodipine group (p=0.609) (Table 2).

Adverse Events

All 181 patients randomised were evaluated for safety. Adverse events were experienced by 19 (21.3%) patients in the irbesartan treatment group and 19 (20.7%) patients in the amlodipine treatment group during the four-week double-blind treatment period. Dizziness was the most common adverse event, occurring in five (5.6%) of patients on irbesartan and one (1.1%) of patients on amlodipine (Table 4).

Two serious adverse events occurred during the active treatment period: one patient in the irbesartan treatment group developed a urethral calculus, and one patient in the amlodipine treatment group died from acute alcohol intoxication. Both events were judged to be unrelated to the study drug.

Discussion

In the current study, irbesartan 150 mg once daily reduced mean trough DBP by 9.4 mmHg, which was comparable to that achieved with amlodipine 5 mg once daily (9.6 mmHg). Importantly, the

Table 3
Mean changes from baseline in trough seated diastolic blood pressure (DBP) at Week 4 for specific patient subgroups defined by age (<50 years or ≥50 years), gender, and baseline DBP (<100 mmHg or ≥100 mmHg).

	Irbesartan 150 mg		Amlodipine 5 mg	
	n	Mean±SD change in DBP, mmHg	n	Mean±SD change in DBP, mmHg
Age				
<50 years	35	-8.7±5.7	33	-8.3±6.5
≥50 years	51	-10.2±6.5	57	-10.4±6.1
Gender				
Men	51	-9.3±5.7	61	-8.9±5.8
Women	35	-9.9±6.9	29	-11.2±7.1
Baseline DBP				
<100 mmHg	50	-9.6±5.6	60	-9.2±6.1
≥100 mmHg	36	-9.5±7.1	30	-10.4±6.7

Table 4
Adverse events reported by ≥2% of patients in either treatment group (safety population).

Adverse event, n (%)	**Irbesartan 150 mg (n=89)**	**Amlodipine 5 mg (n=92)**
Headache	2 (2.2)	2 (2.2)
Infection	0 (0.0)	2 (2.2)
Nausea	0 (0.0)	2 (2.2)
Ecchymosis	0 (0.0)	3 (3.3)
Peripheral oedema	1 (1.1)	3 (3.3)
Myalgia	2 (2.2)	0 (0.0)
Dizziness	5 (5.6)1	(1.1)
Respiratory infection	3 (3.4)	0 (0.0)

strong antihypertensive efficacy observed with both drugs was achieved rapidly, within two weeks of initiating treatment. Amlodipine is commonly considered the gold standard antihypertensive agent in terms of efficacy, particularly in lowering SBP[2] (Data from IMS National Prescription Audit 1990–2001). Compared with the older ARBs, such as losartan (the first ARB introduced in the market) and valsartan,[20] the newer members of this class, such as irbesartan and olmesartan, have demonstrated greater BP-lowering efficacy, especially in terms of DBP.[21–25] However, some physicians harbour reservations regarding the efficacy of ARBs compared with CCBs, which acts to limit the use of ARBs. The present study was designed to compare the antihypertensive efficacy, safety, and tolerability of a once-daily regimen of irbesartan 150 mg with amlodipine 5 mg over a four-week treatment period.

Multiple hypertension trials have demonstrated the importance of lowering BP, such that comparative efficacy is important information to evaluate in the selection of an antihypertensive agent. In addition, beneficial effects beyond BP-lowering influence decision-making. Given their comparable antihypertensive efficacy, it is instructive to explore other factors that might influence the choice of one of these agents over the other. In fact, although the results of this study show no differences in efficacy or tolerability between once-daily monotherapy with irbesartan 150 mg and amlodipine 5 mg in non-African Americans, other investigations point to potential advantages of ARBs in special circumstances. For example, the Irbesartan Diabetic Nephropathy Trial (IDNT),[26] which was designed to determine whether irbesartan or amlodipine protect against the progression of diabetic nephropathy beyond that attributable to lowering BP, found that the risk of the combined primary endpoint (doubling of baseline serum creatinine, development of end-stage renal disease, or death) with irbesartan was 20% lower than with placebo (p=0.02) and 23% lower than with amlodipine (p=0.006). These renal benefits of irbesartan over amlodipine were not explained by differences in achieved BP (140/77 mmHg with irbesartan; 141/77 mmHg with amlodipine).

In line with emerging clinical evidence, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[1] delineates specific high-risk conditions that are compelling indications for the use of a particular antihypertensive drug class. The preferential use of ARBs is recommended for hypertensive patients with heart failure, diabetes or chronic renal disease, while CCBs are recommended in those at high coronary heart disease risk, or diabetes.

One potential limitation of the study is that it was conducted with doses that are lower than the maximum approved doses for either irbesartan (300 mg) or amlodipine (10 mg). The doses chosen are those most commonly used in the treatment of hypertension. Furthermore, it excluded African Americans, who are known to have a high prevalence of hypertension,[27] but have been reported to not respond to ARBs as well as subjects of other ethnicities. Additional studies in this population are warranted.

Conclusions

Once-daily dosing with either irbesartan 150 mg daily or amlodipine 5 mg daily significantly reduced BP in subjects with DBP 95–110 mmHg; both drugs were well tolerated. The results of this study corroborate data from previous studies demonstrating the comparable antihypertensive efficacy of ARBs with CCBs in middle-aged, non-African American patients with DBP 95–110 mmHg.

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